Are pre-/postnatal stress factors and chronic stress linked to breast cancer?

Dissertation zur Erlangung der naturwissenschaftlichen Doktorwürde durch den Fachbereich I – Psychobiologie der Universität Trier

submitted by

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List of abbreviations

Is	In Situ
BRCA1	Breast Cancer 1
BRCA2	Breast Cancer 2
DNA	Deoxyribonucleic Acid
GF	Growth Hormone
IGF	Insulin Growth Factor
β-adrenergic receptors	Beta-adrenergic Receptors
IL	Interleukin
TNM	Tumor size-Node-Metastasis
G	Grade
ER	Estrogen Receptor
PR	Progesterone Receptor
HER2-neu	Human Epidermal growth factor receptor 2
CT	Chemotherapy
HT	Anti-hormonal Treatment
CNS	Central Nervous System
CRH	Corticotrophin-releasing Hormone
LC	Locus Coeruleus
HPAA	Hypothalamic-pituitary-adrenal Axis
NIH	National Institute of Health
ANS	Autonomic Nervous System
E	Epinephrine
NE	Norepinephrine
AVP	Arginine Vasopressin
ACTH	Adreno-corticotropic Hormone
TNF	Tumor Necrosis Factor
NFκB	Nuclear Factor κ B
GAS	General Adaptation Syndrome
SNS	Sympathetic Nervous System
T-cells	Thymus Cells
NK cells	Natural Killer Cells

CAR	Cortisol Awakening Response
PNS	Parasympathetic Nervous System
DRN	Dorsal Raphe Nucleus
VEGF	Vascular Endothelial Growth Factor
GR	Glucocorticoid Receptor
PTSD	Posttraumatic Stress Disorder
E2	Estrogens
OT	Oxytocin
MPOA	Medial Preoptic Area
ERα	Estrogen Receptor α
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone Sulfate
HDL-C	High Density Lipoprotein-Cholesterol
LOH	Loss of heterozygosity
BMI	Body Mass Index
11betaHSD1	11beta-hydroxysteroid Dehydrogenase Type 1
MDSC	Myeloid-derived Suppressor Cells
MMP9	Matrix Metalloproteinase 9
BMDCs	Bone Marrow Derived cells
RNA	Ribonucleic Acid
cAMP PKA	Cyclic Adenosine Monophosphate Protein Kinase A
Hsp27	Heat Shock Protein 27
TEBs	Terminal End Buds
CCND2	Cyclin D2
GSTP1	Glutathione S-TransferaseP1
NES1	Normal Epithelial Cell-Specific1
PHLDA1	Pleckstrin Homology-Like Domain, family A, member 1
HSD17B1	17 beta Hydroxyl Steroid Dehydrogenase type 1
SATB	Special AT-rich Binding Protein
SAFB1	Scaffold Attachment Factor B1
SAFB2	Scaffold Attachment Factor B2
MCF-7	Michigan Cancer Foundation-7
EGF	Epidermal Growth Factor
TC	Total Cholesterol

LDC	Low Density Cholesterol
Ob-RL	Obesity Receptor Leptin
EE	Enriched Environment
BDNF	Brain-Derived Neurotrophic Factor
STAT	Signal Transducer and Activator of Transcription
IGFBP-3	IGF Binding Protein-3
PSQ	Pre-/Peri-/Postnatal Stress Questionnaire
FBK-R23	Fragebogen zur Belastung von Krebskranken-Revised
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
PBI	Parental Bonding Instrument
TICS	Trierer Inventar zum chronischen Stress
PHQ-D	Patient Health Questionnaire-Deutsch
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DAACRO	Diagnostic Assessment and Clinical Research Organization
SPSS	Statistical Package for the Social Sciences
ANOVA	Analysis of Variance
N	Number
SD	Standard Deviation
UEBE	Arbeitsüberlastung, overwork
SOUE	Soziale Überlastung, social overload
ERDR	Erfolgsdruck, pressure of success
UNZU	Unzufriedenheit mit der Arbeit, unsatisfaction with work
UEFO	Überforderung bei der Arbeit, overcharge at work
MANG	Mangel an sozialer Anerkennung, lack of social recognition
SOZS	Soziale Spannungen, social tension
SOZI	Soziale Isolation, social isolation
SORG	Chronische Besorgnis, chronic apprehension
SSCS	Screening Scala chronischer Stress, screening scale chronic stress
MV	Mean Variation
VAR	Variation

df	degrees of freedom
w-u	wake-up
nmol/l	nanomol per liter
w-u+30	wake-up + 30 minutes
w-u+45	wake-up + 45 minutes
w-u+60	wake-up + 60 minutes
AUC	area under the curve
AUCi	area under the curve increase
AUCg	area under the curve ground
MCare	maternal care
PCare	paternal care
MProt	maternal protection
PProt	paternal protection
FACIT-TOI	FACIT-Trial Outcome Index
FACIT-G	FACIT-General
FACIT-F	FACIT-Fatigue Total Score
FACIT-FS	FACIT-Fatigue Subscale

Chapter 1

Introduction, Objectives and Outline

1. Introduction, objectives and outline

1.1. Introduction

Over the past decades, more and more papers and reports about stress and its negative consequences for our mental and physical health have been published. Stress affects not only the nervous and endocrine system but also the immune system. Many psychiatrists and psychologists emphasize the role of psychological factors in both mental and physical diseases.

The problem is that most researchers were and are still convinced that perceived stress is linked to physical consequences. However, more recently, there is increasing evidence that there is a disassociation between perceived stress and the physiological stress response. Covariance is poor or missing between physiological and psychological variables (Engert et al., 2004; Hellhammer & Hellhammer, 2008). To resolve this problem, the Division of Clinical and Theoretical Psychobiology of the University of Trier developed a diagnostic instrument for stress diseases, called *Neuropattern*. With a focus on the interfaces between the brain and the other bodily organs, endophenotypes are defined by alterations of biological, psychological and symptomatological parameters in consequence of stress (Hellhammer & Hellhammer, 2008; Hellhammer et al., 2012).

Cancer and Breast Cancer were already observed by ancient Egyptians. Both Hippocrates and Celsus describe some of the clinical aspects (De Moulin, 1989; Dixon & Sainsbury, 1998). Cancer has a high incidence and unfortunately many people still die from it even though advances have been made in prevention and treatment. The adverse and long-lasting side effects of the treatments are well-known and affect most cancer patients. Many studies examine the psychological consequences of cancer, especially breast cancer, and its treatments. The belief that cancer might be related to stress is as old as the history of medicine. It was linked to melancholia, and over the years the concept of a "cancer-personality" (type C personality) was developed. Nowadays, these theories have been set aside as most of the studies couldn't find a link (Schwarz, 2000). A lot of studies investigate the role of stress, mental illness and negative life events in the tumor onset. However, there are conflicting findings (Dixon and Sainsbury, 1998). Many methodological problems

complicate this research. One of the difficulties is that you can't always extrapolate studies on mice to men.

There are well established risk factors for breast cancer as for example age in general, early onset of menarche, family history, gene defects, central adiposity, etc. High levels of estrogen is another possible risk (Dixon and Sainsbury, 1998). Some of these risk factors are linked to increased sensitiveness to circulating cortisol. Cortisol is the end product of the hypothalamus-pituitary-adrenal axis, one of the two major systems activated by stress. The physiological effects of cortisol are widespread and complex (Hellhammer & Pirke, 1996; Hellhammer & Hellhammer, 2008; Tsigos & Chrousos, 2002; Miller et al., 2008/2009).

1.2. Scope of the thesis

In this thesis, I will first refer to the current knowledge about breast cancer and stress in general, pre-postnatal factors, as well as other factors and their links to cancer, especially to breast cancer. It is based on previous findings in animals and humans.

1.2.1. Objectives

Regarding the question as to whether breast cancer may be a stress-related disorder, the more precise objectives are as follows:

1) to investigate if there is a link between the initiation, prognosis and outcome of breast cancer and the effects of stress (cortisol, perceived chronic stress, etc);
2) to explore whether stress during the pre-postnatal period (early life influences, birth factors, education, etc) has an effect on cortisol and/or may worsen prognosis and/or outcome;
3) to examine if the changes caused by stress to other factors (estrogens, genes, metabolism, etc) may be linked to the initiation of breast cancer.

1.2.2. Approach

HPA axis activity in terms of cortisol levels was analyzed on the day where simulation of the treatment occurred (stressful event), the day after the simulation (comparative measure) and on the first day of treatment to monitor HPA stress reactivity, as a possible biomarker. In addition, questionnaires were used to investigate possible incidences during the pre-postnatal period, other stressful life events, and perceived daily chronic stress as hypothetical predictors of outcome and prognosis.

1.3. Outline of the thesis

Chapter one provides an introduction and a description of the objectives of the thesis. In **Chapter two,** I provide an overview of the theoretical background of breast cancer, biological stress mediators, pre-postnatal factors (early life effects, programming of HPA axis, intrauterine exposures, birth factors, maternal care, etc), and other relevant factors (gene-variants, proteins, estrogens, metabolism, nutrition, fatigue , sleep, etc.). In the second half of this chapter, the links among breast cancer, stress, pre-postnatal factors, and other factors are analyzed. Based on that knowledge, specific hypotheses were developed. **Chapter three** describes the material and methods section, including the experimental protocol. In **Chapter four,** you will find the results, and in **Chapter five** the discussion. **Chapter six** consists of the references used in this thesis.

Chapter 2

Theoretical background

2. Theoretical background

In this chapter, breast cancer, chronic stress and pre-/postnatal stress factors will briefly be described, to see whether there is a link between them and which pathways are used to develop this link.

2.1. Breast Cancer

2.1.1. General

Breast cancer is not a new disease. There are records from the Egyptians, Hippocrates and Celsus already decribing some of the clinical features (De Moulin, 1989). Most breast cancers are localized at diagnosis, and the prognosis is strongly influenced by the stage of the disease. If tumor cells haven't invaded through the basement membrane, the carcinoma is called *in situ* (is) The most common type of breast cancer is the invasive ductal carcinoma. 5 to 10% are thought to be linked to inherited changes in genes. Death rates for breast cancer are decreasing, probably due to early detection and improved treatment regimes. Most of the time it is discovered during a mammogram screening or thanks to a self-examination of the breast (Dixon et al., 1998).

2.1.1.1. Incidence

Breast cancer is the most frequently found cancer amongst women in Luxembourg. In 2011, there were 396 new cases of invasive breast cancer (Morphologic Tumour Registry in the Grand-Duchy of Luxembourg). In the United States, they estimate 295240 new cases for 2014. Women have a one in eight chance of developing breast cancer in a lifetime (American Cancer Society). Incidence is generally higher among women with higher socioeconomic status and among urban populations. It is also higher among Caucasian women in the Western world than among Asian women living in China or Japan (Trichopoulos et al., 2008).

2.1.2. Risk factors

The risk of developing breast cancer increases sharply with age. Other known risk factors include menstruation at an early age (before 12 years), older age at first birth or not having given birth, a mother or sister with breast cancer, variants of breast cancer genes (BRCA1, BRCA2, among others), post-menopausal obesity, later menopause (after 54 years), moderate or heavy alcohol consumption, dense breast tissue, not breast-feeding, and being white

(American Cancer Society, National Cancer Institute; Dixon et al., 1998). Other possible risk factors are: lack of physical exercice, size at birth, high estrogen levels, night work and tobacco (American Cancer Society; Dixon & Sainsbury, 1998). Fatigue is generally associated with a poorer prognosis (Antoni et al., 2006; Spiegel et al., 2006). More and more studies try to elucidate if there's a link between stress and/or psychosocial factors and breast cancer.

2.1.3. Carcinogenesis

It is a multi-step process, which leads to an invasive cancer. A cancer develops over decades and is linked to genetic and epigenetic defects and to defects in the defenses of the immune system. Stem cells, which seem equivalent to healthy stem cells, are found in human tumors and are probably initiated during carcinogenesis (Monier & Tubiana, 2008). There is recent evidence that carcinogenesis is driven by a small group of cells having stem cell properties (Ginestier & Wicha, 2007).

Cell division is a physiological process that occurs in almost all tissues and under many circumstances. Every day, many cell functions need to be restored by specific molecular repair mechanisms. However, if there are too many alterations, preprogrammed cell death may occur, usually in form of apoptosis. The uncontrolled cell division and often rapid proliferation of cells can lead to benign or malignant tumors (Federspiel, 1999).

The initiation of carcinogenesis is due to the alteration of genomes. Alterations in genomes can occur during apotosis, repair of deoxyribonucleic acid (DNA), genetic instability, inflammation, infection or an impaired immune system. Errors may occur during replication of DNA or during mitosis (Grimberg & Cohen, 2000; Monier & Tubiana, 2008; Lever & Sheer, 2010). Carcinogenesis associates a generalized hypomethylation with the hypermethylation of certain genes. Promotion is linked to cell proliferation which provokes clonal expansion of the altered cell. Promotors may also possess epigenetic signatures. In breast cancer, sexual hormones are involved in this process. Also involved are the growth hormone (GF) and insulin like growth factors (IGF I and IGF II). Irregularities in each level of the IGF axis are linked to cancer formation and progression (Grimberg & Cohen, 2000; Monier & Tubiana, 2008). Prolactin is able to promote cell growth and their survival in breast cancer (Antoni et al., 2006). These hormones may have an influence already during fetal life. The alteration of the gene p53 may prevent apoptosis of the cancer cells (Monier & Tubiana, 2008). It is also responsible for the uncontrollable cellular division (Dixon et al., 1998).

Mutations of the genes BRCA1 and BRCA2 increase the risk of developing breast cancer (Monier & Tubiana, 2008). Pro-inflammatory cytokines may play a role in tumorigenesis by provoking DNA damage or by inhibiting DNA repair. They can also deactivate tumor-suppressor genes, promote the survival of tumor cells, stimulate angiogenesis and weaken or destroy immune responses (Antoni et al., 2006; Thaker et al., 2007). Beta-adrenergic receptors (β-adrenergic receptors) are associated with the acceleration of tumor growth in breast cancer (Thaker et al., 2007).

Genetic alterations due to mutations and chromosome rearrangements are crucial for tumor formation as they provoke abnormal gene expression and genes with new functions develop. Nuclear matrix proteins are involved in regulating gene expression, DNA replication and repair (Lever & Sheer, 2010). Genetic instability associated with telomere dysfunction is an early event in carcinogenesis (Wu et al., 2003).

During progression, tumor cells may migrate and invade neighbouring tissues. Angiogenesis is a process where new blood vessels are formed to supply new cancer cells which are then able to migrate. Duration of carcinogenesis depends on the type of cancer, the moment of promotion and its intensity and duration (Monier & Tubiana, 2008). Interleukin-6 (IL-6) and interleukin-8 (IL-8) foster tumor growth (Yang et al., 2006).

2.1.4. Prognostic factors

The prognosis depends on tumor stage and agressiveness of the tumor. The nodal status is important as the more nodes involved, the worse the prognosis. To stage breast cancer, the Tumor size-Node-Metastasis (TNM) classification is used.

Other prognostic factors are the size of the tumor (I-IV) and the tumor grade (G) (I-III). If it's a big tumor, prognosis is worse. If the grade is high, the tumor is more agressive and prognosis is worse. Newer biological factors for the prognosis are the estrogen receptor (ER) state (0-3), the progesterone receptor (PR) state and the receptor state (0-3) of a protein, the Human Epidermal growth factor Receptor 2 (HER2-neu). If the hormonal receptors are positive, prognosis is better. Prognosis is worse if the HER-neu status is positive as the protein stands for higher aggressiveness. It is even worse if it's a triple negative. Of course the prognosis is very bad if there are already distant metastasis. The completeness of excision is another factor (Dixon et al., 1998).

2.1.5. Treatments

There are several treatments for breast cancer and choosing the correct method depends on the prognostic factors. Primary medical treatment consists of complete excsision of the tumor. Unforunately in some cases a mastectomy is the only option. Lymph nodes are also extracted to determine wether they have been invaded or not. Other treatments are called neoadjuvant therapy. Chemotherapy (CT) is administrated if lymph nodes are involved, if there are metastasis and/or if the agressiveness of the tumor is high. The side effects of the drugs are generally quite important and include nausea, vomitting, hair loss, mucositis, neutropenia, etc (Dixon et al., 1998). Serum cortisol level isn't affected by chemotherapy agents (Kailajärvi, 2000/2002). Radiotherapy is used to avoid local recurrence and is usually administrated to every woman with breast cancer (Dixon et al., 1998).

If hormonal receptors are positive, anti-hormonal treatment (HT) is prescribed. The choice of the medication depends on whether the woman is post- or pre-menopausal (Dixon et al., 1998). Most of these medications increase serum cortisol levels (Kailajärvi et al., 2000; Kailjärvi, 2002). If the receptors for HER2-neu are positive, the woman receives Herceptine, usually over a one year period (Dixon et al., 1998).

2.1.6. Psychological consequences of cancer diagnosis and treatments

Most of the patients are able to adjust to their disease after a certain time by going through several episodes of feeling uncertain, sad and anxious which are expected reactions. But some of the patients develop extreme anxiety, depressive or post-traumatic stress disorders (Burgess et al., 2005; Isermann, 2006; Mehnert & Koch, 2007; Stiefel et al., 2007). Due to the malignant disease, a patient's physical, psycholological, social and spiritual equilibrum may become fundamentally disturbed (Isermann, 2006; Stiefel et al., 2007).

Feelings of loneliness, lack of self-confidence and confidence in their body, guilt and loss of purpose and meaning to life are quite common among cancer patients (Burgess et al., 2005; Bouregba, 2008). Restrictions on the physical, functional, emotional, sexual, cognitive and social level are the consequences of a cancer diagnosis and treatments (Koopman et al., 2002; Isermann, 2006; Watzke et al., 2008).

Psychological distress often occurs after the end of treatments. Only then do they realize what has happened, and most of the time, family and friends think everything is over and that the

women are functioning in the same way as before, on every level (Burgess et al., 2005; Isermann, 2006).

2.2. Stress

2.2.1. Theoretical concepts and their evolution

2.2.1.1. The stress response : General

High levels of perceived stress are frequently associated with stronger increases of cortisol levels after awakening (Pruessner et al., 1999). Major physiological changes occur during the cortisol stress response. Energy is diverted from muscles to brain, cardiovascular tone is enhanced, immune function and reproduction are inhibited and cognition is sharpened (Pütz, 2008).

The stress system has central nervous system (CNS) components and peripheral ones. One major central component is the hypothalamus with the corticotrophin-releasing hormone (CRH) and vasopressin neurons of the paraventricular nucleus, the brain stem with the noradrenergic neurons of the locus coeruleus (LC) and other autonomic centers. The peripheral component consists of the hypothalamic-pituitary-adrenal axis (HPAA) and the peripheral autonomic nervous system with the adrenal medullae (Chrousos & Gold, 1992; Papanicolaou et al., 1998; Raison & Miller, 2003). Activation of the LC stimulates the HPA axis and enhances the role of the amygdala, which is a key structure that transforms experiences into feelings. The amygdala stimulates CRH release and brainstem autonomic centers which, in turn, increase HPA and LC activity (Gold & Chrousos, 2002). Activation of the stress system suppresses growth (Papanicolaou et al., 1998; Charmandari et al., 2003/2005), reproduction (Papanicolaou et al., 1998; Sapolsky et al., 2000) and affects thyroid function (Papanicolaou et al., 1998).

If there's an acute stressor, the HPA axis and the autonomic nervous system (ANS) are activated. The activation of the ANS can be measured as the release of epinephrine (E) and norepinephrine (NE) are increased (Hellhammer & Pirke, 1996; Sapolsky et al., 2000; Tsigos & Chrousos, 2002; Yang et al., 2006). Activation of HPAA leads to a release of CRH and arginine vasopressin (AVP) in the hypothalamus and this stimulates synthesis and secretion of adreno-corticotropic hormone (ACTH) in the pituitary gland. ACTH activates the secretion of cortisol in the adrenal glands. Adrenal glands are also stimulated indirectly by interleukin-1 (IL-1), IL-6 and tumor necrosis factor (TNF), as they are powerful stimulants of CRH and

ACTH. Cortisol has a negative feedback on the hypothalamus so that homeostasis of the body can be restored (Hellhammer & Pirke, 1996; Tsigos & Chrousos, 2002; Miller et al., 2008/2009). Cortisol can easily be measured in the saliva (Hellhammer & Pirke, 1996). If the same stressor is repeated several times, HPPA responses generally habituate, while the ANS continues to be activated every time the stressor appears (Hellhammer & Pirke, 1996).

Stress can activate inflammatory cytokines and their signaling pathways (for example nuclear factor κ B (NF κ B)) both in the periphery and the brain (Sapolsky et al., 2000; Raison & Miller, 2003; Johnson et al., 2005; Miller et al., 2009). If the stressor is repeated over a long time or doesn't disappear anymore, stress becomes chronic, and a permanent overactivity of stress response systems may promote stress related psychosomatic disease and/or immune changes due to excess of glucocorticoids and catecholamines (Sapolsky et al., 2000; Raison & Miller, 2003; Segerstrom & Miller, 2004; Charmandari et al., 2005; Chrousos & Kino, 2007).

2.2.1.1.1. Selye's concept

Hans Selye was among the first researchers interested in stress reactions. He developed his concept around 1930 and popularized the term *stress*. Everything that demands an effort to the organism is called a stressor by him, independent from its type. He differentiates between „eustress" (greek: eu = good) and „disstress" (latin: dis = bad). For him, disstress is only responsible for diseases if it's present for a long time. He thought that diseases caused by stress result from a dysfunctional reaction of the organism to a stressor. He developed a model describing the course of a stress disease called « general adaptation syndrome » (GAS). According to this scheme, there are three phases. The **alarm reaction** where the organism shows its first signs of the effect of the stressor is followed by the **adaptation stage** where the body successfully activates the appropriate response systems. If the stressor is still present after a long time or if it continuously reappears, the **exhaustion phase** sets in and then the organism is weakened and diseases may develop as the symptoms of the alarm reaction phase come back. He already noticed that, most of the time, harmful stressors are of a psychological nature (Selye, 1977). The unspecificity of this concept was later challenged by John Mason (1974), showing that the HPAA is differentially responsive to the quality of the stressor. Situations that are uncontrollable, unpredictable and threatening the integrity of the self are more likely to involve HPAA responsivity (Hellhammer & Pirke, 1996.; Gruenewald et al., 2004).

2.2.1.1.2. Chrousos' concept

George P. Chrousos describes the major biological systems activated during a reaction to stress. Chrousos reports evidence that a permanent or excessive exposure to stress may lead to diseases. He describes two different groups of stress diseases : hyperreactivity and hyporeactivity of the stress systems.

Two systems are involved in the initiation and the maintaining of a stress reaction. The first one is the CRH-system. The second one involves the NE neurones wich primarily origin from the LC. Both neuron types innervate the many brain areas. They also communicate with the peripheral systems via the autonomic nervous system (sympathetic pathways mostly) or by releasing corticoids from the adrenals. During a controllable stress reaction, there's an activation of the central nervous system to prepare the body for an appropriate behavior (fight or flight).

The CRH-system is best characterized in the paraventricular nucleus of the hypothalamus. If CRH is released, it activates the pituitary-adrenal axis and the sympathetic nervous system (SNS). This leads to increases of glucose, heart rate and blood pressure. It also enhances arousal, attention and perception whilst some other systems are inhibited (reproduction, growth, food intake).

The LC-NE sympathetic system is located in the brain stem. The activation of this system leads to enhanced arousal, vigilance and anxiety due to release of NE. The NE system can be activated by the CRH-system and vice versa. They have positive feedback on one another. There are also autoregulatory negative feedback loops within the two systems.

One important brain region which is activated during a stress reaction is the amygdala hippocampal system. It is important for the emotional analysis of a stressor. If you think something is uncontrollable and unpredictable, you are far more stressed and this negative rating may re-activiate the stress system. The hippocampus is able to inhibit the CRH-and the NE system. Another important point is that an activation of the stress system inhibits the reaction of the immune system as glucocorticoids have immunosuppressive effects. Some products of the immune system, as for example IL-1, IL-6 and TNF, have a stimulatory effect on HPA axis by enhancing CRH secretion (Chrousos & Gold,1992; Gold & Chrousos, 2002).

2.2.1.1.3. Dallman's concept

Mary Dallmann contributed to the stress model by demonstrating that cortisol has a different influence on the central nervous system depending on whether it is acute stress (some minutes to hours after the stressor) or chronic stress (more than 24 hours). If it is an ongoing stress, cortisol is activating the central systems and therefore also the HPAA and may additionally activate CRH neurons in the amygdala. During chronic stress, the elevated glucocorticoid signal has a positive effect on the brain and further activation of the chronic stress response system is promoted. Persistent high glucocorticoid concentrations may cause hypertension and a disturbed immune system as well as an impaired memory and hightened anxiety. CRF activity seems to be necessary for the engagement of the chronic stress response. CRF is synthesized and secreted by the amygdala after stimulation by glucocorticoids. HPA axis may adapt to chronic stressors that aren't life-threatening. Nevertheless, if the stressors are life-threatening, cortisol response is either consistent or increases.

The stress induced secretion of glucocorticoids increase motivation for food. But also insulin secretion is increased which promotes food intake and obesity (Dallman et al., 2004/2007; Dallman & Hellhammer, 2011).

2.2.1.1.4. Hypercortisolism

Some stress-related disorders are caused or maintained by HPAA hyperactivity. Hypercortisolism may have three causes : genetic, pre-postnatal epigenetic programming, or chronic stress exposure later in life (Tsigos & Chrousos, 2002; Pütz, 2008).

Activity of CRH in the paraventricular nucleus of the hypothalamus is followed by activation of the pituitary gland and the secretion of ACTH, which stimulates the adrenal gland and cortisol is released. Cortisol has a negative feedback action on the hypothalamus in general. If hypercortisolism exists, these activities may be disturbed at several levels (defaults in feedback, hypersensitivity). The paraventricular nucleus is in synergy with adrenergic systems in both the central and the peripheral nervous system. These nerve fibers innervate many brain areas, the adrenal medulla and several organs, where E and NE are released. Cortisol stimulates activities of CRH in the central amygdala. This activation leads to several physical symptoms such as shortness of breath, urinary urge (Tsigos & Chrousos, 2002; Pütz, 2008).

Nowadays, a lot of mental and/or somatic disorders are caused or maintained by chronic HPAA hyperactivity (diabetes type 2, obesity, depression, hypertension amongst others.) (Gold & Chrousos, 2002; Raison & Miller, 2003; Charmandari et al., 2005).

Hypercortisolism can be caused at the central level by CRF hypersecretion (CRF hyperactivity or CRF hyperreactivity) or at the peripherical level by increased adrenal glucocorticoid secretion (Pütz, 2008). Symptoms caused by CRF disregulation are for example loss of appetite, inhibition of reproductive functioning, increased vigilance, sleep disorders, anxiety, depression, irritable bowel syndrome, etc (Gold & Chrousos, 2002). Hypersecretion of cortisol has consequences on growth, reproduction, mood, cardiovascular system, metabolism, thyroid system, immune system and memory (Charmandari et al, 2003; Wolf, 2003).

2.2.1.1.5. Hypocortisolism

20-25% of people with chronic stress disorders are characterized by low cortisol levels. Most of the time, hypocortisolism is accompanied by a lower threshold for stress sensitivity, pain, and fatigue (Heim et al., 2000; Raison & Miller, 2003; Fries et al., 2005; Fries, 2008). There is a reduced activity of the HPA axis. Several mechanisms may be implied: reduced biosynthesis or depletion of the respective hormone on the levels of the HPAA, a reduction in the numbers of receptors of those hormones, increased feedback sensitivity of the HPA axis, or morphological changes (Heim et al., 2000; Heim & Nemeroff, 2001; Raison & Miller, 2003).

A hypoactive HPA axis can be found in burnout, chronic-fatigue syndrome, fibromyalgia, autoimmune diseases, irritable bowel syndrome, atypical depression, rheumatoid arthritis, post-traumatic stress disorder, etc (Gold & Chrousos, 2002; Raison & Miller, 2003; Fries et al., 2005; Fries, 2008).

Hypocortisolism may be caused by CRF and ACTH hypoactivity and hyporeactivity (central level) or cortisol hypoactivity (peripheral level) (Fries, 2008). Symptoms of CRF dysfunction may be hypersomnia, hypoarousal, hyperphagia, loss of energy (Gold & Chrousos, 2002; Fries, 2008). Cortisol hypoactivity causes some symptoms of sickness behavior, probably by promoting increased pro-inflammatory cytokines (Franchimont et al., 2002).

2.2.2. Cortisol

Cortisol is the end product of the HPA-axis, a biological interface between the CNS and peripheral systems. It reflects the activity of the CNS, particularly when a subject attempts to

adapt to situations, which are experienced as novel, unpredictable, uncontrollable, and of personal relevance (Mason, 1968; Hellhammer & Pirke, 1996; Tsigos & Chrousos, 2002; Miller et al., 2009). Conseqently, under social stress, cortisol responses are higher than with other stressors (Dickerson & Kemeny, 2004; Ma et al., 2007). Cortisol has been reported to be elevated in patients with breast cancer prior to and following treatment (Raghavendra et al., 2009).

2.2.2.1. Biosynthesis

Cortisol is a glucocorticoid which is produced by the adrenal cortex, a part of the adrenal gland. It is synthesized from cholesterol by several enzymes in the adrenal glands. The synthesis of cortisol is directly stimulated by ACTH, and indirectly by CRH. The secretion of cortisol and its presence in the blood and saliva undergoes diurnal variation with a maximal peak in the morning (Hellhammer & Pirke, 1996; Tsigos & Chrousos, 2002).

2.2.2.2. Physiological effects

Cortisol is necessary for surviving. If the adrenal glands don't produce enough cortisol, it has to be substituted. Cortisol has a broad spectrum of effects. It influences many functions of the CNS (Raison & Miller, 2003; Chrousos & Kino, 2007). Cortisol affects the metabolism (Chrousos, 2000; Charmandari et al., 2005), gluconeogenesis, immune system, mineral levels, bone metabolism (Chrousos, 2000; Franchimont et al., 2002). In situations of acute and chronic stress, cortisol influences memory (Chrousos, 2000; Sapolsky et al., 2000; Wolf, 2003). If the exposure to glucocorticoids is prolonged, neuronal atrophy is a consequence and memory is disrupted (Sapolsky et al., 2000). It counteracts, for example, insulin by increasing gluconeogenesis and promotes breakdown of lipids and proteins. Cortisol also acts as an anti-diuretic hormone. Most serum cortisol is bound to proteins and only free cortisol is available to most receptors (Raison & Miller, 2003).

2.2.2.2.1. Cortisol, inflammation and the immune system

Miller et al (2009, p17-18) explain stress-induced activation of the inflammatory response as follows: "Psychosocial stressors activate central nervous system stress circuitry, including CRH and ultimately sympathetic nervous system outflow pathways via the locus coeruleus. Acting through alpha and beta adrenergic receptors, catecholamines released from sympathetic nerve endings can increase NF-κB DNA binding in relevant immune cell types, including macrophages, resulting in the release of inflammatory mediators that promote

inflammation. Proinflammatory cytokines, in turn, can access the brain, induce inflammatory signaling pathways including NF-κB, and ultimately contribute to altered monoamine metabolism, increased excitotoxicity, and decreased production of relevant trophic factors. Cytokine-induced activation of CRH and the hypothalamic-pituitary-adrenal axis, in turn, leads to the release of cortisol, which along with efferent parasympathetic nervous system pathways (e.g., the vagus nerve) serve to inhibit NF-κB activation and decrease the inflammatory response. In the context of chronic stress and the influence of cytokines on glucocorticoid receptor function, activation of inflammatory pathways may become less sensitive to the inhibitory effects of cortisol, and the relative balance between the proinflammatory and anti-inflammatory actions of the sympathetic and parasympathetic nervous systems, respectively, may play an increasingly important role in the neural regulation of inflammation."

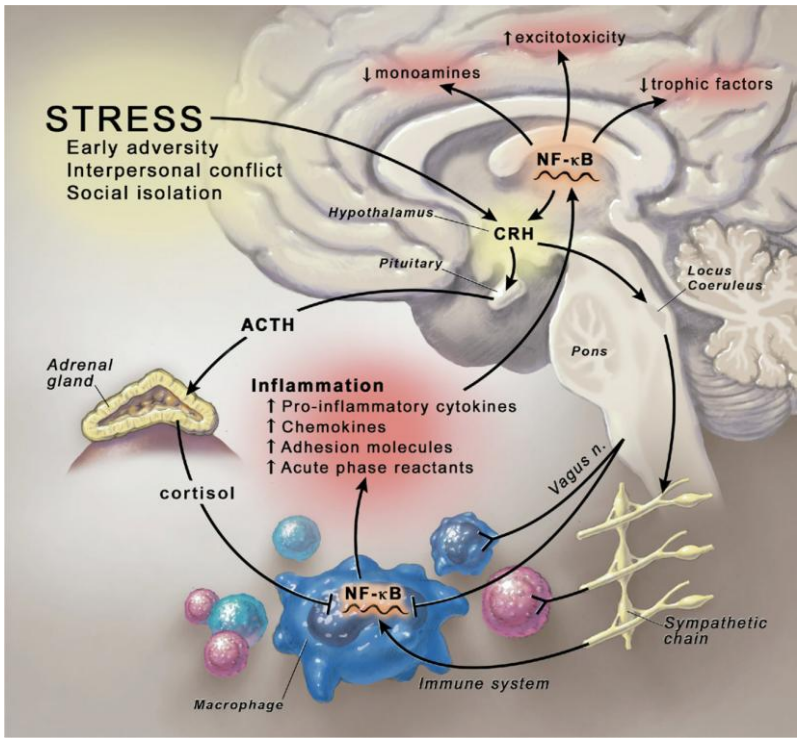

Fig 1: Miller et al., 2009. Stress induced activation of the inflammatory response p17

The immune system communicates bidirectionally with the CNS and the endocrine system and these interactions impact on health (Raison & Miller, 2003; Glaser & Kiecolt-Glaser, 2005; Godbout & Glaser, 2006). Immune dysfunction due to stress results in health consequences for example slowing wound healing, reactivating latent viruses, etc (Sapolsky et al., 2000 ; Kiecolt-Glaser et al., 2002 ; Raison & Miller, 2003; Godbout & Glaser, 2006).

Glucocorticoids induce death of the cells that provoke the inflammation and they protect the other cells by sending apoptotic signals (Amsterdam et al., 2002; Amsterdam & Sasson, 2002).

Cytokines communicate information about immune activity to the brain and the neuroendocrine system (Musselmann et al., 2001). During an inflammatory response, TNF-α is secreted, then IL-1 and IL-6. IL-6 inhibits TNF-α and IL-1 in turn and activates the HPA-axis. Cortisol then has a negative feedback on IL-6. The ANS interacts with the immune system as it innervates many necessary organs (Nussdorfer & Mazzocchi, 1998; Papanicolaou et al., 1998; Musselman et al., 2001; Godbout & Glaser, 2006). Stress elevates levels of IL-6 and its secretion is stimulated through β-adrenergic receptors (Papanicolaou et al., 1998; Johnson et al., 2005; Godbout & Glaser, 2006). Psychological and immune stressors increase sickness behavior by up-regulating IL-6 (Musselman et al., 2001; Dantzer et al., 2007; Brydon et al., 2009). IL-6 is elevated during tissue injury and its clinical manifestations are fever, cachexia, fatigue, thrombocytosis. It is also increased during estrogen-deficiency and its receptor is upregulated (Papanicolaou et al., 1998). High serum levels of IL-6 have been related to increased risks for several diseases and some cancers (Kiecolt-Glaser et al., 2003; Godbout & Glaser, 2006; Miller et al., 2009). NF- κB is a cytoplastic protein which can be found in most cells. It responds to signals from TNF-α, Il-1β and regulates them as well as IL-6 (Sapolsky et al., 2000).

Elevated cortisol levels can weaken the activity of the immune system. It prevents proliferation of thymus cells (T-cells), decreases antibody productions and lymphocyte proliferative responses and inhibits natural killer (NK) cells activation (Papanicolaou et al., 1998; Sapolsky et al., 2000; Amsterdam et al., 2002; Raison & Miller, 2003; Elenkov, 2004; Fries, 2008). Stress dysregulates NK cell function (Kiecolt-Glaser et al., 2002). Cortisol hypersecretion suppresses production of IL-1, Il-6 and TNF, implicated in the early immune response to stress, and enhances secretion of IL-4 or IL-10 by macrophages and T-helper-2 cells (Papanicolaou et al., 1998; Elenkov, 2004; Fries, 2008). Its action on the adaptive immune response is to suppress cellular imunity and to promote humoral immunity (Franchimont et al., 2002; Raison & Miller, 2003). Chronic activation of HPAA and cortisol excess inhibits T-helper-1 directed cellular immunity (Gold & Chrousos, 2002; Koopman et al., 2004).

2.2.2.3. Assessment of cortisol

Cortisol can be assessed in blood serum and in saliva. For the diagnosis of stress diseases a noninvasive method of measuring cortisol levels is often preferred. The cortisol level in saliva represents the level of active free biological cortisol in the blood. Correlation coefficients between cortisol levels in blood serum and saliva vary, depending on the study, between r = .71 - .96. Saliva free cortisol levels are always a little bit lower than those in the blood as some of the saliva cortisol is becoming cortisone. Cortisol production is ruled by a circadian diurnal rhythm. The peak is reached within an hour after awakening and the nadir is reached in the first half of the night. After the morning peak, cortisol levels descend continuously during the rest of the day. Ideally, diurnal variations of cortisol levels should be assessed with different measures during the day to analyze activity of the HPAA (Kirschbaum & Hellhammer, 1989).

The cortisol awakening response (CAR) permits an estimation of the activity of the HPA axis and shows subtle changes in HPAA regulation. The CAR is measured during first hour after awakening (Pruessner et al., 1999; Clow et al., 2004; Kudielka et al., 2005). This marker is quite consistent and it shows intraindividual stability across time. There's an association between the CAR and psychosocial variables, stress and health (Clow et al., 2004).

2.2.3. Stress and perception of stress : missing covariance

One may expect that stress and perception of stress are associated with the same physiological changes and physical symptoms. In other words, subjects high in perceived stress may also have a higher activation of all stress systems (activation of the HPAA, activation of the ANS and activation of other stress-related systems) than those who don't feel stressed. However, lots of researchers demonstrate that this is not the case. Rather, there is a dissociation between the psychological (perception of stress) and the peripheral physiological stress response (Engert et al., 2004; Hellhammer & Hellhammer, 2008). A study demonstrates that endocrine and cardiovascular stress reactions don't coincide with psychological parameters (Schommer et al., 2003). Diagnostic of stress related diseases should include psychological and biological parameters as well as physical symptoms (Engert et al., 2004).

2.2.3.1. Neuropattern

2.2.3.1.1. General

In the past decade, the division of clinical and theoretical psychobiology of the University of Trier developed a diagnostic instrument for stress diseases called *Neuropattern*. It considers

both the missing covariance and the complexity and heterogeneity of the etiopathogenetic mechanism. Each neuropattern is defined by diverse biological, psychological and symptomatological parameters. Genetic and pre-postnatal factors are also taken into account (Engert et al., 2004). Neuropattern focuses on the interfaces between the body and the brain under stressful conditions (Hellhammer & Hellhammer, 2008; Hellhammer et al., 2012). A neuropattern is an endophenotype which is characterized by the activity or reactivity status of a given interface. Thirteen patterns can be assessed and termed (Hellhammer & Hellhammer, 2008).

A kit of questionnaires and devices for physiological measures (saliva collection: cortisol; heart rate variability) was developed for clinical application (see chapters 3.4.3. and 3.5. for more information). The data of all these measures are analyzed and assigned to the respective neuropattern.

2.2.3.1.2. The three systems of interfaces and their 13 patterns

There are three major stress response systems: the glandotropic (neuroendocrine functions), the ergotropic and the trophotropic system. Their functions are affected by other systems and they differ in their adaptation to stress (Hellhammer, 2008).

The glandotropic system involves the activity of the HPAA in response to a stressor. Energy resources are mobilized by elevating glucose levels, inducing gluconeogenesis, preventing an overshooting of the immune response, increasing blood pressure and facilitating the effectiveness of catecholamines. Cortisol level reaches a peak at about 30 minutes after the onset of the stressor. The HPAA consists of different parts and its function and the measures of cortisol can therefore be modified at the level of the hypothalamus, the pituitary and the adrenal level, with respect to receptor status (Hellhammer, 2008).

The patterns of this system are: CRF hyperactivity, CRF hyperreactivity, CRF hypoactivity, cortisol hyperactivity, cortisol hypoactivity and GR resistance.

Ergotropic and tropotropic systems describe the roles of the noradrenergic-sympathetic and serotonergic-parasympathetic systems (Hellhammer, 2008).

During an ergotropic state, the organism is actively adapting to a demand (stressor). Genetic determinants and pre-postnatal programming have an effect on the noradrenergic system. Ergotropic determinants can be found in metabolic, cardiovascular and reproductive disorders and fear and anxiety disorders (Klingmann & Hellhammer, 2008). Its patterns are: NE hyperactivity, NE hyperreactivity, NE hypoactivity, SNS hyperactivity and SNS hyperreactivity.

The trophotropic sytem is the one of regeneration, recovery and reconstitution. A typical trophotropic stress reaction is a passive resonse, such as learned helplessness, conservation-withdrawal behavior, or reactive depression. Trophotropic symptoms and diseases include bradycardia, hypotonia, gastrointestinal complaints, eating disorders, premenstrual syndrome, cognitive disorders, asthma, etc (Hellhammer & Klingmann, 2008). The different patterns are: serotonin hyperreactivity and serotonin hypoactivity.

2.2.4. Psychosocial factors

Stress may induce genomic instability (Forlenza & Baum, 2000). Stressors and depression are linked to decreased T-cell and natural-killer-cell activity that affect immune surveillance of tumors and accumulate somatic mutations and genomic instability (Reiche et al., 2004/2005). Chronic and perceived stress have been reported to be linked to oxidative stress, shortened telomeres and lessened telomerase activity (Epel et al., 2004/2010; McGregor & Antoni, 2009).

Stress hormones, such as E, NE and cortisol may facilitate permanent DNA damage which may also promote cell transformation and tumorigenesis (Flint et al., 2007; Gidron & Ronson, 2008). It was also found that stress hormones like cortisol, NE and E suppress effects of paclitaxel (a chemotherapeutic agent) by modulating induced apoptosis and multiple cell signaling pathways (Flint et al., 2009).

Production and release of IL-6 and other proinflammatory cytokines can be stimulated by depression and other stressful experiences (Musselman et al., 2001; Kiecolt-Glaser et al., 2003; Jehn et al., 2006; Lutgendorf et al., 2008). Cancer patients with major depression have a high IL-6 concentration whereas cancer patients without major depression have low IL-6 levels (Musselman et al., 2001; Jehn et al., 2006; Lutgendorf et al., 2008). Women undergoing biopsy show increased perceived stress, anxiety, mood disturbance, reduced NK cell activity and cytokine dysregulation, regardless of the result being positive or negative (Witek-Janusek et al., 2007). Sleep deprivation and dysregulated sleep in depressed patients are associated with increased IL-6 and NF-κB activation (Miller et al., 2008). Women with a family history of breast cancer have higher cortisol levels during stressful periods of the day (at work) and increased E excretion (Dettenborn et al., 2004).

In times of increased stress, levels of NE increase in the blood. Vascular endothelial growthfactor (VEGF), IL-6 and IL-8 increase in response to NE. In patients with ovarian

cancer, women with more social support have lower serum levels of VEGF (Lutgendorf et al, 2002/2008; McGregor & Antoni, 2009). Lower salivary cortisol levels are associated with social support among patients with metastatic breast cancer (Abercrombie et al., 2004) and among healthy people, social support contributes to alterations in HPA functioning (Gruenewald et al., 2004; Antoni et al., 2006; McEwen, 2007). Social support is also associated with lower IL-6 levels among patients with ovarian cancer (Costanzo et al., 2005; Antoni et al., 2006). Social support is associated with better NK cell activity in breast cancer patients (Kiecolt-Glaser et al., 2002). Marital distress has been found not only to be associated with a poorer psychological outcome for breast cancer survivors (higher levels of stress) but also with a slower recovery with more health consequences (Yang & Schuler, 2008). Women with an insecure relationship show greater stress in reaction to relationship conflict (Powers et al.; 2006). Some parameters as for example social support, marriage, minimizing and denial are associated with better breast cancer prognosis (Falagas et al., 2007).

Women with metastatic breast cancer often have aberrant (flattened) diurnal cortisol rhythms (Spiegel & Giese-Davis, 2003; Abercrombie et al., 2004; Giese-Davis et al., 2004/2006; McGregor & Antoni, 2009). It's possible that the HPA is hyporesponsive for women with metastatic breast cancer (Abercrombie et al., 2004). Depressed women with metastatic breast cancer seem to be unable to mount a cortisol response to acute stress, which may reflect the effects of chronic stress and compound the stress by limiting glucose mobilization necessary for response. Depression has a strong effect on vagal attenuation in metastatic breast cancer survivors (Giese-Davis et al., 2006). Expressing negative affects (fear, anger, sadness) in a group therapy setting is associated with less aberrant cortisol slopes. Expressing positive affects for a long duration is linked to a lower mean level of cortisol (Spiegel & Giese-Davis, 2003; Giese-Davis et al., 2006; McGregor & Antoni, 2009). Flatter daytime cortisol slopes are due to elevations later in the day. It seems to be related to a failure of feedback inhibition rather than to an excessive HPA responsiveness to stimulation (Spiegel et al., 2006). Flatter diurnal cortisol slopes are associated with greater social isolation and increased mortality (Sephton et al., 2000; Filipski et al., 2002; Spiegel & Giese-Davis, 2003; Spiegel et al., 2006). The predictive value of alterations in these rhythms predicting poor outcome is independent from clinical factors (Filipski et al., 2002). Dysregulated rhythms may be involved in the body's inability to resist the growth of tumor cells (Koopman et al., 2004).

Psychological interventions reduce perceived stress and cortisol levels and improve quality of life and for example sleep problems (Cruess et al., 2000; Classen et al., 2001; Spiegel & Giese-Davis, 2003; Carlson et al., 2004/2007; Witek-Janusek et al., 2008; Raghavendra et al.,

2009; Mc Gregor &Antoni, 2009). A study found that psychological intervention (stress reduction, problem solving) improves survival for breast cancer patients. T-cell blastogenesis remains stable or increases among breast cancer patients with intervention (Andersen et al., 2004/2008). Cellular immune function is improved (McGregor et al., 2004/2009). NK cell activity is increased as well as cytokine levels (Witek-Janusek et al., 2008).

2.3. Pre-/postnatal stress factors

Pre-/postnatal factors are known to have adverse effects on health later in adult life. More and more frequently there are studies and discussions about epigenetics and whether pre-/postnatal stress factors are involved (Yehuda et al., 2005/2007; Meaney at al., 2007; Drake et al., 2007; Nijland et al., 2008).

Early stress during a period of neuronal plasticity may result in alterations of neurobiological functions, which may affect adaptability to future stress (Luecken, 1998/2000; Kaufman et al., 2000; Meaney, 2001; Meaney et al., 2007; Seckl & Holmes, 2007). Factors from the environment may influence early in life structural and functional development of people. Variations in maternal glucocorticoids during pregnancy have an impact on neuroendocrine programming of the offspring by affecting growth, metabolism, sexual maturation, stress response and immune system in later life (Seckl, 2004; De Vries et al., 2007; Viltart & Vanbesien-Mailliot, 2007). Exaggerated exposure to glucocorticoids alters adult behaviour. This may be due, in part, to alterations of the amygdalae. Prenatal glucocorticoids exposure increases CRH levels in the central nucleus of the amygdala which has an effect on fear and anxiety (Seckl, 2004).

2.3.1. Programming of HPA axis

Early stress can have an adverse effect on the development of the HPA axis as it alters structures and functions of brain regions (Kaufman et al., 2000; Raison & Miller, 2003; Meaney et al., 2007; Seckl & Holmes, 2007; Silveira et al., 2007; Philips, 2007; Merlot et al., 2008; Quirin et al., 2008), and it may also permanently change metabolism due to “endocrine disruptor compounds” (for example estrogens) and reproduction (Guzmán & Zambrano, 2007). Excessive fetal exposure to glucocorticoids due to stress reduces fetal growth. Inhibited fetal growth increases risk for the development of chronic diseases in adult life.

Reduced birth weight is for example related to cardiovascular risk factors and behavioural abnormities and depression and as an adult, they have higher cortisol levels (Barker, 1995; Kiecolt-Glaser et al., 2002; Raison & Miller, 2003; Kapoor et al., 2006/2008; Meaney at al., 2007; Kajantie et al., 2007; Seckl &Holmes, 2007; Philips, 2007; Silveira et al., 2007). Dampened HPAA activity is associated with posttraumatic stress disorders (PTSD), fatigue, chronic pain and atypical depression (Luecken, 2000/2004; Gold & Chrousos, 2002; Raison & Miller, 2003; Kajantie, 2006/2008). These effects persist through generations and epigenetic effects have been discussed to be involved in this transgenerational transmission (Yehuda et al., 2005/2007; Meaney at al., 2007; Drake et al., 2007; Nijland et al., 2008).

2.3.2. Umbilical cord blood and intrauterine factors or exposures

Obesity during pregnancy leads to exaggerated inflammation in the placenta. Levels of pro-inflammatory cytokines like IL-1, TNF-α and IL-6 are elevated. This may have consequences for the programming of obesity in the children (Challier et al., 2008). Leptin concentrations are associated with body weight and adiposity at birth (Seckl, 2004). Elevated concentrations of insulin during critical periods of early development can program the development of obesity and diabetes (Plagemann, 2008).

Estradiol and progesterone levels increase during pregnancy. Progesterone levels are associated with gestational weight gain (Lof et al., 2009). Intrauterine exposure to estrogens probably increases the number of mammary gland stem cells and therefore automatically also the risk for malignant transformation (Lagiou, 2006). In mice, chronic prepartum mild stress exposure increases estradiol and corticosterone levels during pregnancy (Misdrahi et al., 2005).

2.3.3. Fetal growth, birth size and neonatal growth

Higher birth size is associated with higher levels of pregnancy hormones such as estrogens and IGF-1. This may favour development of a higher number of stem cells with genomic instability (Lagiou & Trichopolous, 2008). Lower birth size is associated with earlier age at menarche (Ghirri et al., 2001 ; Ibáñez & de Zegher, 2006 ; Opdahl et al., 2008).

Cortisol is implicated in retarded fetal growth and glucocorticoids have effects on tissue development. GR are expressed in most fetal tissues from early pregnancy (Seckl, 2004). Reduced fetal growth is linked to impaired ovarian development, reduced size of uterus and ovaries and anovulation in adolescent girls. In girls born small for gestational age, puberty

and menarche begin earlier and this is probably due to insulin resistance (Ibáñez & de Zegher, 2006).

2.3.4. Birth weight

Adults which had a low birth weight have higher plasma cortisol levels throughout life (Phillips et al., 2000; Seckl & Holmes, 2007; de Vries et al., 2007). Low birth weight is associated with altered responses to stress, changes in plasma lipid profiles, specific patterns of hormone secretion and greater incidence of depression. Persons with low birth weight and exposed to glucocorticoids during the fetal period have an increased risk for chronic diseases like diabetes, hypertension, anxiety, depression (Silveira et al., 2007). People with low birth weight have lower peak cortisol concentrations during psychosocial stress (Kajantie et al., 2006). Low birth weight is associated with cardiovascular and metabolic diseases in adulthood (Repetti et al., 2002; Luecken et al., 2004; Seckl, 2004; de Kloet et al., 2005; Mesquita et al., 2009). It induces earlier menarche in girls as they present higher androgen and higher follicle-stimulating hormone levels (Ibáñez & de Zegher, 2006).
An overweight adult who had a low birth weight tends to have higher estradiol levels throughout menstrual cycles (Finstad et al., 2009).

Women with a high ponderal index (Weight/Height) (3) at birth have higher levels of estrogens (E2) in menstrual cycles than those with a low ponderal index at birth (Jasienska et al., 2006). Birth weight increases with high estrogen levels in utero (Lagiou, 2006; Troisi et al., 2007; Park et al., 2008) or IGF-1 (Park et al., 2008). Larger birth weight may be due to elevated tissue stem cell numbers as larger organs are formed (Strohsnitter et al., 2008) and it is associated with leptin concentrations in fetal cord blood (Seckl, 2004).

2.3.5. Maternal behaviour and care during pregnancy

Maternal nutrition and behaviour affect the predisposition of the children to obesity, metabolic syndrome and type II diabetes by affecting the metabolism (Viljoen, 2005; Junien & Nathanielsz, 2007). Alcohol exposure during pregnancy alters neuroendocrine and behavioural functions of the offspring by affecting the metabolism and the physiological as well as the endocrine functions of the offspring (Willoughby et al., 2008; Weinberg et al., 2008; Sarkar et al., 2008; Schlotz & Phillips, 2009).
If the mother is exposed to nicotine during pregnancy, it affects the metabolism and the aging of the lungs in the children (Viljoen, 2005; Maritz, 2008). It has also an impact on fertility

(Rogers, 2009). The risk of delivering a baby too small for gestational age is increased and is even higher when combined with alcohol intake during pregnancy (Aliyu et al., 2009). Smoking during pregnancy can impair neurodevelopment characterized by low birth weight, minor effects on cognitive functions and behavioural abnormalities (Viljoen, 2005; Jauniaux & Burton, 2007; Shea & Steiner, 2008; Winzer-Serhan, 2008). Smoking has an impact on the fetal brain (Viljoen, 2005; Jauniaux & Burton, 2007) and is linked to chromosomal instability which is linked to an increased cancer risk (Jauniaux & Burton, 2007).

Psychosocial stress during pregnancy has the same comparable adverse effects as smoking, alcohol intake, drugs, nutrition through fetal overexposure to stress hormones such as glucocorticoids (Huizink et al., 2008; Sarkar et al., 2008; Schlotz & Phillips, 2009). Offspring of mothers with PTSD have lower cortisol levels (Yehuda et al., 2007). Prenatal PTSD is associated with decrements in head circumference and longer gestational duration (Engel et al., 2005). Maternal stress hormones stimulate the organism of the fetus in quite the same manner than they do with the maternal organism (Krens & Krens, 2005). Exposure to stress hormones such as glucocorticoids during fetal development may lead to cardiac, metabolic, auto-immune, neurological and psychiatric disorders with differences in outcome depending on the exact time of exposure (Repetti et al., 2002; Luecken et al., 2004; Seckl, 2004; de Kloet et al., 2005; Mesquita et al., 2009; Wadhwa et al., 2009). Maternal or fetal stressors alter the development of specific brain structures (Seckl, 2004; Yehuda et al., 2005; Wadhwa et al., 2009).

2.3.6. Childhood trauma and early life influences

The loss of the mother is related to altered cardiovascular and neurohormonal outcomes in adults if the quality of the relationship with the surviving parent is poor (Luecken, 1998; Repetti et al., 2002). Adverse early life influences may implicate structural changes in the hippocampus (de Kloet et al., 2005; Kwiatkowski et al., 2005; Buss et al., 2007; McEwen, 2007) and amygdala, brain regions that regulate cognitions and emotions (McEwen, 2003; de Kloet et al., 2005; Buss et al., 2007), as well as persistent hyperactivity of CRH systems (Heim & Nemeroff, 2001; Raison & Miller, 2003; Pütz, 2008). Adverse conditions during early life, such as lessened maternal care, maternal separation, etc are a risk factor for stress-related disorders (de Kloet et al., 2005; Kaplan et al., 2008). Exposure to stress hormones such as glucocorticoids during early postnatal development may lead to cardiac, metabolic, auto-immune, neurological and psychiatric disorders (Repetti et al., 2002; Luecken et al., 2004; Seckl, 2004; de Kloet et al., 2005; Mesquita et al., 2009). Children from parents with a

PTSD have lower cortisol levels and have a higher risk to develop also a PTSD. Alterations or changes in glucocorticoid receptors very early in development may be caused by environmental events (Yehuda et al., 2005/2007). Children with posttraumatic stress disorder show hippocampal reduction (Carrion et al., 2007). Nutrition in the postnatal period can induce metabolic programming effects which may promote obesity (Srinivasan & Patel, 2008).

Early life and even adolescence are critical times for the maturation of hypothalamic pituitary ovarian axis which regulates the production of estrogens (Ruder et al., 2008).

2.3.7. Maternal behaviour and care during childhood

Postnatal adverse conditions during early childhood such as lack of quality caretaking by the family, especially by the mother, abuse, violence or separation from a parent are related to altered cardiovascular and neurohormonal outcomes in adulthood through alteration of the HPAA (Luecken, 1998; Heim & Nemeroff, 2001; Repetti et al., 2002; Buss et al., 2007; Pütz, 2008; Quirin et al., 2008). Higher levels of attachment anxiety are associated with higher cortisol responses to stressors based on uncontrollable and unpredictable stimuli and higher awakening cortisol levels are associated with lower levels of attachment anxiety (Quirin et al., 2008). An unstable relationship between parents and child may lead to behavioural disorders and to somatic diseases later in adult life (McEwen, 2003; Kaplan et al., 2008). Variations in maternal care alter gene expressions that regulate behavioural and endocrine responses to stress as well as the development of the hippocampus (Meaney, 2001; Seckl, 2004; Champagne et al., 2009; Wadhwa et al., 2009). Prenatal and postnatal experiences are of significance for the development of the hippocampus, HPA functioning and cognitive performance (Seckl, 2004; Buss et al., 2007; Wadhwa et al., 2009). If there has been adverse care by neglect for example, telomeres become shorter and this influences cellular aging (Tyrka et al., 2010).

In rats, maternal care can alter the hippocampal GR expression in the offspring, which changes the HPA axis and the response to stress (Meaney, 2001; Weaver, 2007; Champagne et al., 2009). Offspring of mothers with high maternal care (increased pup licking and grooming: HG) show differences in DNA methylation of the GR gene compared to those with low maternal care (Seckl, 2004; Weaver et al., 2007; Champagne et al., 2009) and have more modest responses to stress and enhanced cognitive abilities (Liu et al., 2000; Champagne et al., 2009). Maternal care has an epigenetic effect as it also influences maternal behaviour of the offspring which seems to be related to the oxytocin (OT) receptor gene (Meaney, 2001;

Champagne et al., 2001). OT receptor binding is increased in the medial preoptic area (MPOA) of the hypothalamus in females with high maternal care. Differences in OT receptor binding are estrogen dependant and seem to involve estrogen receptor α (ERα) (Champagne et al.2003/2006; Champagne & Curley, 2008). In human adults, OT is associated with bonding to ones own parents and may play a role in bonding-related cognitions across the life span (Gordon et al., 2008).

2.4. Other factors

Other biological factors that are known to have adverse effects on health later in life may be involved in epigenetics and are elucidated in several studies and discussions (Hilakivi-Clarke, 2000; Noruzinia et al., 2005; Champagne & Curley, 2008; Dumont et al., 2008; Gicquel et al., 2008; Sunami et al., 2008; Lever & Sheer, 2010).

2.4.1. Genes and proteins

Genetic alterations, such as mutations and chromosome rearrangements, give rise to abnormal gene expressions and to genes with novel functions. These are necessary for malignant transformation (Lever & Sheer, 2010). Signals from the microenvironment are able to induce gene expression changes (Dumont et al., 2008). DNA methylation is an epigenetic modification that may have effects on transcription and is linked to long-term gene silencing (Champagne & Curley, 2008; Dumont et al., 2008). Recent observations suggest that epigenetic changes in regulatory genes play a role in fetal programming and may lead to negative long-term effects for health in later life (Gicquel et al., 2008). Hypermethylation results in gene silencing and is an epigenetic change (Sunami et al., 2008; Champagne & Curley, 2008).

BRCA1 belongs to the class of tumor suppressor genes. Its protein is involved in DNA damage repair. BRCA2 and Tp53 belong to the same group of genes and their proteins have the same activities (Hilakivi-Clarke, 2000; Miyoshi et al., 2008). Tp53 is a tumor suppressor and its activities include cell cycle arrest, apoptosis, cell senescence, angiogenesis, DNA repair and migration as well as stem cell renewal, embryogenesis, innate immunity, metabolism and fertility (Hollstein & Hainaut, 2010). BRCA1 and p53 are regulated by estrogens and BRCA1 expression is induced during puberty and pregnancy when estrogen levels are increased (Hilakivi-Clarke, 2000).

2.4.2. Estrogens

Estrogen and their receptors play a critical role in the development of the mammary gland (Ricketts et al., 1991; Subramanian et al., 2008). Critical stages for the development of the mammary gland are during embryogenesis, puberty and pregnancy (Baik et al., 2004/2005; Savarese et al., 2006/2007; Ginestier & Wicha, 2007; Ruder et al., 2008). Estrogens are mitogenic agents for breast epithelial cells (Doisneau-Sixou et al., 2003; Labrie et al, 2003 ; Seeger et al., 2008; Park et al, 2008) as is IGF-1 (Park et al., 2008). In mice, chronic prepartum mild stress exposure increases estradiol and corticosterone levels during pregnancy (Misdrahi et al., 2005). Estrogens stimulate CRH production and cortisol release and centrally released CRH, as well as higher cortisol levels, contribute to symptoms of depression (Bao et al., 2008; Edwards & Mills, 2008). Luteal estradiol is primarily produced in the ovaries while most of the follicular estradiol comes from nonovarian sources, for example adipose tissue, and that's why they reflect estrogen levels in the breast. Follicular estrogen may have a greater impact on breast tissue than luteal estrogens and estradiol increases the expression of antiapoptotic proteins (Eliassen et al., 2006). Women closer to menopause have menstrual cycles with longer follicular phases and estrogen receptor expression in the breast is higher during the follicular phase (Ricketts et al., 1991; Eliassen et al., 2006). After menopause, estradiol is no longer secreted by the ovaries and almost 100% is produced in peripheral intracrine tissues. Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S) are converted into androgens and/or estrogens in peripheral target tissues (Labrie et al., 2003).

Estrogens also increase proliferation and genetic instability, probably because free radical-mediated DNA damage and mutations have been induced (Hilakivi-Clarke, 2000; Yue et al., 2003; Park et al., 2008). These increase the probability of mutation due to enhanced proliferation and the direct genotoxic effects of estrogen metabolites (Yue et al., 2003; Noruzinia et al., 2005). In a woman with an already mutated BRCA1 gene, estrogens may induce genetic instability because the mutated gene is unable to correct genetic alterations (Hilakivi-Clarke, 2000; Noruzinia et al., 2005).

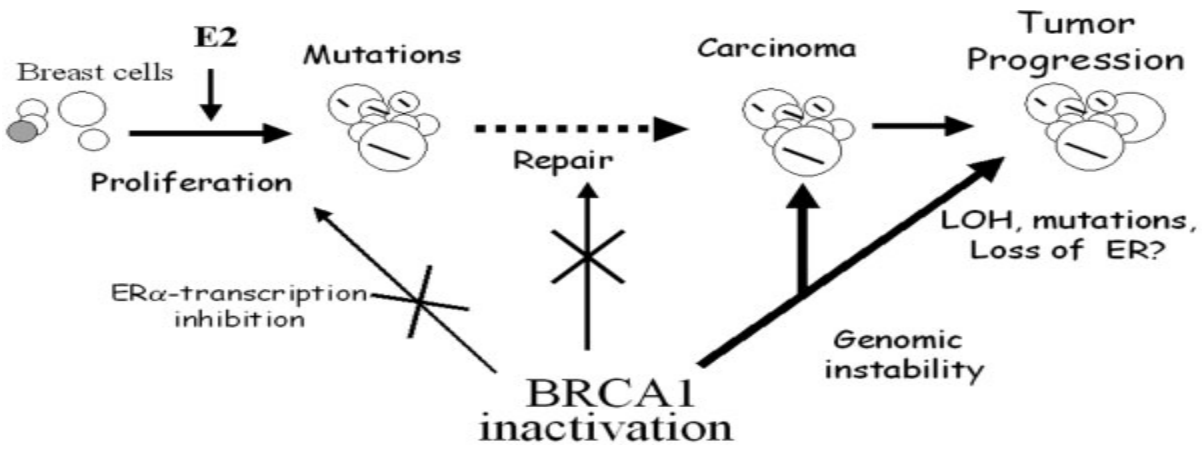

Fig 2: Noruzinia et al., 2005. The role of BRCA1 inactivation in estrogen-promoted carcinogenesis.
LOH= loss of heterozygosity

Estrogen plus progestin increase breast density and breast density is positively associated with serum High Densitiy Lipoprotein-Cholesterol (HDL-C) (Furberg et al., 2004/2005). Estrogens influence adipogenesis and adipose metabolism (Hilakivi-Clarke, 2000; Mattson & Olsson, 2007; Guzmán & Zambrano, 2007). Estrogens and cortisol interact and influence adipocyte metabolism (Mattson & Olsson, 2007). Premenopausal women who reach menarche at an early age and who then are overweight or obese in adulthood have higher levels of estradiol throughout the menstrual cycle (Emaus et al., 2008). Women with low birth weight associated with adult overweight tend to have higher estradiol levels throughout their menstrual cycles (Finstad et al., 2009). Obesity, physical inactivity and the consumption of alcohol are associated with higher estrogen levels (Rod et al., 2009). Higher adult weight in association with high insulin levels increase estradiol levels (Finstad et al., 2009). Fat intake affects estrogen metabolism and increases total estrogen levels (Aubertin-Leheure et al., 2008). Physical activity has a protective effect against breast cancer and this may be due to decreased estradiol levels (Kaaks et al., 2005; Van Gils et al., 2009; Fair & Montgomery, 2009; Rod et al., 2009).
ER undergo changes in methylation (Kim et al., 2004; Dumont et al., 2008; Champagne & Curley, 2008 ; Wilson & Westberry, 2009). Hormonal and environmental factors regulate the expression of ER alpha and this has consequences on maternal behavior and care (Champagne & Curley, 2008).

2.4.3. Fatigue and sleep

Nightshift work alters the nighttime melatonin levels and other hormone profiles (Franzese & Nigri, 2007; Merklinger-Gruchala et al., 2008). Sleep deprivations alter immune function

(Kiecolt-Glaser et al., 2002). Sleep variations are associated with estrogen levels (Merklinger-Gruchala et al., 2008). Alterations in cortisol rhythms may disrupt the suppressive effects of cortisol on proinflammatory cytokine production and this could lead to elevations in circulating cytokines which increases fatigue (Bower et al., 2002/2007; Vgontzas et al., 2004). If this interferes with sleep, a positive feedback loop is created as it can lead to next-day elevations in cytokines and fatigue (Chrousos, 2000; Vgontzas et al., 2004; Bower et al., 2004/2005). A night of total sleep loss is associated with fatigue and an increase in circulating IL-6 and/or TNF-α concentration the next day. During the early part of sleep after one week of sleep restriction, there's a significant decrease in cortisol secretion in women and during the latter part, there's an increase. The 24h- mean cortisol secretion is higher in insomniacs than in controls. There's an around-the clock activation of the HPAA. Because of their hypercortisolism, chronic insomniacs are at risk for medical problems (Vgontzas et al., 1999/2001). Cortisol levels upon awakening are low in primary insomniacs and amongst subjects with frequent nightly awakenings (Vgontzas et al., 2001; Backhaus et al., 2004; Bower et al., 2004). People with sleep deprivation have an increased evening cortisol level (Spiegel K. et al., 1999; Vgontzas et al., 2001). An association exists between exhaustion and loss of habituation to acute psychological stress (Kudielka et al., 2005).

2.4.4. Metabolism and nutrition

Nutrition in the postnatal period can induce metabolic programming effects which can cause obesity (Stoll, 2002; Srinivasan & Patel, 2008). Childhood obesity is also linked to menarche at an early age. Continuation of obesity after adolescence is associated with increased risk of insulin resistance in adult life (Stoll, 2002). Elevated concentrations of insulin during critical periods of early development can program the development of obesity and diabetes (Stoll, 2002; Plagemann, 2008).

Catch-up growth early in life is due to a disproportionately higher rate of fat gain relative to lean tissue gain and is a major risk factor for later obesity and type-II diabetes (Dulloo, 2008). Premenopausal women with higher adult height in combination with high insulin levels have higher estradiol levels (Finstad et al., 2009). Women develop larger amounts of visceral fat after menopause. Increased circulating cortisol, the release of which can be stimulated by estrogens, is associated with central obesity (Stoll, 2002; Mattsson & Olsson, 2007). Estrogen has an influence on adipogenesis and adipose metabolism (Hilakivi-Clarke, 2000; Mattsson & Ollsson, 2007; Guzmán and Zambrano, 2007). A high Body Mass Index (BMI) or fat intake

indirectely indicates increased estrogens (Hilakivi-Clarke, 2000; Kaaks et al., 2005; Rosner et al., 2008; Sunami et al., 2008; Aubertin-Leheudre et al., 2008). Cortisol is also generated in adipose tissue by the enzyme 11beta-hydroxysteroid dehydrogenase type 1 (11betaHSD1) and estrogens seem to have an influence on this enzyme. Estrogens and cortisol interact and influence adipocyte metabolism (Mattson & Olsson, 2007).

Hormonal alteration linked to obesity such as hyperinsulinism, high levels of IGF-1 and high estradiol levels from an enhanced aromatase activity may have mitogenic and antiapoptotic effects (Schlienger et al., 2009; Lautenbach et al., 2009; Gunter et al., 2009; Neilson et al., 2009; Fair & Montgomery, 2009). A low serum level of HDL-C is an unfavorable hormonal profile with increased levels of breast mitogens, consisting mainly of estrogens but also of insulin and IGF-1 in postmenopausal women who are overweight. It is also related to increased levels of free, biologically active estradiol in premenopausal women who are overweight. Free levels of estradiols are higher in women with abdominal obesity than in women with lower-body obesity (Furberg et al., 2004/2005).

2.4.5. Melatonin

Nightshift work alters the nighttime melatonin levels and other hormone profiles (Franzese & Nigri, 2007; Merklinger-Gruchala et al., 2008). Hypothalamus-pineal gland axis is responsible for melatonin production and it may be impaired by chronic stress through sleep disturbances for example (Kwiatkowski et al., 2005). Melatonin can modulate the immune system and fat metabolism. It can also block the ER alpha and has an impact on the production of estradiol through the enzyme aromatase (Viswanathan & Schernhammer, 2009). Melatonin seems to downregulate cortisol production by acting directly on the adrenal gland (Campino et al., 2008) and may normalize cortisol rhythm in untreatable metastatic cancer patients with alterations of cortisol rythms (Brivio et al., 2010).

2.4.6. Stem cells

Stem cells are generated during the perinatal period (Trichopoulos et al., 2005). All tissues in the body are derived from organ-specific stem cells. They can undergo self-renewal and differentiation. By their long-lived nature, they accumulate multiple mutations (Baik et al., 2004/2005; Wicha et al., 2006). The larger the stem cell pool, the greater the chance that one of the stem cells will mutate or make a DNA replicative error (Trichopoulos et al., 2005; Strohsnitter et al., 2008).

Critical stages for the development of the mammary gland are during embryogenesis, puberty and pregnancy (Baik et al., 2005; Savarese et al., 2006; Ginestier & Wicha, 2007; Ruder et al., 2008). A rudimentary mammary gland is formed during embryonic development and is influenced by placental and maternal hormones. The mammary gland is completed during puberty and some morphogenetic changes occur during pregnancy, lactation and involution. If the hormonal milieu changes during these stages of development, the size of the breast stem pool may be influenced (Ginestier & Wicha, 2007; Strohsnitter et al., 2008).

2.5. Breast cancer and stress: a possible link?

2.5.1. Breast cancer, inflammation and immune system

Many cancers develop from sites of infection and/or chronic inflammation (Coussens & Werb, 2002). Chronic inflammation mediates cancer as it is involved in tumorigenesis, proliferation, invasion, angiogenesis and metastasis (Coussens & Werb, 2002; Aggarwal et al., 2006; Bunt et al., 2007; Lin & Karin, 2007; Kundu & Surh, 2008; Gonda et al., 2009). TNF-α, one of the mediators of inflammation, is linked to cancer when dysregulated. It enhances cellular transformation and is associated with poor prognosis and fatigue. IL-1 and Il-6 are also involved in tumorigenesis. TNF-α, IL-1 and IL-6 are regulated by the transcription factor NF-κB and cancer cells express an activated form of it, whereas it is normally in an inactivated form. NF-κB is linked to cellular transformation and is a growth factor for tumor cells (Aggarwal, 2004; Lee et al., 2004; Lin & Karin, 2007; Gonda et al., 2009). Some breast cancer cells rely on it for aberrant cell proliferation and the avoidance of apoptosis (Lee et al., 2004; Aggarwal et al., 2006;). Bone marrow derived cells (BMDCs) are found at the site of chronic inflammation. As they are able to differentiate into cells of diverse lineages, they may be able to initiate tumor cells (Gonda et al., 2009).

Matrix metalloproteinase 9 (MMP9) is associated with more invasive and aggressive breast cancer as they regulate epithelial proliferation through pro-growth factors like VEGF in angiogenesis (Gonda et al., 2009). Reduced inflammation diminishes the number of suppressor cells called myeloid-derivedsuppressor cells (MDSC) and limits tumor progression. MDSC accumulation occurs early in tumor progression. Reduced inflammation in the tumor microenvironment is associated with diminished metastatic potential (Bunt et al., 2007; Gonda et al., 2009). MDSC cells are pro-inflammatory and are able to promote angiogenesis (Gonda et al., 2009).

Overexpression, elevated secretion or abnormal activation of proinflammatory mediators such as cytokines, chemokines and transcription factors facilitate cancer promotion and progression by changing the microenvironment (Coussens & Werb, 2002; Rollins, 2006; Bunt et al., 2007; Lin & Karin, 2007; Kundu & Surh, 2008; Mantovani et al., 2008; Gonda et al., 2009) and by initiating angiogenesis, metastasis and invasion through VEGF (Bunt et al., 2007; Gonda et al., 2009). Cellular micro ribonucleic acids (micro RNAs) may also play a role between inflammation and cancer (Kundu & Surh, 2008).
Polymorphisms of IL1 and IL6 as for example the -174G/C IL6 polymorphism is important for the genesis of breast cancer (Hefler et al., 2005). Genetic polymorphisms that enhance TNF-α production are linked to an increased risk of breast cancer (Lin & Karin, 2007).

Natural killer cell activity before tumor inoculation is greater in mice living in an enriched environment than in other mice (Cao et al., 2010).
Social support is associated with lower IL-6 levels among patients with ovarian cancer (Costanzo et al., 2005; Antoni et al., 2006). Social support is associated with better NK cell activity in breast cancer patients (Kiecolt-Glaser et al., 2002).

2.5.2. Breast cancer and psychosocial factors

Maternal death and chronic severe depression may be involved in cancer development (Jacobs & Bovasso, 2000). Depression and anxiety stimulate the production of IL-6 (Kiecolt-Glaser et al., 2003; Reiche et al., 2005). Chronic depression may be linked to cancer through the impact caused by neuroendocrine dysregulation associated with depression on immune function (Spiegel & Giese-Davis, 2003; Koopman and al., 2004; Reiche et al., 2005). Stressed and depressed patients show high levels of serum basal cortisol, plasma concentration of IL-1, IL-6 and TNF-α as well as decreased NK cell activities (Reiche et al., 2005). But only chronic depression and/or major depression present an increased risk for breast cancer, not other depressive disorders (Jacobs & Bovasso, 2000; Spiegel & Giese-Davis, 2003; Koopman et al., 2004).
There's a link between women with self reported stress and breast cancer (Helgesson et al., 2003). Stressful daily activities don't seem to be linked to breast cancer, whereas it seems to be the contrary for the accumulation of stressful life events (Chen et al., 1995; Lillberg et al., 2003). Death of spouse seems to be related to an increased risk (Duijts et al., 2003; Lillberg et al., 2003) and also divorce/separation and death of a close relative or friend (Lillberg et al.,

2003). There's a positive association between stressful or traumatic events and disease-free intervals in women with breast cancer (Palesh et al., 2007).

It has been demonstrated that psychosocial factors clearly influence progression of breast cancer and/or the formation of metastasis (see chapter 2.2.3.). Stress-related psychosocial factors are associated with poorer survival in breast cancer patients. Women with metastatic breast cancer with a repressive coping style and/or who are very anxious have flatter cortisol rhythm (Giese-Davis et al., 2004/2006).

Psychosocial stress responses involve CNS, ANS and HPAA resulting in release of glucocorticoids, catecholamines, and other hormones that could change multiple components of the tumor micro-environment (Antoni et al., 2006; Chida et al., 2008). Psychological stress has been observed to increase DNA damage, affect the repair of damaged DNA, inhibit apoptosis, and it can promote tumor migration (Kiecolt-Glaser & Glaser, 1999; Forlenza & Baum, 2000; Reiche et al., 2005; Flint et al., 2007; Chida et al., 2008; Gidron & Ronson, 2008). It also stimulates angiogenesis by producing VEGF (Antoni et al., 2006; Chida et al., 2008). High levels of IL-6 have been linked to some forms of cancer (Godbout & Glaser, 2006; Yang et al., 2008). Glucocorticoids can directly mediate processes promoting tumor growth. Cortisol has been shown to enhance proliferation of human breast cancer cells by nearly two-fold (Simon et al., 1985) Activated GR by glucocorticoids prevents apoptosis in cultured malignant human breast epithelial cells (Moran et al., 2000). Glucocorticoids activate survival genes in cancer cells, which could inhibit chemotherapy-induced apoptosis (Wu et al., 2004). In mice, Hydrocortisone down-regulates the expression of BRCA1 and suppresses positive effects of estrogens on BRCA1 expression (Antonova & Mueller, 2008). Cortisol in synergy with catecholamines may facilitate cancer growth (Thaker et al., 2007).

Stress in the body activates a protein that allows cancer cells to survive even after chemotherapy and/or radiotherapy. Experiments using breast cancer cells show that a protein known as heat shock protein 27 (Hsp27), activated by the presence of heat shock factor-1, can block the process that kills cancer cells even after their DNA was damaged by the treatments. The protein is active in the two days following any stressful event *in vitro* that activates heat shock factor-1 (Kanagasabai et al., 2010).

In mice, enriched environment delays tumor growth and increases survival (Cao et al., 2010; Kappeler & Meaney, 2010). In rats, social isolation leads to an at four times higher risk of developing mammary tumors. In socially isolated rats, GR activation is chronic and this increases the risk for mutations of the ductal epithelium causing mammary cancer

(McClintock et al., 2005). Socially isolated rats have greater tumor burden by mid-life even though they entered estropause prematurely. This indicates that isolation does not increase tumorigenesis by prolonging ovarian function (Hermes & McClintock, 2008). In the Sprague-Dawley rat, "social isolation increased the size, number distribution and malignancy of spontaneous mammary tumors" (Hermes et al.). The adrenal axis of socially isolated rats is dysreglated. Isolation induces glucocorticoid hyperresponsiveness in young adults and then mammary tumors in later age. Glucocorticoid receptors are more commonly found in the nucleus of the mammary gland when there has been social isolation (Hermes et al., 2009).

In rats, social isolation alters the hormonal milieu of breast tissues during puberty and adulthood (McKlintock et al., 2005; Hermes & McKlintock, 2008). Social isolation accelerates maturation of ovarian function and delays mammary tissue development and therefore increases exposure of the developing breast to high levels of estrogen (Hermes & McClintock, 2008). Social isolation alters the hormonal milieu of mammary tissue during puberty and adulthood and this may accelerate tumor growth (McClintock et al., 2005).

In patients with ovarian cancer, women with more social support have lower serum levels of VEGF (Lutgendorf et al., 2002/2003; McGregor & Antoni, 2009). VEGF can be stimulated by NE via β-adrenergic receptors, which mediate many functions of NE. These receptors have been seen on mammary tumors and their activation leads to mammary tumor growth. VEGF can also be influenced by cortisol (Lutgendorf et al., 2002/2003). VEGF from tumor cells, induced by progestin in response to progesterone (P), can increase the proliferation of endothelial and breast tumor epithelial cells (Liang & Hyder, 2005). NE levels increase in times of stress. The molecule binds to receptors on cancer cells and this linkage stimulates the release of the proteins that support angiogenesis (Yang et al., 2006). It induces breast cancer migration (Thaker et al., 2007). Epinephrine protects breast cancer cells from apoptosis (Lutgendorf et al., 2003; Sastry et al., 2007). Elevated levels of NE and E due to chronic stress can enhance the capacity of ovarian cancer cells to invade the extracellular matrix. This is mediated through β-adrenergic receptors on cancer cells (Lutgendorf et al., 2003; Sood et al., 2006; Thaker et al., 2006) and through the activation of tumor cell cyclic adenosine monophosphate protein kinase A (cAMP PKA) signaling pathway. The tumors of stressed animals also have for example an overexpression of matrix metalloproteinases-2 and -9 (Thaker et al., 2006; Yang et al., 2006).

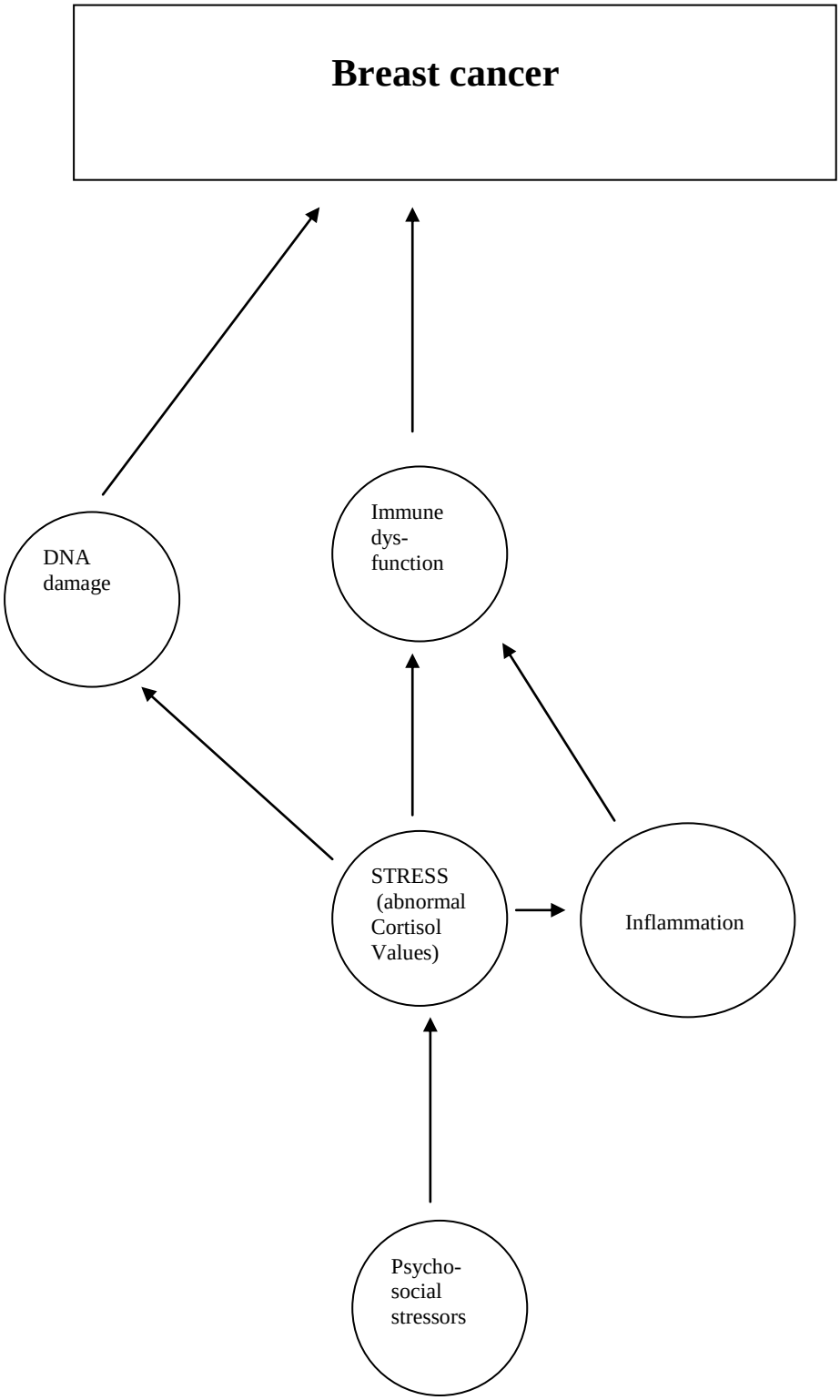

Fig 3: Links and interactions between psychosocial stressors and breast cancer

2.6. Breast cancer and pre-/postnatal factors: a possible link?

2.6.1. Breast cancer, childhood trauma, early life influences and maternal behavior

Maternal death could be involved in cancer development (Jacobs & Bovasso, 2000). Women exposed to stress and starvation during childhood and adolescence are at higher risk of dying from breast cancer (Koupil et al., 2009). In rats, neonatal exposure to handling leading to improved ability to cope with stress, reduces incidence of some mammary tumors (Hilakivi-Clarke et al., 1994).

There's one prospective study until today that found out that adverse childhood experiences are a risk factor for women in cancer development via a direct biological effect. An accumulation of adverse early life influences is a strong predictor of cancer. The adverse childhood experiences studied were public or foster care, physical neglect, an absent family member (for example in prison), parental separation, a family member with mental illness and a family member with alcool abuse (Kelly-Irving et al., 2013).

2.6.2. Breast cancer, umbilical cord blood and intrauterine factors or exposures

Foetal exposure to xenoestrogens is a risk factor for breast cancer (McCormack, 2003; Soto et al., 2008; Ruder et al., 2008; dos Santos Silva et al., 2008). Breast tissue is not entirely differentiated until the end of the first pregnancy, and aside the perinatal period, childhood and adolescence are other important intervals for a higher risk of developing breast cancer (Ruder et al., 2008; dos Santos Silva et al., 2008). In mice, chronic prepartum mild stress exposure increases estradiol and corticosterone levels during pregnancy (Misdrahi et al., 2005). Elevated fetal estrogen levels can alter the morphology of the mammary gland and cause the presence of Terminal End Buds (TEB's), epithelial structures, known to be responsible for malignant growth (Hilakivi-Clarke, 2000). ER, BRCA1 and p53 are as well affected by diet-induced (estrogenic exposure) alterations in programming (De Assis & Hilakivi-Clarke, 2006).

2.6.3. Breast cancer, fetal growth, birth size and growth

A shorter gestational age as well as a smaller head circumference is linked to an increased risk for premenopausal breast cancer (McCormack et al., 2003) and women with a large head circumference present an increased breast cancer risk (dos Santos Silva et al., 2008).

Larger size at birth is associated with an increased risk of breast cancer (Vatten et al., 2002; McCormack et al., 2003; Jasienska et al., 2006; Xue & Michels, 2007; dos Santos Silva et al.,

2008; Ruder et al., 2008). It is also associated with epigenetic modifications that lead to modifications in breast development (Hilakivi-Clarke & de Assis, 2006; Lagiou & Trichopoulos, 2008). In addition, it is associated with higher levels of pregnancy hormones like estrogen and IGF1 which increases the number of susceptible stem cells with compromised genomic stability (Lagiou & Trichopoulos, 2008). In their review, Ruder et al. stated that, regardless of age at diagnosis, each 5-cm increase in height from age 8-14 was associated with a higher breast cancer risk. They also found that breast cancer cases are taller than others during childhood. There also seems to be a risk between childhood and adolescent diet. Those consuming more fat are at higher risk and high glycemic index diets may increase insulin. This increases in turn secretion of IGF1 which is positively associated with premenopausal breats cancer risk (Ruder et al., 2008). Poor fetal growth, usually in combination with adult obesity, is linked to breast cancer (Ozanne et al., 2004).

2.6.4. Breast cancer and birth weight

Birth weight is strongly related to early-onset breast cancer (Innes et al., 2000). Increased birth weight increases breast cancer risk (Vatten et al., 2002; McCormack et al., 2003; De Assis & Hilakivi-Clarke, 2006; Xue and Michels, 2007; dos Santos Silva et al., 2008; Ruder et al., 2008). High ponderal index at birth predicts high estradiol levels in menstrual cycles in adult women and is therefore a risk for developing breast cancer (Jasienska et al., 2006). Birth weight is positively associated with the number of haematopoietic stem cells in the cord blood (Strohsnitter et al., 2008). There's a positive link between high birth weight and premenopausal breast cancer (Vatten et al., 2002; McCormack et al., 2003; Michels & Xue, 2006; Park et al., 2008; Lagiou & Trichopoulos, 2008; Ruder et al., 2008). Elevated levels of growth factors may increase the number of susceptible stem cells in the mammary gland or initiate tumors through DNA mutation (Michels & Xue, 2006; Park et al., 2008; Lagiou & Trichopoulos, 2008). Women with low birth weight and adult obesity have higher estradiol levels during menstrual cycles and therefore have a higher risk of developing breast cancer (Finstad et al., 2009). Weight loss immediately after birth is associated with premenopausal breast cancer risk (Lagiou et al., 2008).

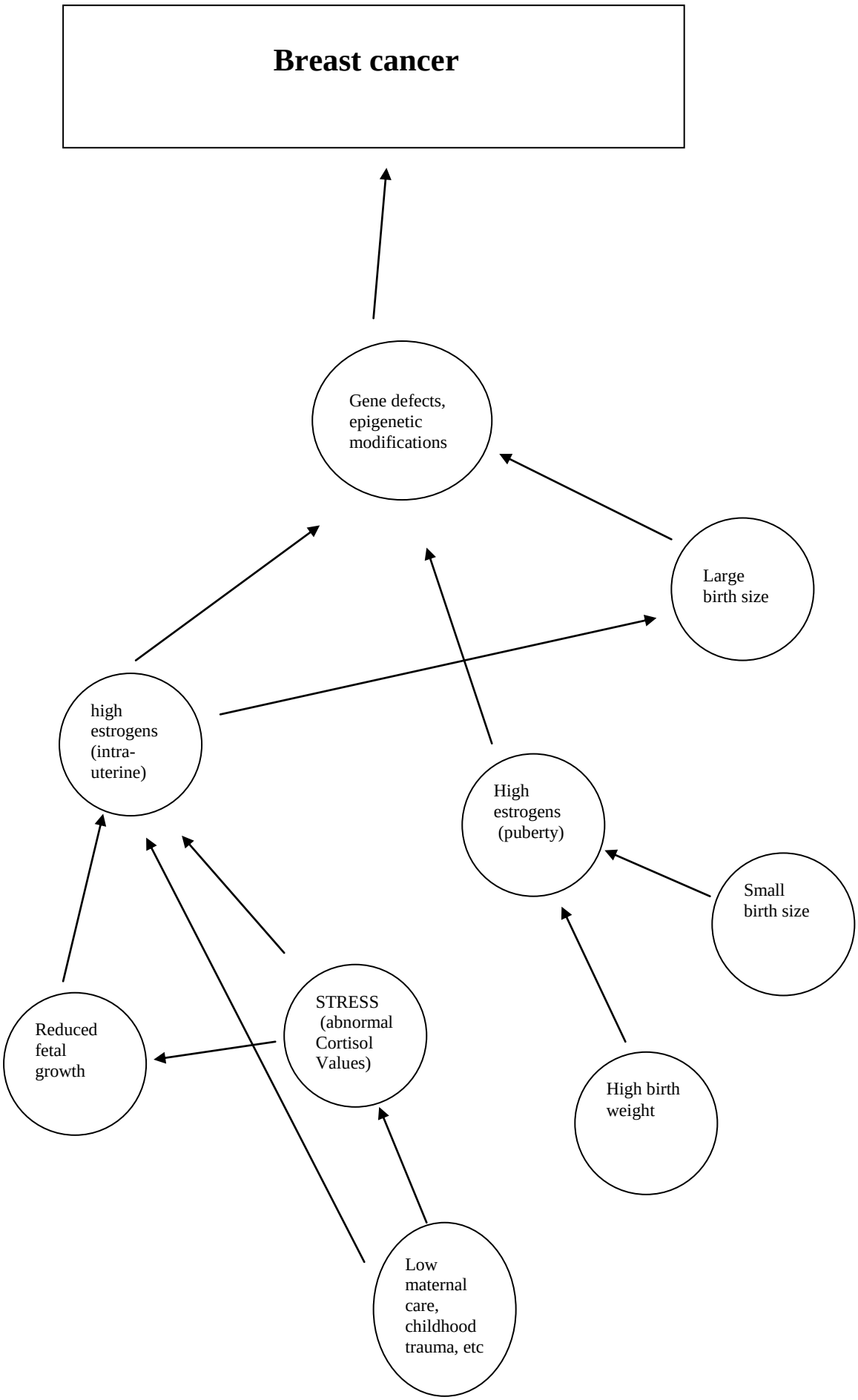

Fig 4: Links and interactions between pre-/postnatal factors and breast cancer

2.7. Breast cancer and other factors: possible links?

Another factor well-known to be involved in breast cancer and progression is fatigue. But there are also other factors involving stress pathways that may be linked directly or indirectly to the development of breast cancer.

2.7.1. Breast cancer, genes and proteins

Breast cancer develops after multiple environmental events have affected the genome as well as from mutations that are inherited (Hilakivi-Clarke, 2000; McKlintock et al., 2005). In breast cancer, regional hypermethylation of specific genes or global hypomethylation may occur. Hypermethylation silences growth regulatory genes and hypomethylation activates genes necessary for metatstasis (Szyf et al., 2004). Hypermethylation of several genes (*Cyclin D2* (CCND2), glutathione S-transferaseP1 (GSTP1), normal epithelial cell-specific1 (NES1)) play a role in tumorigenesis, metastazation and poor prognosis. Hypermethylation of some of these genes is higher in ER-positive tumors. Epigenetic differences between ER positive and ER negative breast cancers arise early in cancer development. There are also epigenetic differences between ER negative/Her2neu negative breast cancers and breast cancers expressing either Her2 neu or ER (Sunami et al., 2008). Hypermethylation of BRCA1 and 17-beta hydroxyl steroid dehydrogenase type 1 (HSD17B1) is responsible for some breast cancers. Those two genes may increase the risk of developing breast cancer due to increased estradiol activity (Bhavani et al., 2009). A gene that is frequently downregulated in primary breast cancer is the Pleckstrin homology-like domain, family A, member 1 (PHLDA1) and this gene is also regulated by estrogens (Marchiori et al., 2008).

The BRCA1 gene plays a role in hereditary breast cancer and is associated with a poor prognosis. In sporadic breast cancer, the lack of expression of BRCA1 is also associated with a poor prognosis (Hilakivi-Clarke, 2000; Ansquer et al., 2005). The level of BRCA1 expression in sporadic breast cancer is linked to invasiveness of the tumor. It is lowest in invasive cancer (Hilakivi-Clarke, 2000). In sporadic breast cancer, the function of BRCA1 might be reduced by environmental factors (exposure to polycyclic aromatic hydrocarbons) or by changes in estrogen levels (Hilakivi-Clarke, 2000). Interaction with the environment changes cellular and genetic functions and somatic alterations occur, such as hypermethylation of BRCA1 which then silences it. BRCA1 is probably also involved in sporadic breast cancers even if it is not mutated (McKlintock et al., 2005). In BRCA1-mutated cancers, Tp53 is also mutated most of the time (Hilakivi-Clarke, 2000; Lacroix et al., 2006;

Miyoshi et al., 2008) and EGFR is overexpressed (Miyoshi et al., 2008). BRCA activity is downregulated by glucocorticoids, potentially leading to malignant transformation (Antonova & Mueller, 2008).

Tp53 and/or its protein are mutated in approximatively 50% of human cancers and in most of the remaining cases its acivity is compromised because of the dysregulation of its signaling pathways (Zuckerman et al., 2009). 70% of breast cancers have wild type p53 indicating that its pathway has been inactivated by alterations other than mutations of the gene Tp53 (Abdel-Fatah et al., 2010). The gene Tp53 and its protein are important to cellular stress response and have a clear role in cancer (Lacroix et al., 2006; Hall et al., 2010). In response to stress, the protein undergoes degeneration. If there are stress signals or DNA damage, p53 is induced to escape its pathways and to undergo rapid nuclear accumulation (Lacroix et al., 2006; Zuckerman et al., 2009; Hollstein & Hainaut, 2010; Hall et al., 2010). Inheritance of a muted Tp53 allele results in the Li-Fraumeni syndrome. This syndrome causes multiple early cancers, including breast cancer (Lacroix et al., 2006). Between 20-35% of breast cancers show a mutation of p53 (Lacroix et al., 2006, Abdel-Fatah et al., 2010). Basal-like breast cancers are triple negative (no expression of ER, PR and HER2neu), have a p53 mutation, an EGFR overexpression and a frequent loss of BRCA1. Those cancers are of high grade, occur in the younger age group and generally and have a poor prognosis (Miyoshi et al., 2008). ER, BRCA1 and p53 are affected by diet-induced (estrogenic exposure) alterations in programming (De Assis & Hilakivi-Clarke, 2006). BRCA1, BRCA2 and p53 are regulated by estrogens (Hilakivi-Clarke, 2000).

2.7.2. Breast cancer and estrogens

Long-term estrogen exposure enhances the tumorigenicity of Michigan Cancer Foundation-7 (MCF-7) breast cancer cells, a breast cancer cell line (Lacroix et al., 2006; Spink et al., 2009). Metabolites of estradiol together with ER mediated mechanisms induce breast cancer (Dickson & Stancel, 1998; Doisneau-Sixou et al., 2003; Yue et al., 2003; Zeleniuch-Jacquotte et al., 2004; Crooke et al., 2006; Parl et al., 2009). Higher levels of endogenous estrogens appear to be associated with increased breast cancer risk, regardless of familiy history of breast cancer (Eliassen et al., 2006). In premenopausal women, higher plasma levels of total and free estradiol in the early follicular phase are associated with an increased risk for breast cancer. This association is even stronger among women having a ER+/PR+ tumor. Follicular estrogen may have a greater impact on breast tissue than luteal estrogen (Eliassen et al., 2006). Women with estrogen receptor positive breast epithelium are at greater risk for

developing breast cancer and this effect is more profound for postmenopausal women (Khan et al., 1998). In postmenopausal women, breast cancer risk is strongly associated with circulating levels of estrogens (Kabuto et al., 2000; Key et al., 2002; The Endogenous Hormones and Breast Cancer Collaborative Group, 2002; Zeleniuch-Jacquotte et al., 2004; Missmer et al., 2004; Kaaks et al., 2005; Hankinso.n, 2005; Rosner et al., 2008; Sieri et al., 2009), especially for ER+/PR+ tumors (Missmer et al., 2004). Estrogens increase proliferation of cells in the breast and this contributes to breast cancer by increasing errors in DNA replication and by enhancing the replication of clones of cells carrying such errors (Dickson & Stancel, 1998; Baik et al., 2005; Lagiou & Trichopoulos, 2008; Strohsnitter et al., 2008). Estrogens promote proliferation of tumorous epithelium by affecting DNA synthesis or through growth factors as IGFs and epidermal growth factors (EGFs) (Doisneau-Sixou et al., 2003; Baik et al., 2005; Lagiou & Trichopoulos, 2008; Strohsnitter et al., 2008). In early stages of breast cancer (T1 or N0 stages), ER expression may influence epigenetic changes (Sunami et al., 2008). The changes in the expression of the methylation of ER are associated with the progression of breast cancer (Kim et al., 2004; Dumont et al., 2008, Champagne & Curley, 2008; Wilson & Westberry, 2009). Estradiol in combination with TNF-α increases VEGF concentration and therefore the risk of metastasis (Seeger et al., 2008). High total levels of testosterone are associated with increased risk of breast cancer (The Endogenous Hormones and Breast Cancer Collaborative Group, 2002; Kaaks et al., 2005; Eliassen et al., 2006; Sieri et al., 2009; Ho et al., 2009), especially of ER-positive cancers, with HER2neu-negative cancers and inversely with HER2neu-positive cancers in postmenopausal women (Zeleniuch-Jacquotte et al., 2004; Sieri et al., 2009). This is because the level of aromatase (an enzyme that may transform testosterone into estrogens) is higher in breast cancer tissue (Friedman, 2009).

Estrogens seem to increase cortsiol levels (Edwards & Mills, 2008) and cortisol is known to affect also the repair of DNA amongst other negative effects (Kiecolt-Glaser & Glaser, 1999; Forlenza & Baum, 2000; Reiche et al., 2004; Flint et al., 2007, Chida et al., 2008, Gidron & Ronson, 2008).

2.7.3. Breast cancer, fatigue and sleep

Sleep variation in women of reproductive age influences estrogens which can be a risk factor for breast cancer (Merklinger-Gruchala et al., 2008). Most studies find no association between type of operation, type of adjuvant treatment, length of treatment, time since treatment and fatigue. Lower physical activity is related to more severe fatigue and there is a strong

association between depression and severe fatigue (Servaes et al., 2002; Collado-Hidalgo et al., 2006). In cancer patients, sleep is fragmented, sleep efficiency is low and circadian rhythms have little variation between night and day with equal amounts of activity during day and night. Sleep is disturbed and fatigue is reported even before the beginning of chemotherapy amongst women with breast cancer. This might be due to depression after learning that they have cancer or due to not having fully recovered from surgery. Women also reported decreased functional outcome. Those with worse functional outcome have phase delayed circadian rhythms (Ancoli-Israel et al., 2006). Chemotherapy leads to increased levels of VEGF, ratings of fatigue and depressed mood (Mills et al., 2005). About 30% of breast cancer survivors complain of fatigue. It often co-occurs with depressed mood and sleep disturbances (Bower et al., 2002/2004; Payne et al., 2006; Bardwell & Ancoli-Israel, 2008). Fatigue also has a negative impact on social relationships, daily activities and overall quality of life (Bower at al., 2002; Bardwell & Ancoli-Israel, 2008) and it often goes on for several years after treatment has ended (Bower et al., 2003, Servaes et al., 2002; Bardwell & Ancoli-Israel, 2008). Women with primary breast cancer with fatigue have greater cytokine release (IL-1beta and IL-6) (Kurzrock, 2001; Bower et al., 2002; Collado-Hidalgo et al., 2006; Schubert et al., 2007), chronic cellular immune response and flatter cortisol response to stress (Bower et al., 2002; Giese-Davis et al., 2004/2006). Fatigued breast cancer survivors have a flatter cortisol slope with a less rapid decline during the day. Those with the highest levels of cortisol have the flattest cortisol slope. The flatter slopes may be due to slower declines, abnormal elevations in the afternoon or in the evening and/or to a lack of peaks throughout the day. There's an increase in circulating T-cells, which may be explained by a chronic inflammatory process (Bower et al., 2003).

2.7.4. Breast cancer, metabolism and nutrition

Women with central adiposity present lots of glucocorticoid receptors and are therefore sensitive to circulating cortisol (Harvie et al., 2003). There's a link between BMI and invasiveness of breast cancer (Carmichael & Bates, 2004; Pfeiler et al., 2009; Binai et al., 2010). In premenopausal women, adult BMI is inversely associated with total estradiol levels (Tworogger et al., 2006) and breast cancer risk (Carmichael & Bates, 2004). Breast cancer patients generally have an increased BMI, Total Cholesterol (TC) and low density lipoprotein (LDL) cholesterol compared to controls. This indicates that there's an association between dyslipidaemia, BMI and an increased breast cancer risk (Owiredu et al., 2009). Obese women have an increased risk of developing postmenopausal breast cancer (Stoll, 2002; Carmichael

& Bates, 2004). Hormonal alterations linked to obesity (hyperinsulism, high IGF-1 levels, high oestradiol levels, leptin) may have mitogenic and antiapoptotic effects which promote cancer (Stoll, 2002; Schlienger et al., 2009; Neilson et al., 2009; Fair & Montgomery, 2009; Lautenbach et al., 2009; Binai et al., 2010). Hyperinsulinemia is a risk factor for breast cancer (Stoll, 2002; Schlienger et al., 2009; Gunter et al., 2009; Fair & Montgomery, 2009). Physical activity reduces the risk because of reduction of fat stores, changes in sex-hormone levels, effects on IGF and insulin levels, and altered immune function (Fair & Montgomery, 2009; Neilson et al., 2009). Weight gain after the age of 18 increases postmenopausal breast cancer risk (Eliassen et al., 2006; Binai et al., 2010). In postmenopausal women, BMI is also linked to an increased risk, and BMI is correlated with estradiol and testosterone (Kaaks et al., 2005; Rosner et al., 2008). Adult obesity has an effect on premenopausal sex hormone levels which affects premenopausal breast cancer risk (Tworoger et al., 2006; Ruder et al., 2008; Rod et al., 2009).

Leptin and it's receptors of obesity (Ob-RL) are expressed in breast cancer (Cirillo et al., 2008; Binai et al., 2010). When leptin is binding to its receptor, it activates different signaling pathways and this induces the growth of breast cancer cells by mediating angiogenesis and by inducing expression of VEGF. In triple negative breast cancer cells, it interacts with IGF-1 and promotes invasion and migration. It is also able to affect the growth of ER-positive breast cancer cells and increases estrogen levels (Cirillo et al., 2008). In mice, enriched environment (EE) delays tumor growth and increases survival by increasing the expression of the gene encoding brain-derived neurotrophic factor (BDNF) in the hypothalamus. BDNF decreases adipokine leptin levels by increasing sympathetic nervous system activity and by activating β-adrenergic receptors in white adipose tissue. EE is considered as eu-stress at the level of the medial prefrontal cortex and therefore leptin is decreased even if glucocorticoids, NA and NE are increased (Kappeler & Meaney, 2010; Cao et al., 2010). Signal transducer and activator of transcription (STAT) dependent target genes are generally implicated in cell proliferation and migration, differenciation and apoptosis, and these are crucial in carcinogenesis and development of the mammary gland. Leptin induces activation of STAT3, a transactivator of important oncogenes. This process depends on Ob-RL expression. ERα also plays a role in leptin indicued STAT3 activation. Leptin and estrogen might cooperate in enhancing the growth of estrogen-dependant breast cancer (Binai et al., 2010).

2.7.5. Breast cancer and melatonin

Higher exposure to light at night (night shift, decrease in sleep duration) suppresses melatonin production which increases estrogen levels (Franzese & Nigri, 2007; Merklinger-Gruchala et al., 2008). In patients with estrogen-receptor-positive breast cancer, the circadian rhythm in plasma melatonin is dampened (Mormont & Levi, 1997). The circadian rhythm of melatonin is related to immune functions, and if it is disturbed, there is an increased risk for cancer incidence (Kwiatkowski et al., 2005). Melatonin seems to downregulate cortisol production by acting directly on the adrenal gland (Campino et al., 2008) and may normalize cortisol rhythm in untreatable metastatic cancer patients with alterations of cortisol rythms (Brivio et al., 2010). This effect seems to be associated with stable disease (Brivio et al., 2010).

2.7.6. Breast cancer and stem cells

Critical stages for the development of the mammary gland are during embryogenesis, puberty and pregnancy (Baik et al., 2004; Savarese et al., 2006; Ginester & Wicha, 2007; Ruder et al., 2008). It seems that both IGF-1 and estrogens are critical to the development of mammary epithelium (Savarese et al., 2006; Ginestier & Wicha, 2007; Strohsnitter et al., 2008). Exposure to estrogens during pregnancy may increase the number of mammary gland stem cells and in the same time the risk of malignant transformation of them (Lagiou, 2006). It's the same for the exposure to growth hormones. If the hormonal milieu changes during these stages of development, the size of the breast stem pool may be influenced and this may be responsible for carcinogenesis (Baik et al., 2004; Savarese et al., 2006; Ginestier & Wicha, 2007; Strohsnitter et al., 2008). Recent studies have demonstrated the existence of cancer stem cells in breast cancer (Dick, 2008). A small group of cells with stem cell properties are responsible for carcinogenesis. By their long-lived nature, they are subject to multiple mutations that are required for carcinogenesis. These cells are able to renew themselves, they can differentiate, have active telomerase expression, can activate antiapoptotic pathways, increase membrane transporter activity and are able to migrate and metastasize. The pathways that regulate self-renewal may lead to tumorigenesis. Hedgehog and Notch signaling pathways are for example dysregulated in mammary cancer stem cells. Hedgehog signaling regulates the production of VEGF by mammary stem cells and breast cancer stem cells (Wicha et al., 2006). The risk of breast cancer is linked to the pool size of breast stem cells (for example cord blood CD34+ cells, progenitors of hematopoietic cells and CD34+CD38- cells, primitive hematopoietic cells) and it may be determined in utero or early in life (Baik et al., 2004; Savarese et al., 2006; Ginestier &Wicha, 2007; Strohsnitter et al., 2008). There is

evidence that the growth hormone/IGF-1 axis may coordinate stem cell numbers in multiple organs. Growth hormone receptor is overexpressed in mammary epithelial stem and progenitor cells. Growth hormone is secreted by the pituitary gland but is also produced by differentiated mammary epithelial cells (Ginestier & Wicha, 2007). Growth factors, for example IGF-1 and hormones act as mammary epithelial cell mitogens (Baik et al., 2004; Savarese et al., 2007; Ginestier &Wicha, 2007; Strohsnitter et al., 2008). IGF-I and estrogens exert critical roles in the primitive mammary epithelium during development. Women with elevated levels of those factors will have relatively large and mitotically active pools of breast stem cells (Savarese et al., 2007; Strohsnitter et al., 2008). This increases the possibility of oncogenetic mutations (Baik et al, 2004; Savarese et al., 2007; Strohsnitter et al., 2008).

Estrogens, testosterone, IGF-I and IGF binding protein-3 (IGFBP-3) predict stem cell potential in cord blood. It's probable that growth hormones during the perinatal period tend to increase the number of stem cells and therefore also the number of replicating immature cells susceptible to malignant transformation (Baik et al., 2004). Elevated serum IGF-I levels and of its binding protein are found for example in prostate cancer, colorectal cancer, lung cancer (Grimberg & Cohen, 2000) and breast cancer (Wicha et al., 2006; Savarese et al., 2007; Ginestier & Wicha, 2007; Strohsnitter et al., 2008).

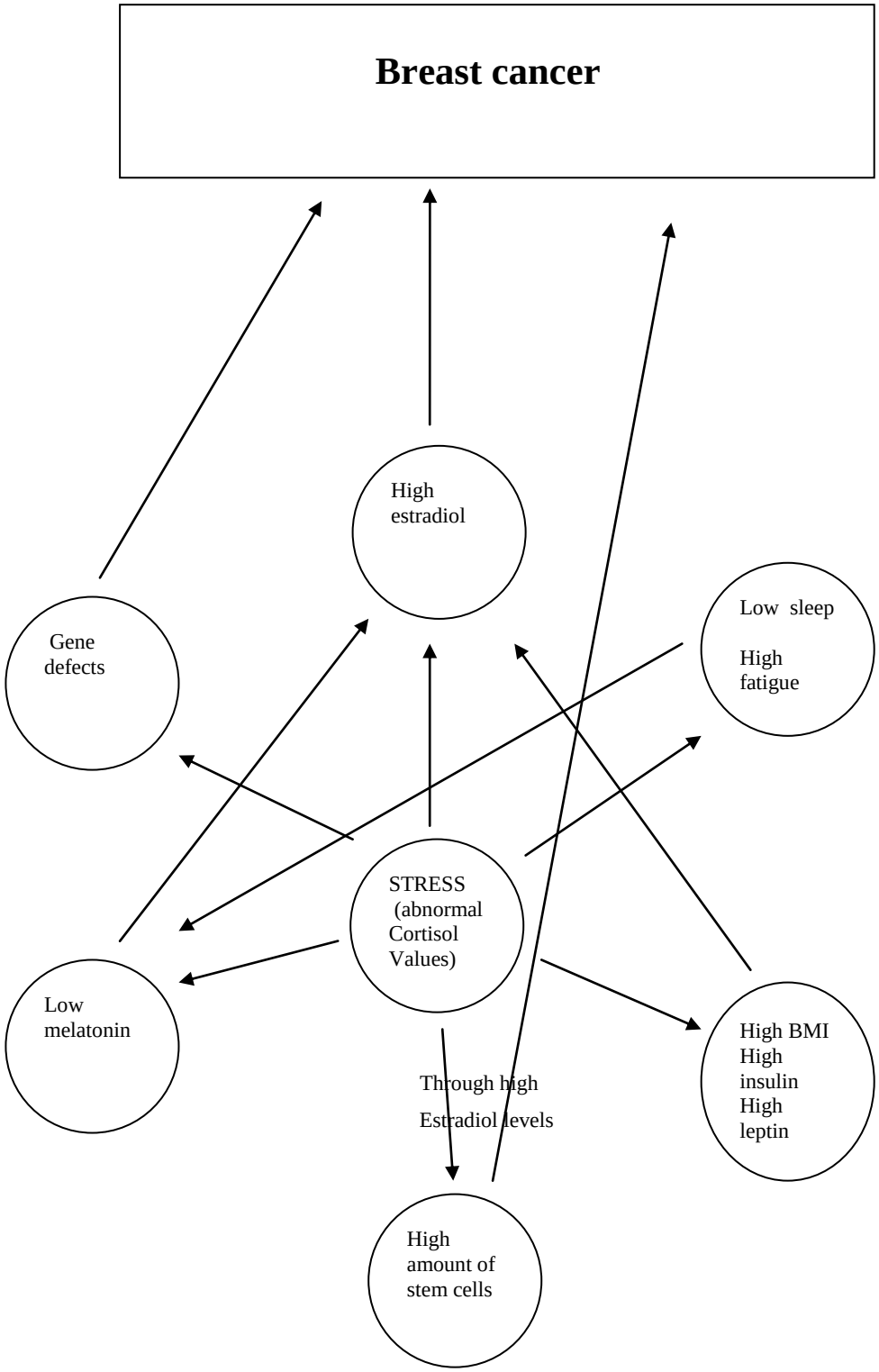

Fig 5: Links and interactions between stress, different factors and breast cancer

2.8. Hypotheses

As can be seen, there are still many questions that haven't been answered yet. After analyzation of the theoretical background, a constant link between all the elements may be defined: cortisol. Cortisol seems to be linked to psychosocial factors, fatigue, estrogens, stem cells, melatonin and breast cancer. In this study, we try to demonstrate this link and we develop the following hypotheses.

One may expect that subjects high in perceived stress may also have a higher activation of all stress systems (activation of the HPAA, activation of the ANS, and activation of other stress-related systems) than those who don't feel stressed. However, lots of researches demonstrate that this is not the case. There seems to be a dissociation between the psychological (perception of stress) and the peripheral physiological stress response (Engert et al., 2004; Hellhammer & Hellhammer, 2008). Persons with perceived stress don't necessarily have an altered HPAA activation (Engert et al., 2004). But in general, perceived stress is linked to worse health outcomes and therefore also in breast cancer patients. We try to test this hypothesis.

Hypothesis 1: Breast cancer patients reporting perceived chronic stress have an abnormal CAR compared to healthy women.

Perceived chronic stress alone has been shown to have no influence on cancer initiation (Chen et al., 1995; Lillberg et al., 2001) whereas impaired cortisol profiles (flatter slopes) have been linked to increased mortality (Sephton et al., 2000; Filipski et al., 2002; Spiegel & Giese-Davis, 2003; Spiegel et al., 2006). Stress hormones (cortisol) are linked to risk factors for breast cancer as for example estrogens, fatigue, metabolism, stem cells (Hilakivi-Clarke, 2000; Stoll, 2002; Mattsson & Olsson, 2007; Guzmán & Zambrano, 2007; Bao et al., 2008; Edwards & Mills, 2008). There's a link between women with self reported stress and breast cancer (Helgesson et al., 2003). Stressful daily activities don't seem to be linked to breast cancer, whereas it seems to be the contrary for the accumulation of stressful life events (Chen et al., 1995; Lillberg et al., 2003). Psychosocial stress responses involve CNS, ANS and HPAA resulting in release of glucocorticoids, catecholamines, and other hormones that could change multiple components of the tumor micro-environment (Antoni et al., 2006; Chida et al., 2008). Psychological stress has been observed to increase DNA damage, affect the repair of damaged DNA, inhibit apoptosis, and it can promote tumor migration (Kiecolt-Glaser &

Glaser, 1999; Forlenza & Baum, 2000; Reiche et al., 2005; Flint et al., 2007; Chida et al., 2008; Gidron & Ronson, 2008). It also stimulates angiogenesis by producing VEGF (Antoni et al., 2006; Chida et al., 2008). Glucocorticoids can directly mediate processes promoting tumor growth. Cortisol has been shown to enhance proliferation of human breast cancer cells by nearly two-fold (Simon et al., 1985). Activated GR by glucocorticoids prevents apoptosis in cultured malignant human breast epithelial cells (Moran et al., 2000).

In the Sprague-Dawley rat, social isolation increases the size, number distribution and malignancy of spontaneous mammary tumors. The adrenal axis of socially isolated rats is dysreglated. Isolation induces glucocorticoid hyperresponsiveness in young adults and then mammary tumors in later age. Glucocorticoid receptors are more commonly found in the nucleus of the mammary gland when there has been social isolation (Hermes et al., 2009).

Hypothesis 2a: Women with abnormal cortisol levels have more aggressive and severe breast cancer (bigger tumor, aggressive grade, lymphnodes, etc) **and a worse prognosis and/or outcome.**

Hypothesis 2b: Women with chronic stress (perceived stress AND abnormal cortisol values) have a more severe and aggressive breast cancer and therefore a worse prognosis and/or outcome.

A night of total sleep loss is associated with fatigue and an increase in circulating IL-6 and/or TNF-α concentration the next day. During the early part of sleep after one week of sleep restriction, there's a significant decrease in cortisol secretion in women and during the latter part, there's an increase. The 24h- mean cortisol secretion is higher in insomniacs than in controls. There's an around-the clock activation of the HPAA. Because of their hypercortisolism, chronic insomniacs are at risk for medical problems (Vgontzas et al., 1999/2001). Cortisol levels upon awakening are low in primary insomniacs and amongst subjects with frequent nightly awakenings (Vgontzas et al., 2001; Backhaus et al., 2004; Bower et al., 2004). People with sleep deprivation have an increased evening cortisol level (Spiegel K. et al., 1999; Vgontzas et al., 2001).

Hypothesis 2c: Women with flattened cortisol levels and fatigue have more severe and aggressive cancer and therefore a worse prognosis and/or outcome.

There's an association between the CAR and psychosocial variables, stress and health (Clow et al., 2004). Adverse early life influences may have a harmful effect later in life and are a risk factor for stress-related disorders (de Kloet et al., 2005; Kaplan et al., 2008). Exposure to

stress hormones such as glucocorticoids during early pre- or postnatal development may lead to cardiac, metabolic, autoimmune, neurological and psychiatric disorders (Repetti et al., 2002; Seckl, 2004; Luecken et al., 2004; de Kloet et al., 2005 ; Mesquita et al., 2009). Excessive fetal exposure to glucocorticoids due to stress reduces fetal growth. Inhibited fetal growth increases risk for the development of chronic diseases in adult life. Reduced birth weight is for example related to cardiovascular risk factors and behavioural abnormities and depression and as an adult, they have higher cortisol levels (Barker, 1995; Kiecolt-Glaser et al., 2002; Raison & Miller, 2003; Kapoor et al., 2006/2008; Meaney at al., 2007; Kajantie et al., 2007; Seckl &Holmes, 2007; Philips, 2007; Silveira et al., 2007). In mice, chronic prepartum mild stress exposure increases estradiol and corticosterone levels during pregnancy (Misdrahi et al., 2005). Fetal exposure to xenoestrogens is a risk factor for breast cancer (McCormack, 2003; Soto et al., 2008; Ruder et al., 2008; dos Santos Silva et al., 2008). Other factors like fetal growth, birth size and birth weight are also linked to breast cancer (please refer to 2.6.3. and 2.6.4.).

Maternal death could be involved in cancer development (Jacobs & Bovasso, 2000). Women exposed to stress and starvation during childhood and adolescence are at higher risk of dying from breast cancer (Koupil et al., 2009). Adverse childhood experiences are a risk factor for women in cancer development via a direct biological effect. An accumulation of adverse early life influences are a strong predictor of cancer (Kelly-Irving et al., 2013).

We'd like to analyze if there's also a link with breast cancer.

Hypothesis 3a: Breast cancer patients with more pre-/postnatal stress have a higher CAR.

Hypothesis 3b: Women with stress during the pre-/postnatal period have more severe and aggressive breast cancer and therefore a worse prognosis and/or outcome.

Chapter 3

Design : Materials and Methods

3. Design: Materials and methods

3.1. Study participants

The study protocol was approved by the National Ethics Committee of Luxembourg on 13th of April 2005 and written consent was given by all the study participants.

Two hundred female patients between 35 and 70 years with breast cancer, before beginning their radiotherapy treatment at the Centre François Baclesse and without exclusion factors (see 3.3.) were recruited. Unfortunately, nearly half of them abandoned the study as it was too much stress for them. So, only 110 were finally enrolled in the study (mean age: 51,06). But even those 110 participants have missing values. None of them were on hormone treatment, some had undergone surgery and chemotherapy before radiotherapy and some of them had only had surgery. The participants were from 13 different nationalities. All of them understood either French or German.

After looking at the results of the questionnaire "Parental Bonding Instrument" (PBI), it was decided to create a separate control group for this questionnaire to see if the results were a coincidence or whether they could be used for interpretation. The 83 members of the control group were all female and only completed the "Parental Bonding Instrument". They were all between 35 and 70 years old and had no serious medical illness. They all understood either French or German.

3.2. Method of recruitment

When receiving the patient's medical record, it was verified that she was a breast cancer patient and whether there were any exclusion factors (see 3.3.). Then, the secretary in charge of admissions was informed that there was a potential participant for the study. After the registration and admission procedure of this patient, the secretary explained that there was an ongoing study in the centre examining the link between stress and breast cancer and that if she wanted to participate, the psychologist would give her more explanations after she had seen the doctor. Once the patient was interested, the whole study was explained in details (questionnaires, samples of saliva cortisol, etc). The patient received a number as participation was anonymous and the questionnaires and material for saliva samples. After having clarified everything, the participants signed an informed consent form and received a written information about the study.

The PBI-control group was recruited using advertisements and personal solicitation. The members of the control group had to be age-matched females with no history of cancer.

3.3. Inclusion and exclusion criteria

The participants had to be female patients with their first diagnosis of breast cancer. They had to be between 35 and 70 years, without hormone therapy and no metastasis. They had to understand either French or German, have no severe psychiatric disorders (psychosis, severe depression, etc), no previous cancer diagnosis and no cortisone treatment.

3.4. Demographic, medical and psychometric assessments

Six different questionnaires were used to make these assessments. One of them was developed by Professor Hellhammer (NPQ-PSQ; see 3.4.3.1.), two of them are regularly used during studies with cancer patients (FACIT-F and FBK-R23: see 3.4.3.3., 3.4.3.2.). The "Trierer Inventar zum chronischen Stress" (TICS) from Schulz, Schlotz and Becker (2004) is a questionnaire which assesses perceived chronic stress during the last three months (see 3.4.3.5.). The "Fragebogen zu ihrer Kindheit" is the German translation from the "Parental Bonding Instrument" (PBI) and it is used to assess the perceived parental upbringing style (see 3.4.3.4.). Finally the German version form the "PRIME MD Patient Health Questionnaire" (PHQ-D) and the translated French version were used to screen for psychiatric disorders (3.4.3.6.).

3.4.1. Demographic assessment

Demographic data including age, marital status, and job situation were assessed by our secretary during the first visit of the participants to the radiotherapy centre. In fact she does this for all our patients, to complete registration. So we didn't need to make them fill in another questionnaire. The investigator could use the regular file of the radiotherapy centre to collect data for the study.

3.4.2. Medical assessment

3.4.2.1. Information about cancer

Some medical information, related to breast cancer (stage, lymphnodes, medical treatment, etc) was collected using the medical records of the participant. This was sent to the centre before their first visit. All information about the illness was digitally recorded and accessible to the investigator.

3.4.3. Psychometric assessment

Most of the questionnaires were also translated to French, as some of the people living in Luxembourg are French speaking only. The participants chose between the German and the French version. They were of course translated back to German afterwards to ensure the accuracy of the translation.

The fatigue questionnaire existed also in French, so it didn't need to be translated.

All the questionnaires answered by the participants before the beginning of the radiotherapy treatment, were handed back to the assessor during the first week of radiotherapy.

3.4.3.1. PSQ – Pre-/Peri-/Postnatal Stress Questionnaire

This questionnaire tries to assess the physical and/or psychological factors of stress before or after birth. It is also completed by the patient at home who may be assisted by parents' information.

3.4.3.2. Questionnaire on Stress in Cancer (QSC-R23)/ (Fragebogen zur Belastung von Krebskranken (FBK – R23))

This is a short (one page), disease-specific questionnaire for the assessment of psychosocial stress in cancer patients. It has been developed and revised twice by Herschbach et al (2003). It consists of 23 items measuring five categories: psychosomatic complaints, anxiety, lack of information, restrictions of daily activities and social complaints. Answers to the different items go from 0 (doesn't apply) to 5 (very high burden). Internal consistency and reliability are satisfying and validity is very good. It has also been shown to have a good construct and convergent validity. Validity studies show high correlation with the QLSM-Health-Module, the Symptom Checklist-90-Revised (SCL-90-R) and the Functional Assessment of Cancer Therapy (FACT). Mean values of every subscale is 3 and for the total score it is 12. There is an indication for psychological help (due to psychosocial stress) if there are a minimum of for example two times 5 or one time 5 and four times 4 or five times 4 (Herschbach et al., 2003).

3.4.3.3. Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT – F)

The FACIT Measurement System is a collection of different quality of life questionnaires targeted to the management of chronic illness. Those questionnaires are some of the most commonly used in national and international research. This one is specific for fatigue and it has 40 items. There are five subdivisions: physical well-being, social well-being, emotional well-being, functional well-being and fatigue. Responses to the items are on a 5-point scale,

ranging from 0 (not at all) to 4 (very much). The higher the score, the better the quality of life. General population norms in females for the G-score (quality of life) range from 77 to 82 and Cancer population norms in females range from 79 to 82. In breast cancer patients mean value is 84.9. It has good reliability and validity (Webster et al., 2003).

3.4.3.4. Parental Bonding Instrument (PBI)

The English version was developed by Parker, Tupling and Brown (1979). The two variables measured are parental styles "care" and "overprotection", as perceived by the child. It is a retrospective measure and it enquires about the quality of parental bonding during the first 16 years of life. There are 25 questions, 12 "care" and 13 "overprotection" items. Numerous populations have been studied (Parker et al., 1979) for reliability. There are four quadrants to which the parents can "belong": optimal parenting = high care and low protection; affectionate constraint = high care and high protection; affectionless control = high protection and low care; neglectful parenting = low care and low protection. Questions are the same for the mother and the father and are answered individually for each parent on a four-point scale. The cut-off scores differ for mothers and fathers. The questionnaire has been found to have good reliability and validity based on several studies. It has also been shown to have satisfactory construct and convergent validity (Parker G., 1983). Mood state and life experience seem to have little effect on the stability of the perception of parenting as measured by the PBI. No differences were found in the scores over time on the variables examined (gender, depression, life events, etc). Parental evaluation is a stable measure which is not affected by dysthymia and depressive episodes for example (Wilhelm et al., 2005).

3.4.3.5. Trierer Inventar zum chronischen Stress (TICS)

This questionnaire has been developed by Schulz, Schlotz and Becker (2004). It measures the stress perceived by the participants during the last three months. It has 57 items divided into nine categories. *Overwork*: if a person has too much to do quantitatively at work or at home, *Social overload:* if someone has too many social requirements to meet which implicate a lot of responsibilities. *Pressure of success*: if not fulfilling a requirement correctly results in negative consequences. *Unsatisfaction with work or duty*: if one doesn't like the duties or the work one has to fulfil. *Overcharge at work or duty*: if one feels at fault at work or at home and if one doesn't succeed, even with great effort. *Lack of social recognition*: even after making great efforts or doing good work, one doesn't' receive recognition, respect or sympathy. *Social tension*: if someone wants to achieve a goal that is in conflict with others around him.

Social isolation: if a person doesn't have enough or satisfactory social contacts and resources. *Chronic apprehension*: internal stress about what negative things may happen in the future. In addition, *chronic stress* can be globally assessed by 12 items. There are different forms of norm data, depending on the age of the persons. Reliability and validity are good for the 10 scales (Schulz et al., 1999).
The breast cancer patients had to fill it out by basing themselves on the time BEFORE cancer diagnosis.

3.4.3.6. Gesundheitsfragebogen für Patienten (PHQ-D)

The PRIME-MD (Primary Care Evaluation of Mental Disorders) is used to screen for psychiatric disorders and the items are based upon the diagnostic criteria from DSM-IV. The "Prime MD Patient Health Questionnaire" (PHQ) was developed afterwards and is a self-administrated version of the original PRIME-MD (Spitzer et al.). It consists of items concerning depression, anxiety, panic disorders, eating disorders, somatic disorders and stress. Internal consistency and validity of this questionnaire is good. The German version (PHQ-D) was developed by Löwe, Spitzer, Zipfel and Herzog (2002). Internal consistency and validity of the german version of this questionnaire is good (Gräfe et al.). The depressive subscale has values from 0-27, the somatic disorders subscale from 0-30 and the stress subscale from 0-20.
There's one German study with a representative random sample (N=2066) and the manual indicates cut-off scores for the depression scale (mean value = 3,56, SD = 4,08). Patients with a score between 5 and 10 have a mild depression. Patients with a score beyond 10 have a Major Depression (10-14: mild; 15-19: heavy; 20-27: very heavy). An american study indicates cut-off scores for the subscale somatic disorder (5 =light, 10 = mild, 15 = heavy). There are no norms or cut-off scores for the stress subscale.

3.5. Experimental protocol

Saliva was collected by passive drooling into small tubes. The participants had to take saliva samples several times a day for three days. They had to make three complete wake-up and daily profiles. The first day was the day when they underwent a simulation of the treatment. A very stressful moment, as they see the machines for the first time. It takes a long time to make the simulation and they are instructed not to move during this procedure. So, this could be considered as an exposure to stress. Saliva samples were taken at time of wake-up, 30 minutes later, 45 minutes later, an hour later than wake-up, at eight o'clock (if it wasn't part of this wake-up hour), before the beginning of the simulation, and after the end of simulation (one

hour later), at 11o'clock (if this wasn't during simulation), at 15h (if this wasn't during simulation) and at 20h. The second day was the day after the simulation and it is used for comparison, the participants had no appointment at the radiotherapy centre. Saliva samples were taken at time of wake-up, 30 minutes later, 45 minutes later, an hour later than wake-up, at eight o'clock (if it wasn't part of this wake-up hour), at the same time as they had begun the simulation the day before, half an hour later and one hour later, at 11 o'clock (if this wasn't during simulation time), at 15h (if this wasn't during simulation time) and at 20h. The third and last day of saliva collection was the first day of treatment. On this day, saliva samples were taken at time of wake-up, 30 minutes later, 45 minutes later, an hour later than wake-up, at eight o'clock (if it wasn't part of this wake-up hour), before the beginning of the treatment and half an hour later, at 11 o'clock (if this wasn't during treatment time), at 15h (if this wasn't during treatment time) and at 20h. During the hour after wake-up, they didn't eat anything, didn't brush their teeth and didn't smoke.

Once the saliva container was full, the saliva sample was stored in the freezer (-20°) by the participant. Once they had finished the three days, they delivered the samples to the investigator who immediately stored them in another freezer (-20°).

The questionnaires were filled in by the participants in the time between simulation and the first treatment day and handed over to the investigator at the same time as the saliva samples.

3.6. Laboratory assays

3.6.1. Salivary Cortisol

All saliva samples were stored at –20° until analyses. During transportation from the home of the assessor to the laboratory of the University, or from the home of the patient to the home of the assessor, they weren't stored at – 20°, but a short interruption would not affect the concentration of cortisol in saliva (Kirschbaum & Hellhammer, 1989). Salivary cortisol was measured with a time-resolved fluorescence immunoassay at the labatory of the University of Trier (Dressendörfer et al., 1992). All samples from the different participants were analyzed in the same run in order to minimize error variance due to inter-assay imprecision. Intra-assay variability was between 4.0% and 6.7% and inter-assay variability between 7.1% and 9%.

3.7. Statistical analyses

All data were analyzed using SPSS with the help and under the supervision of Malgorzata Kaszynska from DAACRO.

Chapter 4

Results

4. Results

Some of the data report descriptive analyses. For other results, tests such as Greenhouse-Geisser, Huynh-Feldt and ANOVA as well as post-hoc tests were applied. We are analyzing and describing the results for the cortisol values, the tests, and we are looking at them in order to verify or not the hypotheses.

4.1. Socio-demographic characteristics

One hundred and ten patients were included in the study. They were between 35 and 70 years old with a mean age of 51,06. All participants were Caucasians, but had 13 different nationalities. 62,72% were Luxembourgers, 4,55% were French, 1,82 % were Spanish, 2,73% were Italian, 11,82% were Belgian, 5,45% were Dutch, 0,91 were Hungarian, 0,91% were Finnish, 2,73% were Portuguese, 0,91% were Danish, 3,64% were German, 0,91% were English and 0,91% were Swedish. Ninety-two patients or 83,64% either had a partner or were married and 18 patients or 16,36% were single.

4.2. Medical characteristics

Fifty-five patients (50%) had chemotherapy whereas 55 patients (50%) did not have chemotherapy. A hundred and two participants (92,73%) did not have Herceptine and eight participants (7,27%) did. All of the patients who received Herceptine also had chemotherapy. 76,4% have a good prognosis whereas 23,6% (27 patients) have quite a poor prognosis. Only one of the patients treated with Herceptine had higher cortisol values, the others were within the norms.

Fifty-six patients were premenopausal and 54 postmenopausal. Fifteen patients with a bad prognosis were premenopausal and 12 were postmenopausal.

4.3. Results for Hypothesis 1: *Breast cancer patients reporting perceived chronic stress have a higher or a lower CAR as compared to healthy women.*

To test hypothesis 1, we analyzed the results of the TICS to test for chronic stress in patients with breast cancer. First we analyzed the results of the FBK-R23 and the PHQ-D to see if these may interfere with, or falsify the results of the TICS.

After that, we studied the cortisol values using ANOVA and post-hoc tests, and we used the Ward-method to see whether breast cancer patients with perceived chronic stress also have abnormal CAR values.

4.3.1. Fragebogen zur Belastung von Krebskranken (FBK)

Please see 3.4.3.2. for description of the questionnaire.

Results couldn't be compared to those of healthy people as the questionnaire had been developed only for cancer patients. The score was higher than compared to other cancer patients (mean=12) but nevertheless not many patients had a result that indicated that they needed psychological help. A possible explanation is that breast cancer patients are only women and nearly for all other cancers, there are men and women. And for women, the scores are normally higher. Anxiety was for example higher compared to other cancer patients (mean=3) as well as psychosomatic complaints (mean=3). These breast cancer patients didn't appear to be extremely stressed by their illness. Even if the average score was higher than the mean of other cancer patients, a score of 23,7 of 115 didnn't seem to be excessive. So the illness in itself (preceived stress due to the illness) didn't seem to interfere much with the results of for example the TICS.

Tab 1: Results for FBK-R

	Mean	N	Standard deviation
FBK-score/115	23,69	107	15,49
FBK-psychosoma/25	8,01	108	5,515
FBK-anxiety/20	5,76	108	5,091
FBK-infolack/20	1,58	108	2,357
FBK-dailyrestr/25	5,27	108	4,525
FBK-soccomp/25	3,19	108	3,785

4.3.2. PHQ-D

Please see 3.4.3.6. for description of the questionnaire.

This is an evaluation essentially based on criteria (DSM-IV) and not on norms. There's one German study with a representative random sample (N=2066) providing norm values for the depression scale (mean value = 3,56, SD = 4,08) and one American study indicating norms for the subscale somatic complaints (5=light, 10=mild, 15=heavy).

These breast cancer patients had an average score for depression of 7,1 (mild depression as the mean value is 3,56) and a score of 8,87 on the somatic subscale (light). The mean value for the stress scale was 5,27, which also seems to be quite low as it may vary between 0 and 20. In this study, 0 was the lowest value for stress and 16 the highest. The results reflected the results of the FBK-R23 where the values for psychosomatic complaints were also a bit higher

than the mean values. As for the FBK, this didn't seem to have an influence on the other results (as for example on the results of the TICS).

4.3.3. Trierer Inventar zum chronischen Stress (TICS) (T-values)

Please go to 3.4.3.5. for description.

The mean values of the single TICS scales deviated, in part, from those of the norms. Our breast cancer patients reported less social overload and pressure for success but higher overcharge, chronic apprehension, and chronic stress. There was also a tendency for higher scores on the social isolation subscale.

Mean values were though between 48 and 54 which showed an average mark on every subscale. The participants seemed to be a "normally" stressed population, they didn't seem to be much more stressed than healthy persons (comparison to the norms).

Tab 2: Results for TICS

	Mean	N	Standard deviation	Minimum	Maximum
TICS-UEBE	48,76	110	12,167	20	78
TICS-SOUE	46,48	110	13,154	16	90
TICS-ERDR	43,16	110	12,397	17	80
TICS-UNZU	49,33	110	11,665	20	78
TICS-UEFO	53,63	110	11,711	32	77
TICS-MANG	51,13	110	11,322	30	78
TICS-SOZS	49,49	110	11,893	27	83
TICS-SOZI	51,65	110	9,847	29	71
TICS-SORG	53,91	110	9,673	29	80
TICS-SSCS	53,25	110	11,704	16	82

Tab 3: Results for TICS

	Mean Value	SD	N	t	df
Norm (x)	50	10	604		357 .20 < p >
UEBE (y)	48,76	12,17	110	1,01	.15
SOUE (y)	46,48	13,15	110	2,67	**p < .01**
ERDR (y)	43,16	12,40	110	5,47	**p < .001** .30 < p >
UNZU (y)	49,33	11,67	110	0,57 -	.25
UEFO (y)	53,63	11,71	110	3,05 -	**p < .01** .20 < p >
MANG (y)	51,13	11,32	110	0,98	.15 .35 < p >
SOZS (y)	49,49	11,89	110	0,42 -	.30 **.10 < p >**
SOZI (y)	51,65	9,85	110	1,61 -	**.05**
SORG (y)	53,91	9,67	110	3,88 -	**p < .001**
SSCS (y)	53,25	11,70	110	2,73	**p < .01**

4.3.4. Cortisol values

Participants had to deliver three daily cortisol profiles. Day 1 was the day of the simulation. Day 2 was the baseline day (no treatment) and day 3 was the first day of radiotherapy (generally a week after the simulation).

Only one of the patients treated with Herceptine had higher cortisol values, the others were within the norms. There was no significant difference in cortisol values between the patients who underwent chemotherapy (with or without Herceptine) and those who didn't. Only the percentile difference between pre- and post values on the baseline day was significant and the absolute values between those values tended to be significant (please refer to Appendix 1 for exact results).

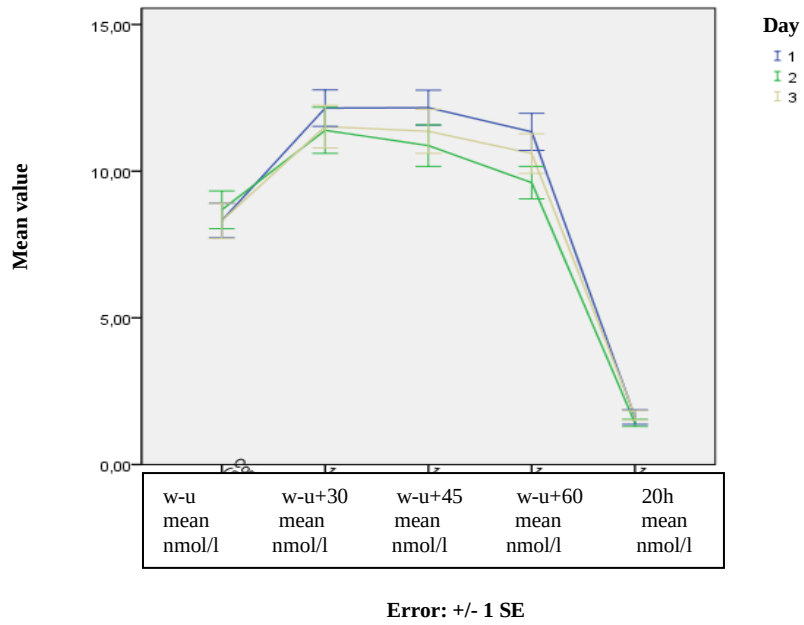

Fig6: mean values for CAR of the 3 days

Using multivariate ANOVA, "time" became significant, but the cortisol profiles of the three days didn't differ significantly.

Looking at the single measure values and the single AUC-values (oneway ANOVA), a significant difference between the 3 days could be observed at the AUCi and at the maximum and mean increase. There was also a tendency at the w-u+60 value. Post-hoc tests (Games Howell) showed that the w-u+60 values of the day of simulation and the baseline day differed from each other. They were higher on the day of simulation than on the baseline day.

As for AUCi, the values of the day of simulation also differed significantly from those of the baseline day. The AUCi was higher on the day of simulation, the mean AUCi was lower on the day of radiotherapy and using Post-hoc tests, these findings were almost significant.

The maximum and mean increases on the day of simulation were significantly higher than on the baseline day.

4.3.4.1. Comparison with norm values

The comparison group consisted of 185 healthy women. They were from three different studies: a teacher-study from Brigitte Kudielka, a world war-study from Petra Pütz and an acne-study from Anna Tegeler. In these three studies, the women had to generate cortisol profiles over two days. That's why day 1 and 2 from this present study could be compared to day 1 and 2 from the comparison group. The mean values of the two days and the three days

respectively could also be compared. The comparison group didn't differ significantly from the breast cancer group (t = -.575, p = .565).

ANOVAS were made with the individual values and Oneway-ANOVAS with the AUCi, AUCg and the maximum and mean increase. In every analysis there were significant group belonging effects. Breast cancer patients had almost the same wake-up values as the norm women (mean values were slightly higher) but the values increased less in the hour following awakening which could also be seen in the AUC measuring. This was true for all three days. But looking at it in a descriptive manner, the difference with the norm group was more evident on the baseline day.

(please refer to appendix 2)

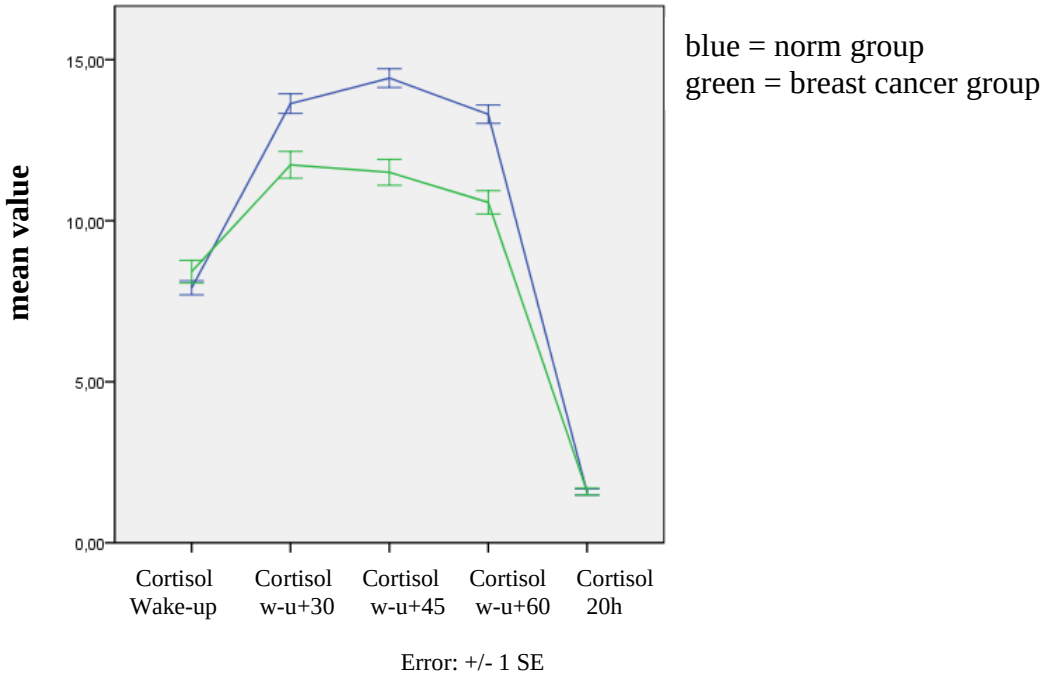

Fig 7 : mean cortisol values of healthy women and women with breast cancer on day 1

Tab 4: descriptive CAR values of norm and breast cancer group

		Group		
		Norm	Breast cancer	Total
Area under the curve ground (AUCg)	Mean	740,9916	633,3885	691,6308
	N	341	289	630
	Standard deviation	251,52839	360,03929	310,53251
	Minimum	199,05	15,75	15,75
	Maximum	1590,00	3066,00	3066,00
Area under the curve increase (AUCi)	Mean	267,6937	125,7760	202,5918
	N	341	289	630
	Standard deviation	231,36793	245,87869	248,24515
	Minimum	-541,99	-1128,00	-1128,00
	Maximum	1221,69	1601,25	1601,25
Mean increase	Mean	5,8868	2,6171	4,3869
	N	341	289	630
	Standard deviation	5,17231	5,48553	5,55855
	Minimum	-10,86	-25,99	-25,99
	Maximum	28,24	32,07	32,07
Maximum increase	Mean	8,2728	4,8621	6,7082
	N	341	289	630
	Standard deviation	5,88690	6,20390	6,26486
	Minimum	-5,04	-21,43	-21,43
	Maximum	31,52	42,38	42,38

(for figures please refer to appendix 3)

Tab 5 : Variances between norm and breast cancer women

One way-ANOVA

		Sum of squares	df	Root mean square	F	Significancy
Cortisol awakening Response (CAR) Area under the curve ground (AUCg) Day 1	Between the groups	1811178,923	1	1811178,923	19,330	**,000**
	In the groups	5,884E7	628	93699,949		
	Total	6,065E7	629			
Cortisol awakening Response (CAR) Area under the curve increase (AUCi) Day 1	Between the groups	3150535,192	1	3150535,192	55,558	**,000**
	In the groups	3,561E7	628	56707,011		
	Total	3,876E7	629			
Cortisol awakening Response (CAR) mean increase Day 1	Between the groups	1672,324	1	1672,324	59,127	**,000**
	In the groups	17762,173	628	28,284		
	Total	19434,497	629			
Cortisol awakening Response (CAR) maximum increase Day 1	Between the groups	1819,729	1	1819,729	49,974	**,000**
	In the groups	22867,585	628	36,413		
	Total	24687,314	629			

(For other tests please refer to appendix 4)

4.3.5. Cortisol profile and perceived chronic stress (TICS)

As already stated, the FBK and PHQ-D showed that the illness didn't seem to interfere with the following results.

The participants were defined as chronically stressed (perceived stress) if they had a T-value higher than 60 on the screening scale. This was one SD above the mean value of 50. Thirty-one breast cancer patients seemed to perceive chronic stress.

No significant correlation was found between TICS-screening data and CAR values. The CAR-values had a significant correlation with each other.

(please see appendix 5 for tables)

Sixty-six participants had a complete CAR profile, a 20h value for cortisol and a complete TICS questionnaire. A cluster analysis with cortisol values (CAR and 20h) and TICS values was made. This led to two clusters. The first cluster had high TICS values and quite normal wake-up values (10nmol/l) with increases to 15,6 nmol/l, whereas the second cluster had normal values for the TICS and a flatter cortisol profile.

The differences between the clusters were significant for the TICS values and for the cortisol values.

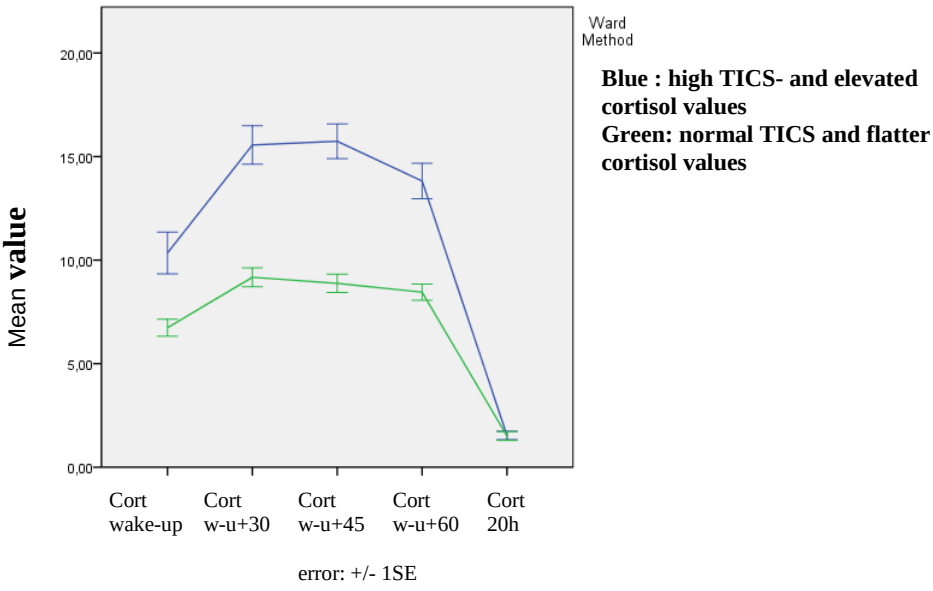

Fig 8 : the difference between the 2 clusters in chronically stressed and not stressed participants

Tab 6: values of TICS and cortisol

Ward Method		TICS-SSCS	Cortisol mean value 20h	Cortisol mean value wake-up	Cortisol mean value w-u+30	Cortisol mean value w-u+45	Cortisol meanvalue w-u+60
1	Mean	58,85	1,5356	10,3475	15,5596	15,7383	13,8202
	N	27	27	27	27	27	27
	Standard deviation	8,904	1,06249	5,24364	4,82068	4,35636	4,44854
2	Mean	48,62	1,5033	6,7381	9,1696	8,8789	8,4525
	N	39	39	39	39	39	39
	Standard deviation	11,796	1,31260	2,55656	2,83465	2,77345	2,45971
Total	Mean	52,80	1,5165	8,2147	11,7837	11,6850	10,6484
	N	66	66	66	66	66	66
	Standard deviation	11,780	1,20792	4,24465	4,90058	4,86178	4,30408

(please refer to appendix 6 for ANOVA)

Hypothesis 1 was falsified. The statistical tests didn't show a link between perceived stress and abnormal CAR values. Their cortisol values were normal compared to a healthy population.

4.4. Results for Hypothesis 2a: ***Women with abnormal cortisol levels have more aggressive and severe breast cancer (****bigger tumor, aggressive grade, lymphnodes, etc)* ***and a worse prognosis and/or outcome.***

To test this hypothesis, t-test and ANOVA were calculated with the increase values (pre-/post values on simulation and baseline day) to see wether the groups (good prognosis/bad prognosis) differed or not. Then a chi-square test of the AUCg was made for the same purpose. Interestingly, most of the persons with a deviation in the AUC had lower values than the norm.

4.4.1. Difference between patients with a poor prognosis and with or without pre-/post cortisol increases

When t-tests were calculated with the difference values (increase values) between the pre/ and post measurement, we could see that the groups don't differ significantly. When an ANOVA was made with the single pre-post values, the effect of the "prognosis group" tended to become slightly significant. Patients with a poor prognosis had slightly higher cortisol pre-/post values on the baseline day and slightly lower on the simulation day. Those with a bad prognosis seemed to have a reduced reaction to an acute stressor (simulation).

4.4.2. Patients with abnormal cortisol values and prognosis

The patients with an AUCg with more than one standard deviation (N=33) were compared to the patients with a normal value of the AUCg using a chi-square test concerning their prognosis. These results were not significant**.** Seven women had an abnormal AUCg *and* perceived chronic stress (TICS). None of them had a bad prognosis.

In sum, hypothesis 2a could not be verified.

4.5. Hypothesis 2b: *Women with chronic stress (perceived stress, pre-/postnatal stress plus abnormal cortisol values) have a more severe and aggressive breast cancer and therefore a worse prognosis and/or outcome.*

To verify or falsify this hypothesis, we first started to study the TICS values using a logistic regression and a chi-square test. After that we made logistic regressions to analyze whether perceived chronic stress, abnormal cortisol values, pre-/postnatal stress factors and the interaction of all three were linked to worse prognosis.

4.5.1 Perceived chronic stress and prognosis

A logistic regression with the criteria "bad prognosis" and the TICS-screening value as predictor was conducted as well as a chi-square test with the dichotomic classification "chronic stress" and "no chronic stress". Perceived chronic stress didn't seem to be a criterion for a worse prognosis.

4.5.2. All three factors and prognosis

Two logistic regressions were made. One with the predictors "TICS-screening value", "AUCg", "pre-/postnatal stress yes/no" and the interaction of these factors. The other with "TICS-screening values", "AUCg", "sum pre-/postnatal stress PSQ" and the interaction of the three factors. There were no significant results, the factors did not predict a bad prognosis. ***Thus, hypothesis 2b couldn't be verified.***

4.6. Results for Hypothesis 2c: *Women with higher and/or flattened cortisol levels and fatigue have more severe and aggressive cancer and therefore a worse prognosis and/or outcome.*

To analyze this one, a chi-square test was made concerning fatigue and bad prognosis. Then ANOVAS were made to see the interaction between abnormal cortisol values and fatigue.

4.6.1. Functional Assessment of chronic illness therapy-Fatigue (FACIT-F)

See 3.4.3.3. for description.

Tab 7: values for the FACIT

	Mean	N	Standard deviation	Minimum	Maximum
FACIT-TOI /108	75,1113	106	21,10961	22,00	106,00
FACIT-G /108	79,0368	106	15,76171	32,00	106,00
FACIT-F /160	114,8033	106	26,26351	41,00	156,00
FACIT-FS /52	35,7844	106	11,97398	4,00	52,00

When comparing to norms, we saw that 32 from 106 patients did suffer from fatigue (FACIT-FS/FACIT-F). Fourteen patients with a bad prognosis suffered from fatigue and 11 didn't. It could also be seen that 18 breast cancer patients had a good prognosis, but did also suffer from fatigue.

A chi-square test was made concerning fatigue and a bad prognosis and the result was significant.

Tab 8: Results for fatigue and bad prognosis

bad prognosis and fatigue ?

			Fatigue		
			no	yes	total
bad prognosis	no	number	63	18	81
		Expected number	56,5	24,5	81,0
	yes	number	11	14	25
		Expected number	17,5	7,5	25,0
Total		number	74	32	106
		Expected number	74,0	32,0	106,0

A chi-square test was performed that revealed significance for an association of fatigue and a bad prognosis.

Tab 9: results of chi-square tests

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-square after Pearson	10,342[a]	1	,001		
Correction of continuation	8,802	1	,003		
Likelihood-Quotient	9,731	1	,002		
Exact Test after Fisher				,002	,002
Link linear-with-linear	10,245	1	,001		
Number of valid cases	106				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 7,55.
b. only calculated for a 2x2 table

Two ANOVAS were calculated with fatigue as a factor for the cortisol daily profile. One ANOVA with only the CAR values and one with the CAR and 20h values. No significant interaction was observed. However, in a descriptive manner, the cortisol profiles from breast cancer patients with fatigue seemed to be slightly flatter.

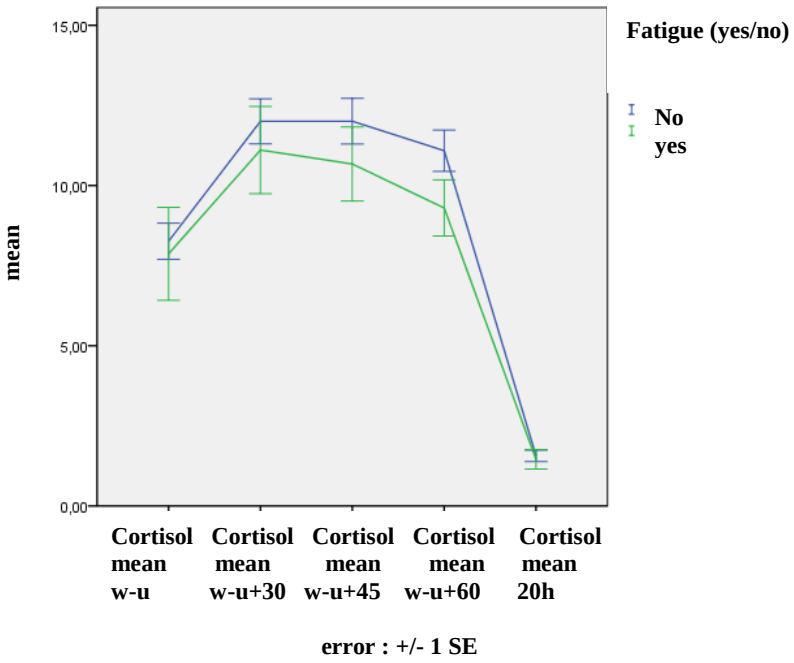

Fig 9: representation of the cortisol profiles from breast cancer patients with and without fatigue

This hypothesis could be verified as there was a link between fatigue and bad prognosis, and breast cancer patients with fatigue had flatter cortisol profiles.

4.7. Results for Hypothesis 3a: *Breast cancer patients with more pre-/postnatal stress have a higher CAR.*

Here, we studied the different results of the questionnaires inquiring about pre-/postnatal stress factors. We first analyzed the results of the PBI in breast cancer patients and the control group using a Oneway ANOVA. After this, we treated the results of the PSQ by using different tests and then we tried to see whether patients with more pre-postnatal stress factors had a higher CAR and which factors did have an influence on the CAR.

4.7.1. Parental bonding Instrument (PBI)

See description of the PBI in 3.4.3.4.

An age-matched healthy control group (N=83) completed the PBI-questionnaire. Comparing the scores of the subscale “care” and “protection” of breast cancer patients with those of the

control group (Oneway ANOVA), significant group effects could be found for “care” and a tendency effect was found for protection ($p < .10$). Breast cancer patients had lower values for the subscale “care” for both parents and higher values for “protection”.

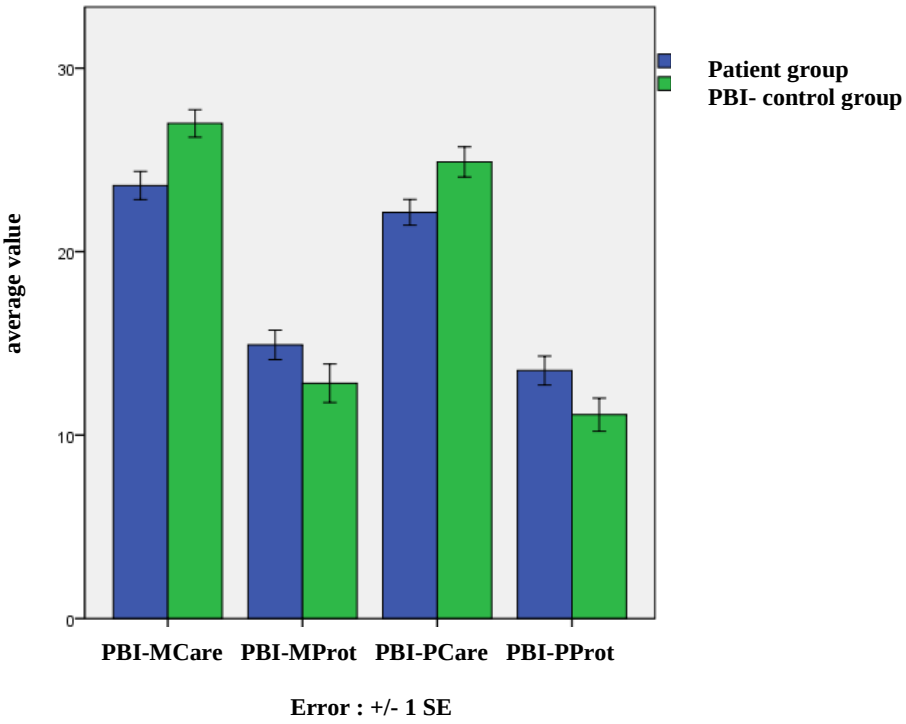

Fig 10 : average values of parental care and protection in control and patient group

Please refer to appendix 7 for results of the PBI.

Tab 10: Results of Oneway Anova for the PBI

ONEWAY ANOVA

		Sum of squares	df	Root mean square	F	Significancy
PBI-MCare	Between the groups	579,865	1	579,865	10,047	,002
	In the groups	10908,439	189	57,717		
	Total	11488,304	190			
PBI-PCare	Between the groups	371,358	1	371,358	6,976	,009
	In the groups	9900,829	186	53,230		
	Total	10272,186	187			
PBI-MProt	Between the groups	236,280	1	236,280	3,055	,082
	In the groups	14616,966	189	77,338		
	Total	14853,246	190			
PBI-PProt	Between the groups	231,649	1	231,649	3,490	,063
	In the groups	12345,011	186	66,371		
	Total	12576,660	187			

In the patient group, the bonding style “Affectionless control” occured more often than “optimal parenting”. The chi-square test was significant.

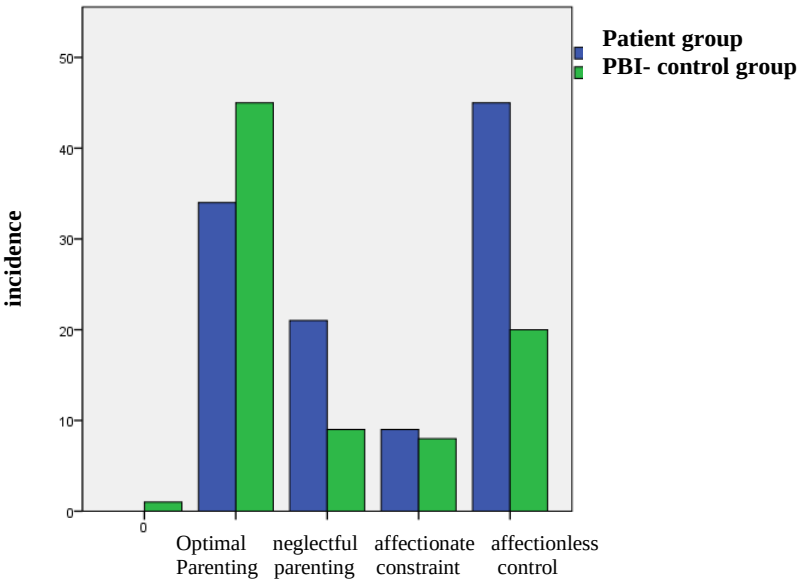

Fig 11 : incidence of bonding style in controls and patients

(please refer to appendix 8 for results for differences in maternal and paternal style)

4.7.2. Pre-/Peri-/Postnatal Stress Questionnaire (PSQ)

For description, please refer to 3.4.3.1. We applied the first version of this test.

The participants were divided into three different categories: prenatal stress, postnatal stress and pre-/postnatal stress. A few more than two thirds of the breast cancer patients reported pre- or postnatal stress.

(please refer to appendix 9 for tables)

The PSQ has mainly dichotomic (yes/no) variables but some are also continuous, for example: during which week of her pregnancy did your mother know that she was pregnant, birth weight, gestational age, length at birth, etc.

Using length at birth and birth weight, the Kaub-Index (g/cm) and the Quetelet-Index/BMI (kg/m^2) were also calculated.

A control group for some data existed, but the mean age for the control group was younger (27,75 versus 51,06 years of age).

Different sums of the dichotomic items were calculated: 1) sum of prenatal stressors, 2) sum of perinatal complications, 3) sum of postnatal stressors, 5) sum of pre- and postnatal stressors. The incidence of the dichotomic items of the patients and the control group were compared using chi-square tests. The sum variables were compared using ANOVA and Mann-Whithney-U-tests.

There were no differences for the continuous variables between the two groups. Excluding the youngest, there were differences in the chi-square tests.

4.7.2.1. Chi-square tests

4.7.2.1.1. Prenatal factors

The test became significant in the category "financial worries". A tendency significance (p=.053 and .066) was found for "tobacco consumption" and "lack of social support". In the patient group, there was less tobacco consumption than expected but more lack of social support. After excluding the youngest women in the control group, the effects became insignificant. And there was a significant effect for "desire of pregnancy". Patients were less desired by their parents than expected.

(please refer to appendix10 for tables)

4.7.2.1.2. Perinatal factors

The dichotomic items were significant in two cases: "other complications during birth" and "other measures after birth" (each time $p < 0.001$). Fewer patients than expected reported of other complications and measures during and after birth. If the youngest controls were excluded, there were no more significant cases (please refer to appendix 11 for results).

4.7.2.1.3. Postnatal factors

The test became significant or tended to become significant in four cases. It tended to become significant in the case of "tobacco smoke" where patients were more often exposed to tobacco smoke than expected. It was significant in the cases of "breast-feeding", "lots of disputes in the family" and "other critical life events". Patients were less breastfed, had less disputes and fewer other life events than expected. When younger persons were excluded, the test for disputes was still significant but the others not. However, another became significant: less patients than expected were exposed to postnatal financial problems (please refer to appendix 12).

4.7.2.2. Mann-Whitney-U-tests with the pre-/peri- and postnatal stress-sum-variables

ANOVA and Mann-Whitney-U-tests showed highly significant group differences for postnatal factors. Breast cancer patients reported less postnatal stress factors than persons from the control group. The sum of pre-peri- and postnatal stress factors was also higher amongst the control group (postnatal factors were included). Breast cancer patients seemed to

have less pre-, peri- and postnatal stress factors (please refer to appendix 113 for descriptive statistics).

Tab 11: Results of Oneway Anova for pre-/peri- and postnatal factors

ONEWAY ANOVA

		Sum of squares	df	Root mean square	F	Significancy
sumPrenatal	Between the groups	,585	1	,585	,272	,602
	In the groups	653,650	304	2,150		
	Total	654,235	305			
sumPerinatal	Between the groups	1,707	1	1,707	1,968	,162
	In the groups	259,402	299	,868		
	Total	261,110	300			
sumPostnatal	Between the groups	15,031	1	15,031	6,909	***,009***
	In the groups	661,387	304	2,176		
	Total	676,418	305			
sumPreperipostnatal	Between the groups	25,164	1	25,164	3,342	***,069***
	In the groups	2311,730	307	7,530		
	Total	2336,893	308			
sumPrepostnatal	Between the groups	12,858	1	12,858	2,034	,155
	In the groups	1940,935	307	6,322		
	Total	1953,793	308			

For Ranks, please refer to Appendix 14

Tab 12: Results of Mann-Whitney-U-Tests for pre-/peri- and postnatal factor

Statistics for Test[a]

	sumPrenatal	sumPerinatal	sumPostnatal	sumPreperipostnatal	sumPrepostnatal
Mann-Whitney-U	10233,000	9241,500	8473,500	8813,500	9072,000
Wilcoxon-W	31554,000	13994,500	13523,500	14066,500	14325,000
Z	-,096	-1,121	-2,620	-2,381	-2,033
Asymptotic Significance (2-sided)	,924	,262	***,009***	***,017***	***,042***

a. Group variable: group

4.7.3. Birth parameters

There was a significant difference between breast cancer patients and the control group regarding gestational age and length at birth. Breast cancer patients were born a week earlier than control persons and were smaller at birth.

Tab 13: Results for birth parameters (patients and controls)

group		week, where the mother found out	birth: week	weight	length	Head circumference	Kaub-Index (g/cm)	Quetelet-Index / BMI (kg/m²)
Patient group	Mean	6,53	37,83	3303,14	50,35	33,50	64,5486	12,8273
	Median	6,00	39,00	3250,00	50,00	34,50	63,8627	12,5844
	N	36	45	70	54	4	52	52
	Standard deviation	3,621	3,212	596,593	2,396	2,380	9,10862	1,77193
	Minimum	2	28	2000	46	30	43,48	9,45
	Maximum	20	41	5000	60	35	94,12	18,45
PSQ-control group	Mean	6,27	39,00	3318,06	51,26	35,24	64,6156	12,6108
	Median	6,00	40,00	3330,00	51,00	35,00	64,8148	12,5740
	N	415	435	445	439	296	432	432
	Standard deviation	3,495	2,375	537,704	2,824	3,864	9,09252	1,81449
	Minimum	0	28	1070	35	21	28,16	5,13
	Maximum	39	46	5500	64	54	100,00	28,57
Total	Mean	6,29	38,89	3316,03	51,16	35,22	64,6084	12,6341
	Median	6,00	40,00	3300,00	51,00	35,00	64,7529	12,5740
	N	451	480	515	493	300	484	484
	Standard deviation	3,502	2,485	545,487	2,792	3,850	9,08483	1,80941
	Minimum	0	28	1070	35	21	28,16	5,13
	Maximum	39	46	5500	64	54	100,00	28,57

(please refer to appendix 15 for other tables)

4.7.4. CAR and pre-/postnatal stress (PBI/PSQ)

The paternal and maternal PBI-scales correlated with each other. Maternal care was also negatively correlated with the sum of postnatal stress. Paternal care was significantly correlated with the w-u+30, w-u+45 and w-u+60 values of cortisol (r from .23 to .26).
(please refer to appendix 16)

Sixty-seven women had CAR values, 20h value and had completed the PBI maternal scale and 65 of them also completed the PBI paternal scale. A cluster analysis was made and it resulted in two clusters (for results using the Ward method, please refer to appendix 17 and 18).

PBI scales mother

The first cluster showed low CAR values, a higher maternal control and a low maternal care. The second cluster (only nine persons) had high CAR values, lower maternal control and higher maternal care (optimal parenting).

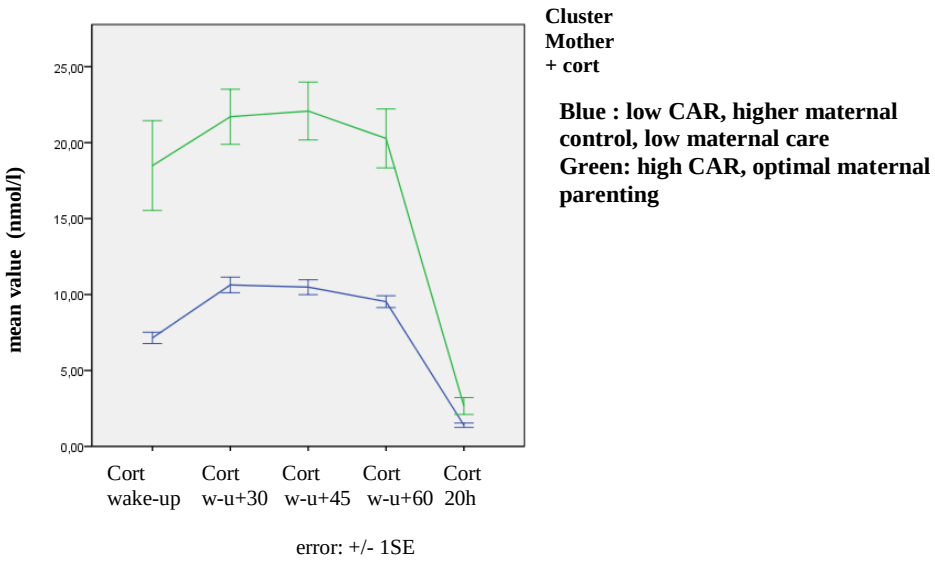

Fig 12 : representation of two clusters: maternal bonding style and cortisol

PBI-scales father

The first cluster had low CAR values, normal to high paternal control and low till normal paternal care whereas the second cluster (only 11 women) had high CAR values, low paternal protection and high paternal care (optimal parenting).

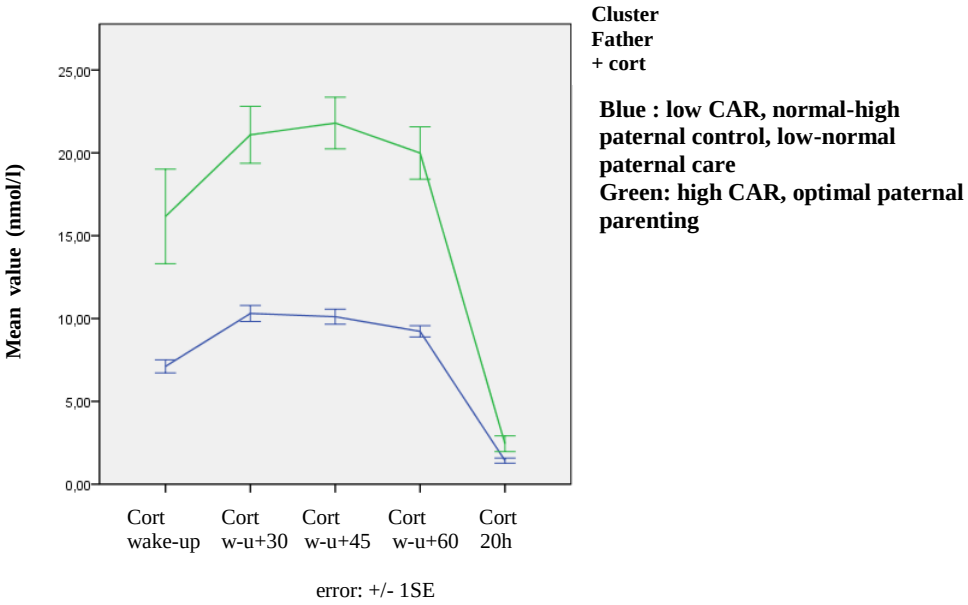

Fig 13: representation of two clusters: paternal bonding style and cortisol

Other cluster analyses were made with the sum of prenatal and postnatal stress of the PSQ. They also resulted in two clusters. Please refer to appendix 19 for exact values.

Breast cancer patients from the first cluster (N=12) had higher CAR values und have had three prenatal stress factors. Those from the second cluster (N=46) have only had two prenatal

stress factors and had quite low CAR values. Those with more pre-postnatal stress factors had higher CAR values.

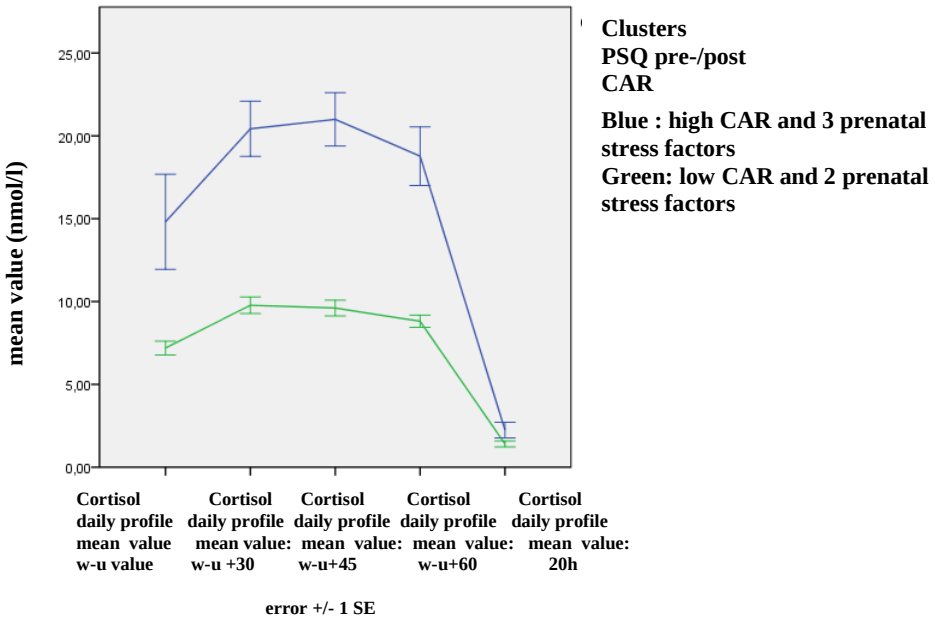

Fig 14 : representation of the two clusters about PSQ pre-/post and CAR

4.7.5. Factors with influence on the CAR

To determine factors that had an influence on the CAR, multipe models of regression were calculated. The chosen method was "stepwise backwards". As predictors, the four scales of the PBI were used, the sum of pre- and postnatal stress factors of the PSQ and the TICS-screening value. Seventy-five breast cancer patients (those who had entire CAR values) and seven predictive factors were used for the regression analysis.

A model was calculated for the following criterias:

- 1) AUCg (mean value)
- 2) AUCi (mean value)
- 3) wake-up value (mean value)
- 4) wake-up +30 (mean value)
- 5) wake-up + 45 (mean value)
- 6) wake-up + 60 (mean value)
- 7) 20h (mean value)

The different models didn't entirely explain the covariance, only 9 to 14% of it. The TICS values and the paternal care as well as the sum of pre-/postnatal stress factors nevertheless often showed as predictors in the various models.

4.7.5.1. Prediction of the AUCg

With the stepwise regression (backwards), each model of prediction of the AUCg failed to become significant (.05), even if it was quite close. The closest were the TICS-screening value and the paternal care.

4.7.5.2. Prediction of the AUCi

Using the stepwise backwards regression, model six became significant. It contained the sum of pre-/postnatal stress factors as predictors and explained nearly 9% of the variance. Betaweight was positive for prenatal stress (more stress → higher AUCi) and tended to be negative for postnatal stress (more stress → lower AUCi).

The table of "model summary" which contained the R-square values (the variance explained by the model) will be shown. You'll find the ANOVA-tables (it indicates if the regression model differed significantly from a model without predictors) and the coefficient-table (shows the β-weight of the predictors and their significancy) in the appendix section.

Tab 14: Results of the prediction for AUCi

Model summary[g]

Model	R	R-square	adjusted R-square	Standard error of the assessor	Change statistics					Durbin-Watson-Statistics
					change in R-square	change in F	df1	df2	Sig. change in F	
1	,373[a]	,139	,040	163,33111	,139	1,409	7	61	,218	
2	,370[b]	,137	,054	162,19918	-,002	,144	1	61	,706	
3	,368[c]	,136	,067	161,04487	-,001	,106	1	62	,745	
4	,356[d]	,126	,072	160,63486	-,009	,675	1	63	,415	
5	,326[e]	,106	,065	161,23826	-,020	1,489	1	64	,227	
6	,299[f]	,089	,062	161,49218	-,017	1,208	1	65	,276	2,115

a. independent variables: (constant), TICS-SSCS, PBI-PProt, sumPostnatal, PBI-MCare, PBI-PCare, sumPrenatal, PBI-MProt

b. independent variables: (constant), TICS-SSCS, PBI-PProt, sumPostnatal, PBI-MCare, PBI-PCare, sumPrenatal

c. independent variables: (constant), TICS-SSCS, sumPostnatal, PBI-MCare, PBI-PCare, sumPrenatal

d. independent variables: (constant), sumPostnatal, PBI-MCare, PBI-PCare, sumPrenatal

e. independent variables: (constant), sumPostnatal, PBI-PCare, sumPrenatal

f. independent variables: (constant), sumPostnatal, sumPrenatal

g. dependent variable: Cortisol awakening Reaction (CAR) AUCi

(please refer to appendix 20 for ANOVA and coefficients)

4.7.5.3. Prediction of the CAR values

For the wake-up and 20h values, no significant regression model could be found.

For the prediction of the wake-up+30 value, all six models were significant and model 6 was the most significant compared to a model without predictors. It contained the TICS-screening value and the paternal care as predictors and explained nearly 14% of the variance. Both predictors had a positive betaweight: the higher the paternal care and the higher the TICS value, the higher the wake-up+30 value.

Tab 15: Results for the prediction for the cortisol wake-up+30 value

Model	R	R-Square	Adjusted R-square	Standard deviation of the assessor	Change statistics					Durbin-Watson-Statistic
					Change in R-square	Change in F	df1	df2	Sig. change in F	
1	,444[a]	,197	,118	5,42037	,197	2,484	7	71	,024	
2	,437[b]	,191	,124	5,40171	-,006	,505	1	71	,480	
3	,427[c]	,182	,126	5,39354	-,009	,779	1	72	,380	
4	,421[d]	,177	,133	5,37329	-,005	,445	1	73	,507	
5	,393[e]	,154	,120	5,41163	-,023	2,074	1	74	,154	
6	,370[f]	,137	,114	5,43040	-,017	1,528	1	75	,220	2,055

a. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-MCare, PBI-PCare,-sumPostnatal, PBI-MProt

b. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-PCare, sumPostnatal, PBI-MProt

c. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-PCare, sumPostnatal

d. independent variables : (constant), TICS-SSCS, sumPrenatal, PBI-PCare, sumPostnatal

e. independent variables : (constant), TICS-SSCS, PBI-PCare, sumPostnatal

f. independent variables : (constant), TICS-SSCS, PBI-PCare

g. dependent variable: Cortisol daily profile average value: 30 min after awakening

(please refer to appendix 21 for ANOVA and coefficients)

Concerning the prediction of the w-u+45 value, model 5 became significant with the predictors sum prental, sum postnatal and paternal care. This model explained nearly 13% of the variance. Betaweight was positive for prenatal stress and paternal care and negative for postnatal stress.

Tab 16: Results for the prediction for the cortisol wake-up+45 value

Model summary[f]

Model	R	R-square	Adjusted R-square	Standard deviation of the assessor	Change statistics					Durbin-Watson-Statistic
					change in R-square	change in F	df1	df2	Sig. Change in F	
1	,408[a]	,167	,089	5,08982	,167	2,146	7	75	,049	
2	,408[b]	,166	,100	5,05810	-,001	,055	1	75	,815	
3	,399[c]	,159	,105	5,04594	-,007	,630	1	76	,430	
4	,388[d]	,151	,107	5,03966	-,009	,806	1	77	,372	
5	,354[e]	,126	,092	5,08086	-,025	2,297	1	78	,134	2,450

a. independent variables: (constant), TICS-SSCS, PBI-VProt, sumPränatal, PBI-MCare, PBI-VCare, sumPostnatal, PBI-MProt

b. independent variables: (constant), TICS-SSCS, PBI-VProt, sumPränatal, PBI-VCare, sumPostnatal, PBI-MProt

c. independent variables: (constant), TICS-SSCS, PBI-VProt, sumPränatal, PBI-VCare, sumPostnatal

d. independent variables: (constant), TICS-SSCS, sumPränatal, PBI-VCare, sumPostnatal

e. independent variables: (constant), sumPränatal, PBI-VCare, sumPostnatal

f. dependent variable: Cortisol daily profile mean value: 45 min after awakening

(please refer to appendix 22 for ANOVA and coefficients)

The wake-up+60 was best predicted with model 6. The predictors were again the TICS-screening value and paternal care. The model explained nearly 9% of the variance and betaweight was positive for both predictors.

Tab 17: Results for the prediction for the cortisol wake-up+60 value

Model summary[g]

Model	R	R-square	Adjusted R-square	Standard deviation of the assessor	Change statistics					Durbin-Watson-Statistic
					change in R-square	change in F	df1	df2	Sig. change in F	
1	,399[a]	,159	,080	4,53200	,159	2,000	7	74	,066	
2	,398[b]	,158	,091	4,50353	-,001	,061	1	74	,806	
3	,385[c]	,148	,092	4,50101	-,010	,915	1	75	,342	
4	,355[d]	,126	,081	4,52837	-,022	1,939	1	76	,168	
5	,316[e]	,100	,065	4,56727	-,027	2,346	1	77	,130	
6	,299[f]	,089	,066	4,56467	-,011	,910	1	78	,343	1,988

a. independent variables: (constant), TICS-SSCS, PBI-PCare, sumPrenatal, PBI-MProt, PBI-MCare, sumPostnatal, PBI-PProt

b. independent variables: (constant), TICS-SSCS, PBI-PCare, sumPrenatal, PBI-MProt, sumPostnatal, PBI-PProt

c. independent variables: (constant), TICS-SSCS, PBI-PCare, PBI-MProt, sumPostnatal, PBI-PProt

d. independent variables: (constant), TICS-SSCS, PBI-PCare, PBI-MProt, PBI-PProt

e. independent variables: (constant), TICS-SSCS, PBI-PCare, PBI-PProt

f. independent variables: (constant), TICS-SSCS, PBI-PCare

g. dependent variable: Cortisol daily profile average value: 60 min after awakening

(please refer to appendix 23 for ANOVA and coefficients)

4.7.6. Pre-/postnatal stress correlation and CAR

Logistic regressions with the criteria "bad prognosis" and the mean values of cortisol of "wake-up", "w-u+30", "w-u+45" and "w-u+60" as predictors were calculated. Again the methods were "inclusion" and "stepwise backwards". Another logistic regression was made with the mean AUCg and AUCi. All the regression analyses weren't significant**.**

Hypothesis 3a couldn't be verified. Breast cancer patients with more pre-/postnatal stress factors didn't have a higher CAR.

4.8. Analysis concerning Hypothesis 3b: *Breast cancer patients with stress during the pre-/postnatal period have more severe and aggressive breast cancer and therefore a worse prognosis and/or outcome.*

Logistic regressions with the criteria "bad prognosis" and the four PBI-scales as well as the sum variables for pre-/peri-/ and postnatal stress were used as predictors to answer the question whether there's a difference in prognosis between patients with or without pre-/postnatal stress factors. Two methods were used: "inclusion" and "stepwise backwards". Another logistic regression was made with the categories from the PSQ. All three regression analyses weren't significant.

Thus, hypothesis 3b couldn't be verified. Breast cancer patients with pre-/postnatal stress factors don't have a worse prognosis and/or outcome.

Chapter 5

General discussion

5. General discussion

The objectives (chapter 1) and the hypotheses described in chapter 2 will now be discussed. Objectives 1 and 2 were investigated both by theoretical background and experimental results whereas objective 3 had been examined by looking at theoretical facts. A critical discussion of the study will follow and conclude with the potential for further studies.

In fact, studies investigating whether there is a link between stress and breast cancer have existed for decades. The mechanisms of how psychological stress can lead to a down-regulation of the immune response through cortisol for example, has expanded greatly. Reiche and colleagues stated that there may be a path from stress to cancer through the modulation of the development and accumulation of somatic mutations and genomic instability, such as increases in DNA damage, alterations in DNA repair as well as inhibition of apoptosis. Nevertheless, empirical data remain contradictory (Reiche et al., 2005). It was also shown that women with the highest level of perceived stress have shorter telomeres compared to those with lower stress levels (Epel et al., 2010).

Unfortunately, there are still not many studies or reviews on psychosocial factors and breast cancer development that have assessed how hormonal, immunological, and cellular stress responses correlate.

5.1. Discussion of the results of chronically stressed breast cancer patients

Breast cancer patients didn't seem to be enormously stressed by their disease and its implications (results from FBK-R questionnaire). They didn't indicate that subjective stress was linked to their illness and the cortisol values didn't differ from the norms. PHQ-D results went in the same direction. Breast cancer patients also didn't differ significantly in their TICS values (perceived chronic stress) when compared to a healthy population.

5.1.1. Women with perceived chronic stress (Hypothesis 1)

One hundred and ten women with breast cancer completed the TICS to be screened for perceived chronic stress. As was explained in chapter 3, they had to complete the questionnaire based on how they felt before their cancer diagnosis. This perception of how they felt could result in potential for recall bias.

The average values showed that the participants seemed to be a „normally" stressed population as far as norm values are concerned. Breast cancer patients seemed to have had even less social overload and pressure for success than healthy subjects. However, they

complained of higher overcharge and they also scored higher on the chronic apprehension and chronic stress subscales. Most social isolation scores were also a bit higher than those of the norm. In rats, social isolation leads to a higher risk of developing a mammary tumor. In humans, social isolation is associated with an alterd hormonal milieu of mammary tissue and this may accelerate tumor growth (McKlintock et al., 2005). Thirtyone patients seem to be chronically stressed (T-value higher than 60 on the screening scale).

Hypothesis 1 could be falsified. The statistical test didn't show a link between perceived stress and abnormal CAR values. Their cortisol values were normal compared to a healthy population.

It will be interesting to see in a later study if perceived chronic stress plays a role in real outcome. Until now, 12 of the 110 breast cancer patients have had a recurrence or are dead. Seven of these initially had a good prognosis. So the question is why those with a good prognosis have had a recurrence or have already died from cancer.

Looking at the seven patients in a descriptive manner, only one of them scored for perceived chronic stress on the TICS subscale and this woman also showed abnormal cortisol values.

So perceived chronic stress doesn't seem to be a criterion for a poorer prognosis. These results confirm those from other studies (Lillberg et al., 2001; Chen et al., 1995).

5.1.2. Women with an abnormal cortisol daily profile (stress/fatigue): Hypothesis 2a and 2c

There is no significant difference in cortisol values between the patients who had chemotherapy and those who didn't. This has already been demonstrated in another study (Kailajärvi, 2000). The cortisol daily profiles didn't differ significantly from those of the comparison group.

Stress-related psychosocial factors are linked to poorer survival rates in breast cancer patients. These factors are associated with a release of glucocorticoids and other hormones that could change components of the tumor micro-environment. They stimulate angiogenesis by producing VEGF (Chida et al., 2008; Antoni et al., 2006). They can increase DNA damage, affect the repair of already damaged DNA and inhibit apoptosis (Chida et al., 2008; Flint et al., 2007; Forlenza & Baum, 2000; Kiecolt-Glaser & Glaser, 1999; Reiche et al., 2004; Gidron & Ronson, 2008). Cortisol downregulates the expression of BRCA1 (Antonova & Mueller, 2008).

Comparing the patients with an abnormal AUCg to those with a normal one, no significant result could be found concerning the prognosis. Patients with a poor prognosis have slightly higher pre-/post simulation values on the baseline day and slightly lower levels on the simulation day. This could indicate that they react less to stressful events than the others.
Looking at the seven women with recurrence and a good prognosis in a descriptive manner, it can be noticed that three had an abnormal AUCg, one an abnormal AUCi and the others had various abnormal cortisol values (lower values, flatter, higher, etc). Activated glucocorticoids prevent apoptosis in cultured malignant human breast epithelial cells (Moran et al., 2000).
Thus, hypothesis 2a couldn't be verified regarding a poor prognosis (clinical factors). This has already been reported in another study (Filipski et al., 2002). As for the outcome, no conclusion can be drawn as only 12 patients have a recurrence at the end of this study. Nevertheless, of the patients with a recurrence and a good prognosis all had abnormal cortisol values which seems quite interesting. Filipski et al. already showed that abnormal alterations in cortisol rhythms are independent from clinical factors.

The patients complaining of fatigue had a worse prognosis and looking at the daily profiles in a descriptive manner, they also seemed to have a flatter profile than those without fatigue. These results have already been observed in other studies (Septhon et al., 2000; Filipski et al., 2002; Spiegel & Giese-Davis, 2003; Spiegel et al., 2006). Hypothesis 2c could be verified as the link between fatigue and poor prognosis became significant. It will be interesting to see in a future analysis of the results of the present study if there's a link between the outcome of the patients with a good prognosis and fatigue and flatter cortisol daily profiles. This has already been found in several other studies. Looking at the data in a descriptive manner, more patients than expected with a good prognosis suffer from fatigue.

5.1.3. Women with perceived chronic stress AND abnormal cortisol daily profile: Hypothesis 2b

Sixty-six breast cancer patients had a complete daily cortisol profile and a complete TICS screening. Those with normal TICS values seemed to have a flatter cortisol profile whereas those with abnormal TICS values had a fairly normal cortisol daily profile. Only seven women suffered from perceived chronic stress AND had an abnormal daily cortisol profile and none of them had a poor prognosis. The interaction between the two wasn't significant.
Breast cancer patients had a flatter cortisol profile than healthy women. It seems as if breast cancer patients don't have the same reactivity to stress than women without breast cancer.

Looking at the breast cancer patients with a good prognosis who nevertheless had a recurrence, we can see that only one indicated perceived chronic stress and had abnormal cortisol values. Those with an abnormal AUCg or AUCi didn't report chronic stress.
Hypothesis 2b couldn't be verified. Perceived chronic stress in combination with abnormal cortisol values doesn't seem to play a role. However, the abnormal cortisol values seem to be predominant for the outcome (see 5.1.2.).

5.2. Discussion of the results of breast cancer patients with pre-/postnatal stress (including bonding style)

The results of the PSQ and PBI were used to examine whether these hypotheses can be verified or not. Pre-postnatal factors are often found to be linked to breast cancer (Kaufman et al., 2000; Meaney et al., 2007; Seckl & Holmes, 2007). Adverse conditions during early life are risk factors for stress-related disorders (de Kloet et al., 2005; Kaplan et al., 2008) and exposure to glucocorticoids during early postnatal development may cause cardiac, metabolic, autoimmune, neurological and psychiatric disorders (Repetti et al., 2002; Seckl, 2004; Luecken et al., 2004; de Kloet et al., 2005; Mesquita et al., 2009). Neglect during childhood influences cellular aging (Tyrka et al., 2010). Cellular aging is linked to cancer as the risk of errors in cell reproduction is higher. Adverse childhood experiences are seemingly a risk factor for cancer development for women. Early life and adolescence are critical periods for the maturation of the hypothalamic pituitary axis which affects the production of estrogens (Ruder et al., 2008). Breast tissue is not entirely differentiated until the end of the first pregnancy and perinatal period as well as childhood and adolescence are important intervals for a high risk of developing breast cancer (Ruder at al., 2008; dos Santos Silva et al., 2008). Estrogens increase proliferation of cells in the breast and this contributes to breast cancer by increasing errors in DNA replication and by enhancing the replication of clones of cells carrying such errors (Dickson & Stancel, 1998; Baik et al., 2005; Lagiou & Trichopoulos, 2008; Strohsnitter et al., 2008). Social isolation alters the hormonal milieu of mammary tissue during puberty and this may accelerate tumor growth (McKlintock et al., 2005). In rats, maternal care can alter the hippocampal GR expression in the offspring which changes the HPA axis and the response to stress (Meaney, 2001; Champagne et al., 2003/2006; Weaver, 2007). An unstable relationship between parents and child may lead to somatic diseases later in life (McEwen, 2003; Kaplan et al., 2008). Lack of quality caretaking by the family and especially by the mother are related to an altered HPAA (Luecken, 1998; Heim & Nemeroff, 2001; Repetti et al., 2002; Buss et al., 2007; Pütz, 2008; Quirin et al., 2008). In rats, neonatal

exposure to handling leads to improved ability to cope with stress, and reduces incidence of mammary tumors (Hilakivi-Clarke et al., 1994).

If the mother is exposed to nicotine during pregnancy, there's a risk of delivering a baby too small for gestational age (Aliyu et al., 2009). A shorter gestational age is linked to an increased risk for premenopausal breast cancer (McCormack et al., 2003). Smoking during pregnancy can impair neurodevelopment characterized for example by low birth weight (Viljoen, 2005; Jauniaux & Burton, 2007; Shea & Steiner, 2008; Winzer-Serhan, 2008). If women with low birth weight develop adult obesity, they have higher estradiol levels during menstrual cycles and are therefore at higher risk of developing breast cancer (Finstad et al., 2009). Smoking is also linked to chromosomal instability which is linked to an increased cancer risk (Jauniaux & Burton, 2007).

5.2.1. Women with pre-/postnatal stress factors and effect on CAR values: Hypothesis 3a

Those with optimal parenting from the mother had high CAR values and those with affectionless control (mother) had low CAR-values. Optimal parenting from the father resulted in high CAR values whereas affectionless control from the father in low CAR values. Patients with three prenatal stress factors had higher CAR-values and those with two had quite low CAR values.

Factors of influence on the AUCg were perceived chronic stress and, tendencially, paternal care. For the AUCi it was the sum of postnatal and prenatal stress. The more prenatal stress, the higher was the AUCi whereas postnatal stress tended to lower the AUCi. Four of the seven patients with a good prognosis and recurrence had abnormal AUCg or AUCi values and reported pre-/postnatal stress. Looking at the seven breast cancer patients with a good prognosis and a recurrence in a descriptive manner, six had abnormal cortisol values and pre-/postnatal stress.

Apparently, optimal parenting (maternal and paternal) as well as more prenatal stress factors result in high CAR values amongst breast cancer patients. Postnatal stress can heighten adrenal stress-reactivity and lower HPAA activity if traumatic events occur. If there is optimal parenting, a normal CAR could be expected. But if they get ill (for example breast cancer), the HPAA is probably first activated (high CAR, high AUCg) and if the stressor becomes chronic, this can result in a decreased adrenal cortisol synthesis (Hellhammer & Wade, 1993). It is possible that patients with optimal parenting can't cope as well with stress as those used to stress and react in a more sensitive manner to uncontrollable events as for example breast cancer.

In people with prenatal stress, the HPAA is normally programmed in a manner that stress management is better later in life. It's possible that if there are too many prenatal stress factors, the HPAA is completely dysregulated and they react in a more sensitive manner to breast cancer (like those with optimal parenting).
Felitti & al. (1998) found in their study that the more adverse childhood experiences, the higher the risk for adopting bad health behaviours and for developing diseases in adult life (including cancer). Kelly-Irving and al. (2013) found the same results in their study and after adjusting for health behaviours they found arguments for a direct biological pathway.

Hypothesis 3a couldn't be verified for the poorer prognosis, but, again, in patients who had a recurrence and a good prognosis, almost all had pre-/postnatal stress factors and abnormal cortisol values. So it seems possible that it plays a role for the outcome.

5.2.2. Women with pre-/postnatal stress: Hypothesis 3b

5.2.2.1. Women with postnatal stress factors

Sixty-one percent of the breast cancer patients had pre- or postnatal stress. For example, breast cancer patients were less desired than persons of the comparison group and had less social support. The cancer patients also had less breastfeeding and were more often exposed to tobacco smoke than expected. Nevertheless, by summing up all the factors, women of the present study seem to have less pre-/postnatal stress factors. But most of them were born not long after World War II, so it's quite possible that there were stress factors (financial problems, etc) involved. In addition, breast cancer patients seemed to be more neglected as a child by their parents compared to the control group.
Women with breast cancer reported less parental care and love (undesired pregnancy, no breast-feeding, more parental neglect). It is possible that if the child wasn't desired, a feeling of isolation became relevant again, once they got breast cancer.
Looking at the seven breast cancer patients with a recurrence and good prognosis in a descriptive manner, six had pre-/postnatal stress. Five of those six persons had a compromised bonding (PBI) and four had suffered from both the compromised bonding and pre-/postnatal stress factors.

5.2.2.2 Women with pre-/perinatal stress factors (birth factors)

Larger size at birth is associated with an increased risk of premenopausal breast cancer (Vatten et al., 2002; McCormack et al., 2003; Jasienska et al., 2006; Xue & Michels, 2007; dos Santos Silva et al., 2008; Ruder et al., 2008) and with epigenetic modifications that lead to modifications in breast development (Hilakivi-Clarke & de Assis, 2006; Lagiou & Trichpoulos, 2008). It is also linked to higher levels of estrogen which increases the number of stem cells (Lagiou & Trichopulos, 2008) and therefore the chance of mutations or DNA replicative error (Trichopoulos et al., 2005; Strohsnitter et al., 2008). Elevated fetal estrogen levels can alter the morphology of the mammary gland by causing the presence of TEB's known to be responsible for malignant growth (Hilakivi-Clarke, 2000). BRCA1 is also affected by estrogenic exposure (De Assis & Hilakivi-Clarke, 2006). Please refer to 2.4.2. for further information on adverse effects of estrogens and prolonged estrogen exposure. A shorter gestation has been linked to an increased risk for premenopausal breast cancer (McCormack et al., 2003).

Higher birth weight is also associated with breast cancer (Vatten et al., 2002; McCormack et al., 2003; De Assis & Hilakivi-Clarke, 2006; Jasienska et al., 2006; Xue & Michels, 2007; dos Santos Silva et al., 2008; Ruder et al., 2008). According to this study, breast cancer patients were born a week earlier than control persons. From the seven patients that had a good prognosis but nevertheless a recurrence, four had a shorter gestational time and the other three did not provide the data. Three of them had a larger birth size and are premenopausal (no birth size data for the other four) and four of them had a higher birth weight (no data for the other three).

Looking at the patients with poor prognosis in a descriptive manner, 17 of the 27 people had at least one of the risk factors (weight, size or gestational age). Everyone had either larger birth size and was premenopausal, had larger birth weight or shorter gestational time. So, there seems to be a link between those factors and poor prognosis. There may well be a link with outcome, as some of the patients with good prognosis had at least one of those risk factors.

5.3. Limitations

Of course the present study has limitations. As it took quite a long time to recruit the patients, the Neuropattern diagnostic instrument and theory were further developed and ameliorated. Hence, not all the results of this present study could be analyzed and compared to control groups as most of the results collected by the Trierer University are from the recent version.

Nevertheless, it was possible to evaluate pre-/postnatal stress factors, fatigue and cortisol values so that the hypothesis could be analyzed.

All of our patients were Caucasian women so that there was no problem with ethnicity. Even if we had a lot of different nationalities in our sample, it is unlikely that our results were biased by this factor.

Another critical issue is that 200 breast cancer patients initially agreed to participate in the study but only 110 patients actually participated. The others thought that it was way to stressful to fill in all those questionnaires and to make a cortisol profile over three days. For some analyses, only few patients could be included. Hence the results should be interpreted with caution and further studies are necessary to receive solid answers.

In addition, birth factors for example, length at birth, birth weight, etc. were not well documented or were unknown by a lot of the participants. Some other risk factors were documented (early menstruation, breast-feeding, etc.) but the results were not adjusted for them. Other pre-/postnatal stress factors had to be recalled and this may be a source for biases.

Another limitation is that the time that has elapsed between the end of the treatments and the writing of this dissertation isn't long enough to analyze for real outcome of these patients. A lot of recurrences occur after the fourth year and they can still occur after ten years. Results based on real outcome will only be possible after several years.

5.4. Outlook

It will be very interesting to look at the results of these patients and to analyze them again in several years time to determine whether abnormal cortisol values play a role in outcome in patients with a good prognosis. Interestingly, all the patients with a recurrence and a good prognosis had abnormal cortisol values. Larger studies including more breast cancer patients will be needed to confirm this.

Of course, it would also be of interest to examine other biological stress factors for example E, NE or oxytocin, which may directly or indirectly affect carcinogenesis. Further studies will be needed to confirm the hypothesis that pre-/postnatal stress factors play a role in recurrence and outcome within breast cancer patients with a good prognosis. Interestingly, nearly all had pre-/postnatal stress factors. And a large amount of the patients with bad prognosis had pre-/postnatal stress factors. This calls for a more individualized analysis of the data. A longitudinal study collecting those factors directly at birth and following the participants during their life to examine whether they develop breast cancer or not would, of course be ideal to minimize the threat of recall.

Chapter 6

References

6 : References

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Chapter 7

Appendixes

Appendix 1

Tab 18 : Cortisol values for the three days

	Average	N	Standard deviation	Minimum	Maximum
Cort day 1 (simulation day):wake-up:mean (nmol/l)	7,7849	104	5,41009	,14	43,54
1:w-u+30:mean (nmol/l)	11,2432	104	6,03022	,27	34,13
1:w-u+45:mean (nmol/l)	11,5604	104	5,78879	,31	31,31
1:w-u+60:mean (nmol/l)	10,8538	103	5,88805	,39	37,06
1:8h:mean (nmol/l)	7,7209	46	5,02093	,00	22,77
1:11h:mean (nmol/l)	5,3860	67	3,78685	1,02	23,59
1:15h:mean (nmol/l)	3,4940	73	2,88237	,94	21,85
1:20h:mean (nmol/l)	1,6966	98	2,35606	,29	18,94
Cort day 1: before simulation (nmol/l)	5,5621	104	4,25741	1,08	28,03
Cort day 1: 60 min after simulation (nmol/l)	4,0706	95	4,16381	,80	27,56
Cort day 2 (Baseline): wake-up:mean (nmol/l)	8,6089	99	5,83607	,23	33,61
2:w-u+30:mean (nmol/l)	11,0838	99	7,13718	,25	45,25
2:w-u+45:mean (nmol/l)	10,4489	102	6,41660	,31	35,41
2:w-u+60:mean (nmol/l)	9,1876	102	5,08476	,51	30,73
2:8h:mean (nmol/l)	5,1079	34	2,84019	,51	10,63
2:11h:mean (nmol/l)	4,1975	73	3,28766	,13	23,85
2:15h:mean (nmol/l)	2,6992	71	1,34037	,14	5,62
2:20h:mean (nmol/l)	1,4551	98	1,20776	,00	6,61
Cort day 2: at the same time than took place the simulation (nmol/l)	3,8167	91	2,28701	,25	10,86
Cort day 2: same time as 30 min after simulation (nmol/l)	3,1792	86	2,17672	,15	10,10
Cort day 2: same time as 60 min after simulation (nmol/l)	3,1015	94	2,29372	,34	11,77
Cort day 3 (first session of radiotherapy):wake-up :mean (nmol/l)	8,5551	103	8,23116	,40	69,90
3:w-u+30:mean (nmol/l)	11,3764	101	7,73272	,18	48,47
3:w-u+45:mean (nmol/l)	11,2944	102	7,60158	,18	46,90
3:w-u+60:mean (nmol/l)	10,3726	102	7,06953	,46	42,95
3:8h:mean (nmol/l)	6,9773	33	4,25075	1,39	20,14
3:11h:mean (nmol/l)	6,1304	90	10,91084	,82	100,00
3:15h:mean (nmol/l)	3,0927	67	2,18966	,19	11,48
3:20h:mean (nmol/l)	1,6914	96	1,54669	,00	8,78
Cort day 3:before radiotherapy (nmol/l)	4,4671	96	2,71197	,24	16,76
Cort day 3: 30 min after radiotherapy (nmol/l)	4,2172	92	3,55700	,19	19,14

Appendix 2

Tab 19 : Comparsion of cortisol values between breast cancer patients and norms (baseline day)

		Group		
		Norm	Breast cancer	Total
Wake-up value	Average	7,8685	8,3108	8,0745
	N	351	306	657
	Standard deviation	3,98090	6,60526	5,36554
	Minimum	1,11	,14	,14
	Maximum	27,90	69,90	69,90
30 min after awakening	Average	13,5945	11,2356	12,4980
	N	350	304	654
	Standard deviation	5,69731	6,97030	6,42484
	Minimum	1,98	,18	,18
	Maximum	39,52	48,47	48,47
45 min after awakening	Average	14,3426	11,1042	12,8291
	N	351	308	659
	Standard deviation	5,49368	6,63505	6,26164
	Minimum	1,26	,18	,18
	Maximum	33,81	46,90	46,90
60 min after awakening	Average	13,2583	10,1404	11,8080
	N	353	307	660
	Standard deviation	5,20825	6,08918	5,84194
	Minimum	2,95	,39	,39
	Maximum	37,10	42,95	42,95
20h	Average	1,6502	1,6306	1,6414
	N	351	289	640
	Standard deviation	1,95264	1,77074	1,87128
	Minimum	,15	,24	,15
	Maximum	24,75	18,94	24,75

Appendix 3

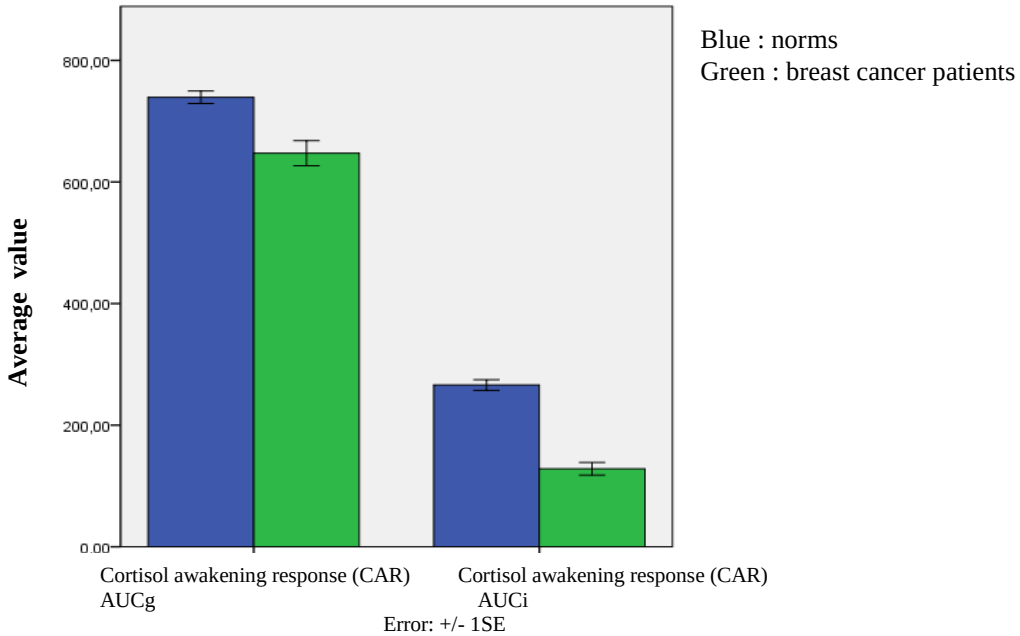

Fig 15 : representation of the CAR values (AUCg and AUCi) of breast cancer patients and norms

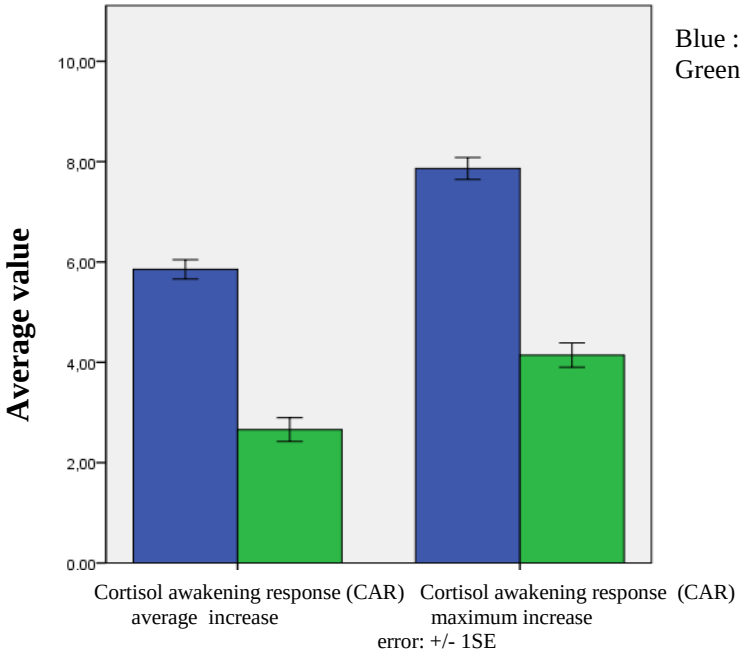

Fig 16 : representation of increases of CAR values of breast cancer patients and norms

Appendix 4

Table 20: Results of other tests to verify the equality of the average values

		Statistics[a]	df1	df2	Sig.
Cortisol awakening Response (CAR) Area under the curve ground (AUCg) Day 1	Welch-Test	18,260	1	502,678	,000
	Brown-Forsythe	18,260	1	502,678	,000
Cortisol awakening Response (CAR) Area under the curve increase (AUCi) Day 1	Welch-Test	55,003	1	597,442	,000
	Brown-Forsythe	55,003	1	597,442	,000
Cortisol awakening Response (CAR) average increase Day 1	Welch-Test	58,555	1	597,955	,000
	Brown-Forsythe	58,555	1	597,955	,000
Cortisol awakening Response (CAR) maximum increase Day 1	Welch-Test	49,543	1	599,531	,000
	Brown-Forsythe	49,543	1	599,531	,000

a. Asymptotic F distributed

Appendix 5

Table 21 : correlations of TICS-data and CAR values

		TICS-SSCS	Cort_ w-u	Cort_ w-u+30	Cort_ w-u+45	Cort_ w-u+60	Cort_ 20h	Middle increase	Maximum increase	AUCg	AUCi
TICS-SSCS	correlation after Pearson	1	-,033	,079	-,059	-,012	-,083	,028	,084	-,030	,057
	Significancy (2-sided)		,750	,447	,565	,910	,447	,801	,451	,788	,612
	N	110	97	94	98	97	86	82	82	82	82
Cortisol daily profile Mean value w-u value	correlation after Pearson	-,033	1	,766**	,721**	,723**	,303*	-,466**	-,343**	,888**	-,429**
	Significancy (2-sided)	,750		,000	,000	,000	,007	,000	,002	,000	,000
	N	97	97	89	94	92	79	82	82	82	82
Cortisol daily profile Mean value: 30 min after w-u	correlation after Pearson	,079	,766**	1	,917**	,849**	,102	,082	,227*	,971**	,152
	Significancy (2-sided)	,447	,000		,000	,000	,374	,463	,041	,000	,172
	N	94	89	94	90	89	78	82	82	82	82
Cortisol daily profile Mean value: 45 min after w-u	correlation after Pearson	-,059	,721**	,917**	1	,939**	,230*	,224*	,332**	,954**	,250*
	Significancy (2-sided)	,565	,000	,000		,000	,040	,043	,002	,000	,023
	N	98	94	90	98	94	80	82	82	82	82
Cortisol daily profile Mean value: 60 min after w-u	correlation after Pearson	-,012	,723**	,849**	,939**	1	,280*	,209	,290**	,916**	,206
	Significancy (2-sided)	,910	,000	,000	,000		,012	,059	,008	,000	,064
	N	97	92	89	94	97	80	82	82	82	82
Cortisol daily profile Mean value: 20h	correlation after Pearson	-,083	,303**	,102	,230*	,280*	1	-,104	-,091	,359**	-,115
	Significancy (2-sided)	,447	,007	,374	,040	,012		,401	,466	,003	,354
	N	86	79	78	80	80	86	67	67	67	67
Cortisol awakening reaction (CAR) middle increase	correlation after Pearson	,028	-,466**	,082	,224*	,209	-,104	1	,970**	-,012	,990**
	Significancy (2-sided)	,801	,000	,463	,043	,059	,401		,000	,918	,000
	N	82	82	82	82	82	67	82	82	82	82
Cortisol awakening reaction (CAR) maximum increase	correlation after Pearson	,084	-,343**	,227*	,332**	,290**	-,091	,970**	1	,119	,980**
	Significancy (2-sided)	,451	,002	,041	,002	,008	,466	,000		,287	,000
	N	82	82	82	82	82	67	82	82	82	82
Cortisol awakening reaction (CAR) AUCg	correlation after Pearson	-,030	,888**	,971**	,954**	,916**	,359*	-,012	,119	1	,033
	Significancy (2-sided)	,788	,000	,000	,000	,000	,003	,918	,287		,766
	N	82	82	82	82	82	67	82	82	82	82

Cortisol awakening reaction (CAR) AUCi	correlation after Pearson	,057	-,429**	,152	,250*	,206	-,115	,990**	,980**	,033	1
	Significancy (2-sided)	,612	,000	,172	,023	,064	,354	,000	,000	,766	
	N	82	82	82	82	82	67	82	82	82	82

**. The correlation is on 0,01 (2-sided) significant.
*. The correlation is on 0,05 (2-sided) significant.

Appendix 6

Table 22 : ANOVA of TICS and cortsiol

			Sum of squares	df	Root mean square	F	Significancy
TICS-SSCS * Cluster TICS + Cort	Between the groups	(combined)	1671,801	1	1671,801	14,560	,000
	In the groups		7348,638	64	114,822		
	Total		9020,439	65			
Cortisol daily profile average value: wake-up value* Cluster TICS + Cort	Between the groups	(combined)	207,853	1	207,853	13,810	,000
	In the groups		963,258	64	15,051		
	Total		1171,111	65			
Cortisol daily profile average value: 30 min after wake-up* Cluster TICS + Cort	Between the groups	(combined)	651,469	1	651,469	45,840	,000
	In the groups		909,552	64	14,212		
	Total		1561,021	65			
Cortisol daily profile average value: 45 min after wake-up * Cluster TICS + Cort	Between the groups	(combined)	750,679	1	750,679	61,146	,000
	In the groups		785,721	64	12,277		
	Total		1536,401	65			
Cortisol daily profile average value: 60 min after wake-up * Cluster TICS + Cort	Between the groups	(combined)	459,697	1	459,697	39,521	,000
	In the groups		744,432	64	11,632		
	Total		1204,129	65			
Cortisol daily profile average value: 20h* Cluster TICS + Cort	Between the groups	(combined)	,017	1	,017	,011	,916
	In the groups		94,822	64	1,482		
	Total		94,839	65			

Appendix 7

Table 23 : Results of the PBI for the breast cancer patients and the control group

		group		
		Patient group	PBI-control group	Total
PBI-Maternal Care	Average	23,39	26,91	24,91
	N	109	82	191
	Standard deviation	8,188	6,730	7,776
	Minimum	3	2	2
	Maximum	36	35	36
PBI-Maternal Protection	Average	15,03	12,78	14,06
	N	109	82	191
	Standard deviation	8,318	9,391	8,842
	Minimum	0	0	0
	Maximum	36	35	36
PBI-Paternal Care	Average	22,14	24,98	23,38
	N	106	82	188
	Standard deviation	7,217	7,397	7,412
	Minimum	4	2	2
	Maximum	36	36	36
PBI-Paternal Protection	Average	13,52	11,28	12,54
	N	106	82	188
	Standard deviation	8,090	8,220	8,201
	Minimum	1	1	1
	Maximum	38	38	38

Appendix 8

Table 24 : PBI-M style

			group		
			Patient group	PBI-control group	Total
PBI-MStyle	0	number	0	1	1
		expected number	,6	,4	1,0
	optimal parenting	number	34	45	79
		expected number	44,8	34,2	79,0
	neglectful parenting	number	21	9	30
		expected number	17,0	13,0	30,0
	affectionate constraint	number	9	8	17
		expected number	9,7	7,3	17,0
	affectionless control	number	45	20	65
		expected number	36,9	28,1	65,0
Total		number	109	83	192
		expected number	109,0	83,0	192,0

Table 24 : Chi-square tests of PBI-M style

	Value	df	Asymptotic significancy (2-sides)
Chi-Quadrat after Pearson	13,737[a]	4	**,008**
Likelihood-Quotient	14,255	4	,007
linear-with-linear connection	9,109	1	,003
Incidence of valid cases	192		

Table 25: PBI-P style

			group		
			Patient group	PBI-control group	Total
PBI-PStyle	optimal parenting	number	31	50	81
		expected number	45,7	35,3	81,0
	neglectful parenting	number	25	6	31
		expected number	17,5	13,5	31,0
	affectionate constraint	number	9	7	16
		expected number	9,0	7,0	16,0
	affectionless control	number	41	19	60
		expected number	33,8	26,2	60,0
Total		number	number	82	188
		Expected number	expected number	82,0	188,0

Table 26 : Chi-square tests of PBI-P style

	Value	df	Asymptotic significancy (2-sides)
Chi-Quadrat after Pearson	21,709[a]	3	**,000**
Likelihood-Quotient	22,448	3	,000
linear-with-linear connection	10,592	1	,001
Incidence of valid cases	188		

Appendix 9

Table 27 : Results for prenatal stress

		incidence	Percent	Valid percents	Cumulated percents
valid	no	39	35,5	39,0	39,0
	yes	61	***55,5***	61,0	100,0
	total	100	90,9	100,0	
lacking	system	10	9,1		
total		110	100,0		

Table 28: Results for postnatal stress

		incidence	Percent	Valid percents	Cumulated percents
valid	no	45	40,9	45,0	45,0
	yes	55	***50,0***	55,0	100,0
	total	100	90,9	100,0	
lacking	system	10	9,1		
total			100,0		

Table 29 : Results for both pre- and postnatal stress

		incidence	Percent	Valid percents	Cumulated percents
valid	no	27	24,5	26,5	26,5
	yes	75	***68,2***	73,5	100,0
	total	102	92,7	100,0	
lacking	system	8	7,3		
total			100,0		

Appendix 10

Tables 30-37 : Results for the significancy of several prenatal stress factors and chi-square tests

			group		
			patient group	PSQ-control group	Total
NPQPSQ_2c: financial worries	no	number	68	303	371
		expected number	76,8	294,2	371,0
	yes	number	26	57	83
		expected number	17,2	65,8	83,0
Total		number	94	360	454
		expected number	94,0	360,0	454,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	6,978[a]	1	***,008***		
Correction of continuity[b]	6,209	1	,013		
Likelihood-quotient	6,452	1	,011		
Exact test after Fisher				,011	,008
Link linear-with-linear	6,963	1	,008		
Number of valid cases	454				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 17,19.
b. only calculated for a 2x2 table

			group		
			patient group	PSQ-control group	Total
NPQPSQ_5a: Was the pregnancy desired ?	no	number	12	91	103
		expected number	15,8	87,2	103,0
	yes	number	72	372	444
		expected number	68,2	375,8	444,0
Total		number	84	463	547
		expected number	84,0	463,0	547,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	1,341[a]	1	,247		
Correction of continuity[b]	1,013	1	,314		
Likelihood-quotient	1,419	1	,234		
Exact test after Fisher				,290	,157
Link linear-with-linear	1,338	1	,247		
Number of valid cases	547				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 15,82.
b. only calculated for a 2x2 table

			group		
			patient group	PSQ-control group	Total
NPQPSQ_3a: Tabacco consumption	no	number	94	419	513
		Expected number	89,3	423,7	513,0
	yes	number	3	41	44
		expected number	7,7	36,3	44,0
Total		number	97	460	557
		expected number	97,0	460,0	557,0

Chi-sqare tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	3,730[a]	1	***,053***		
Correction of continuity[b]	2,973	1	,085		
Likelihood-quotient	4,564	1	,033		
Exact test after Fisher				,061	,034
Link linear-with-linear	3,723	1	,054		
Number of valid cases	557				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 7,66.
b. only calculated for a 2x2 table

			group		
			patient group	PSQ-control group	Total
NPQPSQ_2b: lack of social support	no	number	78	426	504
		Expected number	82,6	421,4	504,0
	yes	number	13	38	51
		Expected number	8,4	42,6	51,0
Total		number	91	464	555
		Expected number	91,0	464,0	555,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	3,388[a]	1	***,066***		
Correction of continuity[b]	2,697	1	,101		
Likelihood-quotient	3,036	1	,081		
Exact test after Fisher				,074	,055
Link linear-with-linear	3,382	1	,066		
Number of valid cases	555				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 8,36.

Appendix 11

Tables 38-41: Results for the significancy of several perinatal stress factors and chi-square tests

			group		
			Patient group	PSQ-control group	Total
NPQPSQ_13h:other complications during birth	no	number	75	177	252
		Expected number	36,3	215,7	252,0
	yes	number	5	299	304
		Expected number	43,7	260,3	304,0
Total		number	80	476	556
		Expected number	80,0	476,0	556,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	88,429[a]	1	***,000***		
Correction of continuity[b]	86,161	1	,000		
Likelihood-quotient	100,247	1	,000		
Exact test after Fisher				,000	,000
Link linear-with-linear	88,270	1	,000		
Number of valid cases	556				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 36,26.
b. only calculated for a 2x2 table

			group		
			Patient group	PSQ-control group	Total
NPQPSQ_11d: other measures after birth	no	number	84	183	267
		Expected number	41,3	225,7	267,0
	yes	number	3	292	295
		Expected number	45,7	249,3	295,0
Total		number	87	475	562
		Expected number	87,0	475,0	562,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	99,278[a]	1	***,000***		
Correction of continuity[b]	96,965	1	,000		
Likelihood-quotient	118,350	1	,000		
Exact test after Fisher				,000	,000
Link linear-with-linear	99,101	1	,000		
Number of valid cases	562				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 41,33.
b. only calculated for a 2x2 table

Appendix 12

Tables 42-49: Results for the significancy of several postnatal stress factors and chi-square tests

			group		
			Patient group	PSQ-control group	Total
NPQPSQ_12: were you breastfed ?	no	number	34	93	127
		Expected number	20,4	106,6	127,0
	yes	number	55	371	426
		Expected number	68,6	357,4	426,0
Total		number	89	464	553
		Expected number	89,0	464,0	553,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	13,919[a]	1	***,000***		
Correction of continuity[b]	12,912	1	,000		
Likelihood-quotient	12,675	1	,000		
Exact test after Fisher				,000	,000
Link linear-with-linear	13,894	1	,000		
Number of valid cases	553				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 20,44.
b. only calculated for a 2x2 table

			group		
			Patient group	PSQ-control group	Total
NPQPSQ_14: were you exposed to tobacco smoke?	no	number	52	314	366
		Expected number	59,3	306,7	366,0
	yes	number	36	141	177
		Expected number	28,7	148,3	177,0
Total		number	88	455	543
		Expected number	88,0	455,0	543,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	3,303[a]	1	***,069***		
Correction of continuity[b]	2,867	1	,090		
Likelihood-quotient	3,206	1	,073		
Exact test after Fisher				,082	,047
Link linear-with-linear	3,297	1	,069		
Number of valid cases	543				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 28,69.
b. only calculated for a 2x2 table

			group		
			Patient group	PSQ-control group	Total
NPQPSQ_16a: lots of disputes in the family	no	number	84	333	417
		Expected number	75,5	341,5	417,0
	yes	number	14	110	124
		Expected number	22,5	101,5	124,0
Total		number	98	443	541
		Expected number	98,0	443,0	541,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
	5,051[a]	1	***,025***		
Chi-Quadrat after Pearson	4,472	1	,034		
Correction of continuity[b]	5,499	1	,019		
Likelihood-quotient				,024	,015
Exact test after Fisher	5,041	1	,025		
Link linear-with-linear	541				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 22,46.
b. only calculated for a 2x2 table

			group		
			Patient group	PSQ-control group	Total
Other critical life events (postnatal)	no	number	86	103	189
		Expected number	37,9	151,1	189,0
	yes	number	10	280	290
		Expected number	58,1	231,9	290,0
Total		number	96	383	479
		Expected number	96,0	383,0	479,0

Chi-square tests

	value	df	Asymptotic Significancy (2-sided)	Exact Significancy (2-sided)	Exact Significancy (1-sided)
Chi-Quadrat after Pearson	126,284[a]	1	***,000***		
Correction of continuity[b]	123,673	1	,000		
Likelihood-quotient	132,464	1	,000		
Exact test after Fisher				,000	,000
Link linear-with-linear	126,020	1	,000		
Chi-Quadrat after Pearson	479				

a. 0 (0%) have an expected incidence less than 5. The minimal expected incidence is 37,88.
b. only calculated for a 2x2 table

Appendix 13

Table 50:descriptive statistics for the sum of pre-/peri/- and postnatal stress factors

group		sumPrenatal	sumPerinatal	sumPostnatal	sumPreperipostnatal	sumPrepostnatal
Patient group	Average	2,2000	,4124	1,6100	4,1275	3,7353
	Median	2,0000	,0000	1,0000	3,0000	3,0000
	N	100	97	100	102	102
	Standard deviation	1,62057	,80042	1,31729	2,78494	2,61726
	Minimum	,00	,00	,00	,00	,00
	Maximum	7,00	4,00	6,00	14,00	13,00
PSQ-control group	Average	2,1068	,5735	2,0825	4,7343	4,1691
	Median	2,0000	,0000	2,0000	4,0000	4,0000
	N	206	204	206	207	207
	Standard deviation	1,38573	,98735	1,54541	2,72385	2,46242
	Minimum	,00	,00	,00	,00	,00
	Maximum	7,00	5,00	7,00	15,00	14,00
Total	Average	2,1373	,5216	1,9281	4,5340	4,0259
	Median	2,0000	,0000	1,0000	4,0000	4,0000
	N	306	301	306	309	309
	Standard deviation	1,46459	,93293	1,48922	2,75451	2,51863
	Minimum	,00	,00	,00	,00	,00
	Maximum	7,00	5,00	7,00	15,00	14,00

Appendix 14

Table 51: Ranks for the sum of the stress factors

	group	N	Middle Rank	Rank sum
sumPrenatal	Patient group	100	154,17	15417,00
	PSQ-control group	206	153,17	31554,00
	Total	306		
sumPerinatal	Patient group	97	144,27	13994,50
	PSQ-control group	204	154,20	31456,50
	Total	301		
sumPostnatal	Patient group	100	135,24	13523,50
	PSQ-control group	206	162,37	33447,50
	Total	306		
sumPreperipostnatal	Patient group	102	137,91	14066,50
	PSQ-control group	207	163,42	33828,50
	Total	309		
sumPrepostnatal	Patient group	102	140,44	14325,00
	PSQ-control group	207	162,17	33570,00
	Total	309		

Appendix 15

Table 52: One-way ANOVA for birth parameters

		Sum of squares	df	Root mean square	F	Significancy
Week where the mother found out	Between the groups	2,245	1	2,245	,183	,669
	In the groups	5516,283	449	12,286		
	Total	5518,528	450			
Birth : week	Between the groups	55,071	1	55,071	9,071	***,003***
	In the groups	2901,991	478	6,071		
	Total	2957,062	479			
weight	Between the groups	13460,506	1	13460,506	,045	,832
	In the groups	1,529E8	513	298110,238		
	Total	1,529E8	514			
length	Between the groups	39,630	1	39,630	5,125	***,024***
	In the groups	3796,711	491	7,733		
	Total	3836,341	492			
Head circumference	Between the groups	11,994	1	11,994	,809	,369
	In the groups	4420,486	298	14,834		
	Total	4432,480	299			
Kaub-Index (g/cm)	Between the groups	,208	1	,208	,003	,960
	In the groups	39863,809	482	82,705		
	Total	39864,017	483			
Quetelet-Index / BMI (kg/m²)	Between the groups	2,176	1	2,176	,664	,415
	In the groups	1579,146	482	3,276		
	Total	1581,322	483			

Table 53: tests to examine equality of average values

		Statistics[a]	df1	df2	Sig.
NPQPSQ_5c: In which week did your mother know that she was pregnant?	Welch-Test	,172	1	40,863	,680
	Brown-Forsythe	,172	1	40,863	,680
Birth : week of pregnancy	Welch-Test	5,574	1	49,101	***,022***
	Brown-Forsythe	5,574	1	49,101	***,022***
weight	Welch-Test	,039	1	87,538	,844
	Brown-Forsythe	,039	1	87,538	,844
length	Welch-Test	6,620	1	72,397	,012
	Brown-Forsythe	6,620	1	72,397	,012
Head circumference	Welch-Test	2,071	1	3,217	,240
	Brown-Forsythe	2,071	1	3,217	,240
Kaub-Index (g/cm)	Welch-Test	,003	1	63,859	,960
	Brown-Forsythe	,003	1	63,859	,960
Quetelet-Index / BMI (kg/m²)	Welch-Test	,689	1	64,566	,409
	Brown-Forsythe	,689	1	64,566	,409

a. Asymptotic F-distributed

Appendix 16

Table 54: correlation of PBI-scales, cortisol and sums of pre-/ and postnatal stress factors

		PBI-MCare	PBI-MProt	PBI-PCare	PBI-PProt	sumPrenatal	sumPostnatal
PBI-MCare	correlation after Pearson	1	-,510**	,457**	-,340**	-,160	-,377**
	Significancy (2-sided)		,000	,000	,000	,114	,000
	N	191	191	187	187	99	99
PBI-MProt	correlation after Pearson	-,510**	1	-,296**	,618**	-,010	,142
	Significancy (2-sided)	,000		,000	,000	,918	,161
	N	191	191	187	187	99	99
PBI-PCare	correlation after Pearson	,457**	-,296**	1	-,500**	-,176	-,197
	Significancy (2-sided)	,000	,000		,000	,085	,054
	N	187	187	188	188	96	96
PBI-PProt	correlation after Pearson	-,340**	,618**	-,500**	1	,118	,187
	Significancy (2-sided)	,000	,000	,000		,254	,068
	N	187	187	188	188	96	96
sumPrenatal	correlation after Pearson	-,160	-,010	-,176	,118	1	,569**
	Significancy (2-sided)	,114	,918	,085	,254		,000
	N	99	99	96	96	100	98
sumPostnatal	correlation after Pearson	-,377**	,142	-,197	,187	,569**	1
	Significancy (2-sided)	,000	,161	,054	,068	,000	
	N	99	99	96	96	98	100
Cortisol daily profile average value: wake-up value	correlation after Pearson	,087	,055	,156	,102	-,081	-,081
	Significancy (2-sided)	,400	,598	,135	,333	,458	,452
	N	96	96	93	93	87	88
Cortisol daily profile average value: 30 min after wake-up	correlation after Pearson	,070	,029	,263*	-,025	,054	-,125
	Significancy (2-sided)	,507	,784	,012	,812	,627	,253
	N	93	93	91	91	84	85
Cortisol daily profile average value: 45 min after wake-up	correlation after Pearson	,067	,021	,235*	,013	,045	-,127
	Significancy (2-sided)	,516	,836	,023	,903	,677	,234
	N	97	97	94	94	89	90

Cortisol daily profile average value: 60 min after wake-up	correlation after Pearson	,057	,075	,239*	,044	,009	-,084
	Significancy (2-sided)	,583	,468	,021	,676	,932	,431
	N	96	96	93	93	88	89
Cortisol daily profile average value: 20h	correlation after Pearson	,017	,093	-,070	,186	-,085	-,088
	Significancy (2-sided)	,875	,397	,531	,093	,465	,448
	N	86	86	83	83	76	77
Cortisol awakening Response (CAR) average increase	correlation after Pearson	-,118	-,032	,058	-,080	,199	-,016
	Significancy (2-sided)	,294	,780	,612	,481	,089	,894
	N	81	81	79	79	74	75
Cortisol awakening Response (CAR) maximal increase	correlation after Pearson	-,138	-,018	,051	-,064	,194	-,034
	Significancy (2-sided)	,219	,874	,656	,574	,097	,770
	N	81	81	79	79	74	75
Cortisol awakening Response (CAR) AUCg	correlation after Pearson	,056	,078	,173	,102	,031	-,119
	Significancy (2-sided)	,622	,491	,127	,373	,791	,311
	N	81	81	79	79	74	75
Cortisol awakening Response (CAR) AUCi	correlation after Pearson	-,132	-,026	,063	-,077	,207	-,026
	Significancy (2-sided)	,239	,816	,584	,500	,077	,825
	N	81	81	79	79	74	75

**. The correlation is on 0,01 (2-sided) significant.

*. The correlation is on 0,05 (2-sided) significant.

Appendix17

Table 55 : Results of Ward Method for cortsiol values and PBI scales mother

Ward Method		Cortisol average value wake-up	Cortisol average value w-u+30	Cortisol average value w-u+45	Cortisol average value w-u+60	Cortisol average value 20h	PBI-MCare	PBI-MProt
1	Average	7,1453	10,6318	10,4856	9,5321	1,3979	23,10	15,16
	N	58	58	58	58	58	58	58
	Standard deviation	2,82219	3,89911	3,73278	2,97809	1,11989	8,229	7,100
2	Average	18,4904	21,7048	22,0793	20,2744	2,6626	29,44	11,00
	N	9	9	9	9	9	9	9
	Standard deviation	8,86008	5,44429	5,71725	5,82523	1,67718	4,187	9,618
Total	Average	8,6693	12,1193	12,0429	10,9751	1,5678	23,96	14,60
	N	67	67	67	67	67	67	67
	Standard deviation	5,62030	5,58537	5,64470	5,03935	1,27000	8,084	7,536

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Table 56 : Results of Ward Method for cortsiol values and PBI scales father

Ward Method		Cortisol average value wake-up	Cortisol average value w-u+30	Cortisol average value w-u+45	Cortisol average value w-u+60	Cortisol average value 20h	PBI-PCare	PBI-PProt
1	Average	7,1152	10,3048	10,1102	9,2232	1,4227	23,44	12,37
	N	54	54	54	54	54	54	54
	Standard deviation	2,87812	3,55543	3,31319	2,49496	1,15112	6,957	6,187
2	Average	16,1658	21,0915	21,7988	19,9906	2,4442	25,55	9,45
	N	11	11	11	11	11	11	11
	Standard deviation	9,46504	5,70163	5,17780	5,25107	1,58127	6,890	8,214
Total	Average	8,6468	12,1302	12,0883	11,0454	1,5955	23,80	11,88
	N	65	65	65	65	65	65	65
	Standard deviation	5,70562	5,67115	5,72606	5,10076	1,27947	6,938	6,592

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Table 57: values of the results of the 2 clusters for CAR and paternal parenting

Cluster PSQ pre post CAR		Cortisol daily profile average value: wake-up value	Cortisol daily profile average value: 30 min after wake-up	Cortisol daily profile average value: 45 min after wake-up	Cortisol daily profile average value: 60 min after wake-up	Cortisol daily profile average value: 20h	sumPrenatal	sumPostnatal
1	Average	14,8147	20,4261	20,9969	18,7722	2,2400	3,0833	1,5000
	N	12	12	12	12	12	12	12
	Standard deviation	9,93584	5,77479	5,57011	6,12495	1,62181	1,62135	,90453
	Median	13,6267	20,0100	19,4200	18,5400	1,6750	2,0000	1,0000
	Minimum	2,95	12,44	13,43	9,78	,38	1,00	,00
	Maximum	38,67	34,27	35,67	32,54	5,49	6,00	3,00
2	Average	7,1939	9,7743	9,6091	8,8086	1,4023	2,0000	1,4565
	N	46	46	46	46	46	46	46
	Standard deviation	2,83767	3,39628	3,22536	2,49562	1,23155	1,67332	1,31160
	Median	7,0650	9,4783	9,9350	8,7417	1,0500	1,5000	1,0000
	Minimum	1,29	3,16	3,63	2,63	,28	,00	,00
	Maximum	14,89	17,16	17,41	13,37	6,97	7,00	6,00
Total	Average	8,7706	11,9781	11,9652	10,8701	1,5756	2,2241	1,4655
	N	58	58	58	58	58	58	58
	Standard deviation	5,92500	5,87253	5,98778	5,36025	1,34987	1,70698	1,23140
	Median	7,4867	10,5317	10,7283	9,8583	1,1350	2,0000	1,0000
	Minimum	1,29	3,16	3,63	2,63	,28	,00	,00
	Maximum	38,67	34,27	35,67	32,54	6,97	7,00	6,00

Appendix 20

Table 58 : ANOVA [g] for the prediction of AUCi

Model		Sum of squares	df	Root mean square	F	Sig.
1	Regression	263132,491	7	37590,356	1,409	,218[a]
	Not standardised Residual	1627300,219	61	26677,053		
	Total	1890432,710	68			
2	Regression	259301,187	6	43216,865	1,643	,151[b]
	Not standardised Residual	1631131,523	62	26308,573		
	Total	1890432,710	68			
3	Regression	256499,357	5	51299,871	1,978	,094[c]
	Not standardised Residual	1633933,353	63	25935,450		
	Total	1890432,710	68			
4	Regression	239005,041	4	59751,260	2,316	,067[d]
	Not standardised Residual	1651427,669	64	25803,557		
	Total	1890432,710	68			
5	Regression	200577,275	3	66859,092	2,572	,062[e]
	Not standardised Residual	1689855,435	65	25997,776		
	Total	1890432,710	68			
6	Regression	169171,019	2	84585,510	3,243	,045[f]
	Not standardised Residual	1721261,691	66	26079,723		
	Total	1890432,710	68			

a. independent variables: (constant), TICS-SSCS, PBI-PProt, sumPostnatal, PBI-MCare, PBI-PCare, sumPrenatal, PBI-MProt
b. independent variables: (constant), TICS-SSCS, PBI-PProt, sumPostnatal, PBI-MCare, PBI-PCare, sumPrenatal
c. independent variables: (constant), TICS-SSCS, sumPostnatal, PBI-MCare, PBI-PCare, sumPrenatal
d. independent variables: (constant), sumPostnatal, PBI-MCare, PBI-PCare, sumPrenatal
e. independent variables: (constant), sumPostnatal, PBI-PCare, sumPrenatal
f. independent variables: (constant), sumPostnatal, sumPrenatal
g. dependent variable: Cortisol awakening Response (CAR) AUCi

Table 59: coefficient [a] for the prediction of AUCi

Model	Not standardised coefficients		Standardised coefficients	T	Sig.	95,0% Confidence interval for B		correlations			Correlation statistics	
	Coefficient of regressionB	Standarddeviation	Beta			lower limit	upper limit	Zero order	Part II	Part	Toleration	VIF
1 (constant)	-7,306	184,346		-,040	,969	-375,930	361,317					
sumPrenatal	37,276	14,848	,387	2,510	,015	7,584	66,967	,203	,306	,298	,594	1,683
sumPostnatal	-40,521	20,076	-,314	-2,018	,048	-80,666	-,376	-,049	-,250	-,240	,584	1,712
PBI-MCare	-2,574	3,141	-,122	-,820	,416	-8,854	3,706	-,096	-,104	-,097	,642	1,558
PBI-MProt	1,611	4,252	,072	,379	,706	-6,891	10,113	,016	,048	,045	,393	2,545
PBI-PCare	3,810	3,055	,173	1,247	,217	-2,299	9,919	,098	,158	,148	,730	1,369
PBI-PProt	-1,827	3,676	-,090	-,497	,621	-9,177	5,523	-,072	-,063	-,059	,433	2,309
TICS-SSCS	1,628	2,302	,092	,707	,482	-2,975	6,231	,096	,090	,084	,837	1,195
2 (constant)	5,438	179,997		,030	,976	-354,371	365,247					
sumPrenatal	36,321	14,532	,377	2,499	,015	7,272	65,369	,203	,303	,295	,612	1,635
sumPostnatal	-41,400	19,804	-,321	-2,091	,041	-80,987	-1,813	-,049	-,257	-,247	,592	1,689
PBI-MCare	-3,110	2,784	-,147	-1,117	,268	-8,676	2,455	-,096	-,140	-,132	,805	1,242
PBI-PCare	4,004	2,991	,182	1,339	,186	-1,975	9,983	,098	,168	,158	,751	1,331
PBI-PProt	-,847	2,594	-,042	-,326	,745	-6,032	4,339	-,072	-,041	-,038	,857	1,166
TICS-SSCS	1,808	2,237	,102	,809	,422	-2,663	6,279	,096	,102	,095	,874	1,144
3 (constant)	-15,070	167,470		-,090	,929	-349,733	319,593					

	sumPrenatal	36,395	14,426	,378	2,523	,014	7,567	65,224	,203	,303	,295	,612	1,634
	sumPostnatal	-41,510	19,660	-,321	-2,111	,039	-80,797	-2,223	-,049	-,257	-,247	,592	1,689
	PBI-MCare	-3,057	2,760	-,144	-1,108	,272	-8,572	2,458	-,096	-,138	-,130	,808	1,238
	PBI-PCare	4,333	2,796	,197	1,549	,126	-1,256	9,921	,098	,192	,181	,847	1,180
	TICS-SSCS	1,823	2,220	,103	,821	,415	-2,613	6,260	,096	,103	,096	,874	1,144
4		99,346	92,709		1,072	,288	-85,861	284,553					
	(constant)												
	sumPrenatal	37,322	14,346	,387	2,602	,012	8,663	65,980	,203	,309	,304	,616	1,624
	sumPostnatal	-40,538	19,574	-,314	-2,071	,042	-79,643	-1,434	-,049	-,251	-,242	,594	1,683
	PBI-MCare	-3,334	2,732	-,157	-1,220	,227	-8,792	2,124	-,096	-,151	-,143	,820	1,219
	PBI-PCare	3,843	2,725	,175	1,410	,163	-1,601	9,288	,098	,174	,165	,888	1,127
5		30,070	73,572		,409	,684	-116,863	177,004					
	(constant)												
	sumPrenatal	37,853	14,393	,393	2,630	,011	9,109	66,598	,203	,310	,308	,616	1,623
	sumPostnatal	-35,257	19,162	-,273	-1,840	,070	-73,525	3,012	-,049	-,222	-,216	,625	1,601
	PBI-PCare	2,877	2,618	,131	1,099	,276	-2,351	8,104	,098	,135	,129	,970	1,031
6		101,324	34,842		2,908	,005	31,760	170,888					
	(constant)												
	sumPrenatal	35,953	14,311	,373	2,512	,014	7,380	64,526	,203	,295	,295	,625	1,599
	sumPostnatal	-35,855	19,184	-,278	-1,869	,066	-74,157	2,447	-,049	-,224	-,220	,625	1,599

a. dependent: Cortisol awakening Response (CAR) AUCi

Appendix 21

Table 60: ANOVA [g] for the prediction of CAR value (W-U+30)

Model		Sum of squares	df	Root mean square	F	Sig.
1	Regression	510,807	7	72,972	2,484	,024[a]
	Not standardised Residual	2086,008	71	29,380		
	Total	2596,814	78			
2	Regression	495,968	6	82,661	2,833	,016[b]
	Not standardised Residual	2100,847	72	29,178		
	Total	2596,814	78			
3	Regression	473,223	5	94,645	3,253	,010[c]
	Not standardised Residues	2123,591	73	29,090		
	Total	2596,814	78			
4	Regression	460,267	4	115,067	3,985	,006[d]
	Not standardised Residual	2136,547	74	28,872		
	Total	2596,814	78			
5	Regression	400,383	3	133,461	4,557	,005[e]
	Not standardised Residual	2196,431	75	29,286		
	Total	2596,814	78			
6	Regression	355,629	2	177,814	6,030	,004[f]
	Not standardised Residual	2241,185	76	29,489		
	Total	2596,814	78			

a. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-MCare, PBI-PCare, sumPostnatal, PBI-MProt

b. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-PCare, sumPostnatal, PBI-MProt

c. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-PCare, sumPostnatal

d. independent variables : (constant), TICS-SSCS, sumPrenatal, PBI-PCare, sumPostnatal

e. independent variables : (constant), TICS-SSCS, PBI-PCare, sumPostnatal

f. independent variables : (constant), TICS-SSCS, PBI-PCare

g. dependent variable: Cortisol daily profile average value: 30 min after awakening

Table 61: coefficients for the prediction of CAR value (W-U+30)

Model		Not standardised coefficients		Standardised coefficients	T	Sig.	95,0% Confidence interval for B		Correlations			Correlation statistics	
		Coefficient of regressionB	Standarddeviation	Beta			lower limit	upper limit	Zero order	Part II	Part	Toleration	VIF
1	(constant)	-1,611	4,829		-,334	,740	-11,240	8,018					
	sumPrenatal	,567	,472	,164	1,202	,233	-,374	1,508	,059	,141	,128	,610	1,640
	sumPostnatal	-1,160	,613	-,265	-1,893	,062	-2,381	,062	-,117	-,219	-,201	,580	1,725
	PBI-MCare	-,071	,100	-,100	-,711	,480	-,271	,129	,073	-,084	-,076	,570	1,753
	PBI-MProt	-,140	,126	-,203	-1,113	,270	-,392	,111	-,047	-,131	-,118	,339	2,948
	PBI-PCare	,263	,095	,346	2,762	,007	,073	,452	,250	,312	,294	,719	1,390
	PBI-PProt	,141	,114	,211	1,242	,218	-,086	,369	-,042	,146	,132	,391	2,556
	TICS-SSCS	,170	,062	,314	2,740	,008	,046	,294	,242	,309	,291	,862	1,160
2	(constant)	-3,253	4,226		-,770	,444	-11,678	5,171					
	sumPrenatal	,587	,470	,169	1,251	,215	-,349	1,523	,059	,146	,133	,612	1,635
	sumPostnatal	-1,042	,587	-,238	-1,773	,080	-2,213	,130	-,117	-,205	-,188	,626	1,598
	PBI-MProt	-,097	,110	-,141	-,883	,380	-,318	,123	-,047	-,103	-,094	,440	2,274
	PBI-PCare	,239	,089	,316	2,691	,009	,062	,417	,250	,302	,285	,815	1,226
	PBI-PProt	,120	,109	,178	1,094	,278	-,098	,337	-,042	,128	,116	,422	2,369
	TICS-SSCS	,168	,062	,310	2,717	,008	,045	,291	,242	,305	,288	,864	1,157
3	(constant)	-2,856	4,196		-,681	,498	-11,217	5,506					
	sumPrenatal	,671	,459	,194	1,460	,149	-,245	1,586	,059	,168	,155	,638	1,568

	sumPostnatal	-1,104	,582	-,252	-1,895	,062	-2,264	,057	-,117	-,217	-,201	,635	1,575
	PBI-PCare	,232	,088	,307	2,628	,010	,056	,409	,250	,294	,278	,822	1,217
	PBI-PProt	,052	,078	,078	,667	,507	-,103	,207	-,042	,078	,071	,828	1,207
	TICS-SSCS	,152	,059	,280	2,575	,012	,034	,269	,242	,289	,273	,946	1,057
4	(constant)	-1,746	3,837		-,455	,651	-9,391	5,900					
	sumPrenatal	,658	,457	,190	1,440	,154	-,253	1,569	,059	,165	,152	,639	1,566
	sumPostnatal	-1,064	,577	-,243	-1,843	,069	-2,213	,086	-,117	-,210	-,194	,642	1,558
	PBI-PCare	,210	,081	,277	2,579	,012	,048	,372	,250	,287	,272	,965	1,036
	TICS-SSCS	,153	,059	,283	2,608	,011	,036	,270	,242	,290	,275	,947	1,056
5	(constant)	-1,231	3,848		-,320	,750	-8,896	6,434					
	sumPostnatal	-,591	,478	-,135	-1,236	,220	-1,543	,361	-,117	-,141	-,131	,949	1,054
	PBI-PCare	,201	,082	,265	2,457	,016	,038	,363	,250	,273	,261	,971	1,030
	TICS-SSCS	,161	,059	,298	2,745	,008	,044	,279	,242	,302	,291	,957	1,045
6	(constant)	-1,826	3,831		-,477	,635	-9,455	5,803					
	PBI-PCare	,213	,081	,282	2,626	,010	,052	,375	,250	,288	,280	,987	1,013
	TICS-SSCS	,149	,058	,275	2,559	,012	,033	,264	,242	,282	,273	,987	1,013

a. : Cortisol daily profile average value: 30 min after awakening

Appendix 22

Table 62: ANOVA $_f$ for the CAR value (W-U+45)

ANOVA[f]

Model		Sum of squares	df	Root mean square	F	Sig.
1	Regression	389,125	7	55,589	2,146	,049[a]
	Not standardised Residual	1942,973	75	25,906		
	Total	2332,098	82			
2	Regression	387,689	6	64,615	2,526	,028[b]
	Not standardised Residual	1944,409	76	25,584		
	Total	2332,098	82			
3	Regression	371,564	5	74,313	2,919	,018[c]
	Not standardised Residual	1960,534	77	25,461		
	Total	2332,098	82			
4	Regression	351,041	4	87,760	3,455	,012[d]
	Not standardised Residual	1981,057	78	25,398		
	Total	2332,098	82			
5	Regression	292,701	3	97,567	3,779	,014[e]
	Not standardised Residual	2039,398	79	25,815		
	Total	2332,098	82			

a. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-MCare, PBI-PCare, sumPostnatal, PBI-MProt

b. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-PCare, sumPostnatal, PBI-MProt

c. independent variables : (constant), TICS-SSCS, PBI-PProt, sumPrenatal, PBI-PCare, sumPostnatal

d. independent variables : (constant), TICS-SSCS, sumPrenatal, PBI-PCare, sumPostnatal

e. independent variables : (constant), sumPrenatal, PBI-PCare, sumPostnatal

f. dependent variable: Cortisol daily profile average value: 45 min after awakening

Table 63: coefficients for the CAR value (W-U+45)

Model		Not standardised coefficients		Standardised coefficients	T	Sig.	95,0% Confidence interval for B		correlations			Correlation statistics	
		Coefficient of regressionB	Standarddeviation	Beta			lower limit	upper limit	Zero order	Part II	Part	Toleration	VIF
1	(constant)	,837	4,782		,175	,862	-8,690	10,363					
	sumPrenatal	,855	,442	,264	1,935	,057	-,025	1,736	,073	,218	,204	,598	1,672
	sumPostnatal	-1,461	,574	-,354	-2,547	,013	-2,604	-,318	-,156	-,282	-,268	,574	1,743
	PBI-MCare	-,022	,091	-,032	-,235	,815	-,204	,161	,110	-,027	-,025	,616	1,622
	PBI-MProt	-,086	,107	-,131	-,800	,426	-,299	,128	-,069	-,092	-,084	,415	2,409
	PBI-PCare	,239	,090	,322	2,655	,010	,060	,418	,230	,293	,280	,756	1,323
	PBI-PProt	,117	,097	,183	1,207	,231	-,076	,310	,000	,138	,127	,485	2,061
	TICS-SSCS	,096	,060	,183	1,599	,114	-,024	,216	,070	,182	,169	,845	1,184
2	(constant)	,323	4,228		,076	,939	-8,099	8,744					
	sumPrenatal	,866	,437	,267	1,979	,051	-,006	1,737	,073	,221	,207	,604	1,656
	sumPostnatal	-1,436	,560	-,348	-2,564	,012	-2,551	-,321	-,156	-,282	-,269	,595	1,681
	PBI-MProt	-,073	,092	-,112	-,794	,430	-,256	,110	-,069	-,091	-,083	,555	1,801
	PBI-PCare	,233	,085	,313	2,722	,008	,062	,403	,230	,298	,285	,828	1,208
	PBI-PProt	,111	,093	,173	1,196	,236	-,074	,296	,000	,136	,125	,523	1,911
	TICS-SSCS	,096	,060	,182	1,600	,114	-,023	,215	,070	,181	,168	,847	1,181
3	(constant)	,349	4,218		,083	,934	-8,050	8,748					
	sumPrenatal	,926	,430	,285	2,156	,034	,071	1,782	,073	,239	,225	,623	1,606

	sumPostnatal	-1,486	,555	-,360	-2,676	,009	-2,591	-,380	-,156	-,292	-,280	,602	1,660
	PBI-PCare	,228	,085	,307	2,682	,009	,059	,397	,230	,292	,280	,831	1,203
	PBI-PProt	,065	,072	,101	,898	,372	-,079	,208	,000	,102	,094	,863	1,159
	TICS-SSCS	,087	,059	,166	1,488	,141	-,030	,204	,070	,167	,156	,873	1,145
4	(constant)	1,686	3,941		,428	,670	-6,160	9,533					
	sumPränatal	,928	,429	,286	2,163	,034	,074	1,782	,073	,238	,226	,623	1,605
	sumPostnatal	-1,463	,554	-,355	-2,642	,010	-2,566	-,361	-,156	-,287	-,276	,604	1,657
	PBI-PCare	,202	,080	,272	2,531	,013	,043	,360	,230	,275	,264	,944	1,060
	TICS-SSCS	,089	,059	,169	1,516	,134	-,028	,206	,070	,169	,158	,874	1,144
5	(constant)	6,734	2,125		3,170	,002	2,505	10,963					
	sumPrenatal	,957	,432	,295	2,214	,030	,097	1,817	,073	,242	,233	,624	1,602
	sumPostnatal	-1,292	,547	-,313	-2,364	,021	-2,381	-,204	-,156	-,257	-,249	,630	1,588
	PBI-PCare	,178	,079	,240	2,258	,027	,021	,335	,230	,246	,238	,982	1,018

a. dependent variable: Cortisol daily profile average value: 45 min after awakening

Appendix 23

Table 64 : ANOVA g for the CAR value (W-U+60)

Model		Sum of squares	df	Root mean square	F	Sig.
1	Regression	287,480	7	41,069	2,000	,066[a]
	Not standardised Residual	1519,885	74	20,539		
	Total	1807,365	81			
2	Regression	286,230	6	47,705	2,352	,039[b]
	Not standardised Residual	1521,134	75	20,282		
	Total	1807,365	81			
3	Regression	267,675	5	53,535	2,643	,029[c]
	Not standardised Residual	1539,690	76	20,259		
	Total	1807,365	81			
4	Regression	228,391	4	57,098	2,784	,032[d]
	Not standardised Residual	1578,974	77	20,506		
	Total	1807,365	81			
5	Regression	180,289	3	60,096	2,881	,041[e]
	Not standardised Residual	1627,076	78	20,860		
	Total	1807,365	81			
6	Regression	161,306	2	80,653	3,871	,025[f]
	Not standardised Residual	1646,059	79	20,836		
	Total	1807,365	81			

a. independent variables: (constant), TICS-SSCS, PBI-PCare, sumPrenatal, PBI-MProt, PBI-MCare, sumPostnatal, PBI-PProt

b. independent variables: (constant), TICS-SSCS, PBI-PCare, sumPrenatal, PBI-MProt, sumPostnatal, PBI-PProt

c. independent variables: (constant), TICS-SSCS, PBI-PCare, PBI-MProt, sumPostnatal, PBI-PProt

d. independent variables: (constant), TICS-SSCS, PBI-PCare, PBI-MProt, PBI-PProt

e. independent variables: (constant), TICS-SSCS, PBI-PCare, PBI-PProt

f. independent variables: (constant), TICS-SSCS, PBI-PCare

g. dependent variable: Cortisol daily profile average value: 60 min after awakening

Table 65: coefficients for the CAR value (W-U+60)

Model		Not standardised coefficients		Standardised coefficients	T	Sig.	95,0% Confidence interval for B		correlations			Correlation statistics	
		Coefficient of regressionB	Standard deviation	Beta			lower limit	upper limit	Zero order	Part II	Part	Toleration	VIF
1	(constant)	-,075	3,807		-,020	,984	-7,660	7,510					
	sumPrenatal	,364	,396	,127	,920	,361	-,424	1,152	,028	,106	,098	,593	1,687
	sumPostnatal	-,864	,511	-,238	-1,692	,095	-1,881	,153	-,104	-,193	-,180	,576	1,735
	PBI-MCare	-,020	,082	-,033	-,247	,806	-,184	,143	,116	-,029	-,026	,632	1,583
	PBI-MProt	-,128	,099	-,220	-1,297	,199	-,325	,069	-,037	-,149	-,138	,395	2,533
	PBI-PCare	,209	,079	,322	2,656	,010	,052	,367	,227	,295	,283	,773	1,294
	PBI-PProt	,143	,088	,254	1,633	,107	-,031	,317	,039	,187	,174	,471	2,122
	TICS-SSCS	,115	,051	,265	2,249	,027	,013	,216	,165	,253	,240	,819	1,221
2	(constant)	-,501	3,371		-,149	,882	-7,216	6,214					
	sumPrenatal	,374	,391	,131	,956	,342	-,405	1,153	,028	,110	,101	,599	1,669
	sumPostnatal	-,838	,496	-,230	-1,688	,096	-1,826	,151	-,104	-,191	-,179	,602	1,660
	PBI-MProt	-,116	,086	-,200	-1,356	,179	-,287	,055	-,037	-,155	-,144	,518	1,931
	PBI-PCare	,203	,074	,313	2,732	,008	,055	,352	,227	,301	,289	,856	1,168
	PBI-PProt	,137	,084	,243	1,638	,106	-,030	,304	,039	,186	,173	,509	1,966
	TICS-SSCS	,113	,050	,261	2,250	,027	,013	,213	,165	,251	,238	,832	1,202
3	(constant)	-,155	3,350		-,046	,963	-6,826	6,516					
	sumPostnatal	-,559	,401	-,154	-1,393	,168	-1,357	,240	-,104	-,158	-,147	,921	1,086
	PBI-MProt	-,131	,084	-,225	-1,550	,125	-,299	,037	-,037	-,175	-,164	,534	1,871
	PBI-PCare	,197	,074	,304	2,663	,009	,050	,345	,227	,292	,282	,862	1,160
	PBI-PProt	,147	,083	,261	1,770	,081	-,018	,312	,039	,199	,187	,517	1,935
	TICS-SSCS	,118	,050	,273	2,360	,021	,018	,217	,165	,261	,250	,841	1,190
4	(constant)	-,156	3,370		-,046	,963	-6,867	6,554					
	PBI-MProt	-,130	,085	-,223	-1,532	,130	-,299	,039	-,037	-,172	-,163	,535	1,871
	PBI-PCare	,201	,075	,309	2,698	,009	,053	,350	,227	,294	,287	,863	1,159
	PBI-PProt	,143	,083	,254	1,718	,090	-,023	,310	,039	,192	,183	,517	1,934
	TICS-SSCS	,100	,049	,232	2,061	,043	,003	,197	,165	,229	,220	,899	1,112
5	(constant)	,492	3,372		,146	,884	-6,221	7,205					
	PBI-PCare	,187	,075	,287	2,502	,014	,038	,335	,227	,273	,269	,877	1,140
	PBI-PProt	,062	,065	,110	,954	,343	-,067	,191	,039	,107	,102	,871	1,148
	TICS-SSCS	,080	,047	,184	1,692	,095	-,014	,174	,165	,188	,182	,972	1,029
6	(constant)	1,563	3,178		,492	,624	-4,763	7,888					

PBI-PCare	,163	,070	,251	2,318	,023	,023	,303	,227	,252	,249	,985	1,015
TICS-SSCS	,085	,047	,196	1,813	,074	-,008	,178	,165	,200	,195	,985	1,015

a. dependent variable: Cortisol daily profile average value: 60 min after awakening

Hiermit versichere ich, dass ich die vorliegende Arbeit selbständig verfasst und keine anderen als die angegebenen Quellen oder Hilfsmittel verwendet habe.

Colpach-Haut, den 17.07.2014 _____

Dipl.-Psych. Nathalie Kipgen