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The influence of personality and psychological variables on immunological response in recently diagnosed breast cancer patients

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Andrew Antony Walker
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PG Cert Research Training, MICR

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The influence of personality and psychological variables on immunological response in recently diagnosed breast cancer patients

Andrew A Walker

Department of Clinical Psychology

University of Hull

Abstract: In Study one, 183 women were assessed 6 weeks post-surgery for early breast cancer using the revised Eysenck Personality Questionnaire (EPQ-R), the Positive and Negative and Affect Schedule (PANAS), the Multidimensional Health Locus of Control Scale (MHLCS) and the Courtauld Emotional Control Scale (CECS). Blood samples were collected for neuroendocrinological and immunological (NI) analyses. Based on structured literature reviews hypotheses were generated regarding personality and NI relationships. Following normalisation of distributions as required, the relationship between personality variables and NI variables were computed using Pearson's Product-Moment Correlation coefficients. As Psychoneuroimmunological (PNI) relationships may be effected by age, multiple linear regression was used to establish the extent to which significant relationships remained. At least one NI measure correlated significantly with at least one personality dimension. Five immunological variables were predicted by two or more personality variables. (1) Psychoticism and Extraversion both correlated significantly with the Th1-like response CD4/IL10. When entered simultaneously with age, Psychoticism and Extraversion accounted for 7.1% of the variance, better than either trait alone. (2) Neuroticism, Positive Affect (PA) and Anger correlated significantly with the Th1-like response CD4/IFNγ, together accounting for almost 10% of the variance, again greater than any single variable alone. (3) Neuroticism, Negative Affect (NA), Internal Locus of Control (ILOC) and Chance Locus of Control (CLOC) were all significantly correlated with the Th1-like response CD8/IL2 and collectively accounted for almost 10% of the variance, greater than any one variable alone. However, only CLOC was a significant independent predictor of percentage of CD8/IL2. (4) CLOC and Powerful-other Locus of Control (PLOC) correlated with NK cell activity, but were less predictive than each individual dimension alone, and (5) Anxiety combined with Depressed mood correlated with percentage cells expressing CD2, but was less predictive than each individual dimension alone. The direction of the relationships are not always easy to reconcile with the existing literature on host defences and prognosis on the one hand, and personalty and survival on the other. This could be due to the particular characteristics of the participants, a very well adjusted group of women with early breast cancer six weeks post surgery, or it may reflect the subtlety of how the many components of the immune system interact to produce an effective anti-cancer response.

Study two investigated the stability of personality and NI correlations over 18 weeks, and to investigate interaction effects between NI and higher and lower scorers

on various measures of personality. 62 women with early breast cancer were studied. Personality was assessed 6 weeks post-surgery using the revised Eysenck Personality Questionnaire (EPQ-R), the Positive and Negative and Affect Schedule (PANAS), the Multidimensional Health Locus of Control Scale (MHLCS) and the Courtauld Emotional Control Scale (CECS). Blood samples were collected at 6, 18 and 24 weeks post surgery for NI analysis. Pearson's product-moment correlations were computed for each personality variable and each NI measure to identify variables that produced statistically significant correlations at more than one time point, thereby indicating a significant degree of longitudinal stability. In order to identify possible differences between above and below average scorers on the personality variables (interaction effects), median values were derived for each of the personality variables and these were used to create groups of above and below median scorers. Personality and NI relationships were examined across the three time points by ANOVA. A statistically significant interaction between Extraversion and CD19 was obtained for T1 and T2 ($F=9.496$, $p=.004$) and T1 and T3 ($F=5.037$, $p=.030$) indicating that in lower scorers CD19 decreased significantly over time whereas in higher scorers it was relatively stable. This is a novel finding which deserves further study. A number of interesting statistically non-significant interesting effects were observed for Lie and CD8/IL10, Lie and LAK, Positive Affect (PA) and LAK, Negative Affect (NA) and PRL-R, NA and Cortisol, NA and Growth Hormone, NA and GH-R, CLOC and Growth Hormone, and Powerful-other Locus of Control (PLOC) and PRL-R.

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Preface

The investigation of trait personality (herafter personality) variables and immunological response in recently diagnosed breast cancer patients requires familiarity with the fundamentals of personality (specifically trait personality) cancer (specifically breast cancer) and the immune system (in particular the elements of the immune system known to be related to cancer). In what follows, a review of current health policy and assumptions sets the scene in terms of the healthcare landscape in which this thesis is set. The end product of this thesis is, at its simplest, a set of snap shots of personality and neuroendocrinological-immunological (hereafter NI) correlates, first using a single time point design, exploring the associations between personality and immunological response shortly after surgery for early breast cancer. Second, we focus on a smaller group of participants, and follow-them up over 18 weeks to look for evidence of a personality effect on immune response, as evidenced by an interaction effect of time and between group differences.

Prior to undertaking empirical study, it was first necessary to explore and understand what is already known about the relationship between personality and cancer. Structured literature reviews were conducted on Eysenckian personality dimensions and cancer incidence and survival (Chapter three), affect and cancer incidence and survival (Chapter four), locus of control and cancer incidence and survival (Chapter five) and emotional control and risk of cancer (Chapter six).

A structured literature review of personality and immunology is presented in Chapter seven, this is positioned between the epidemiological literature and the present study as it acts as a conduit between that what is known and that which is not. The purpose of the literature review on personality and immunology was:

1. To evaluate the known relationships of personality and NI variables in subjects with a diagnosis of cancer.

2. To identify the nature and quality of the evidence available on this subject.

Methods and results are presented and set in the context of their strengths before the included studies are critically evaluated and suggestions for further research presented, two lines of which are presented within this thesis.

Background review indicated that a number of measures of personality have been used to determine associations with cancer incidence and/or survival. A surface review of the results suggest that there may be little value in such a line of enquiry. However, a more critical evaluation revealed that methodological shortcomings (most notably choice

of personality measure and heterogeneous sample selection) may obscure the true picture.

A Randomised Controlled Trial (RCT) provided the context for the research undertaken as part of this thesis. The Hull and East Yorkshire Local Research Ethics Committee provided a favorable opinion (reference 01/01/010) for the RCT registered with the International Standard Randomized Controlled Trial Registry (ISRCTN87652313). The purpose and results of these trials can be found in the associated peer-reviewed publications (Sharp et al., 2010; Green et al., 2010) presented in appendices one and two respectively. The author was employed as a research associate on the trial and is a coauthor of both papers.

1. Study one (Chapter eight) is an investigation of the relationships between personality and NI variables in women with early breast cancer.

2. Study two (Chapter nine) is an investigation of the predictive value of high and low scores of personality variables on NI response over time.

An overall discussion is presented in Chapter 10 to summarise, interpret and discusses the strengths and weaknesses of the results of the research in the context of the background literature and to consider their implications for psychological theory, future research and clinical practice.

Chapter 1: Context and Overview

1.1 Chapter overview

This chapter presents the justification for, and and overview of, this thesis. Cancer is presented as a major population health problem accounting for over 150,000 deaths in the United Kingdom (UK) alone in 2010 (Cancer Research UK, 2013d). Breast cancer is the single biggest cancer killer in the UK (Cancer Research UK, 2013c), although survival rates are increasing (Cancer Research UK, 2013c).

Recent interest has focussed on the immunological mechanisms associated with cancer development and progression (Eremin & Sewell, 2011; Lewis et al., 2002). However, there is no consensus as to whether the risk of developing cancer, or having cancer progression or recurrence, is associated with individual differences, or, as it will be refereed hereafter, personality.

This chapter gives an overview of the incidence and nature of cancer, and in particular breast cancer, components of the immune system, and more specifically, components of the immune system believed to be involved in a cancer response, NI pathways, and psychoneuroimmunology (hereafter PNI) (Vedhara & Irwin, 2005; R. Ader et al., 1991). Here personality is introduced as an under-explored construct which fits comfortably with a PNI paradigm (Kuhn, 1970).

1.2 Background

A key focus for psychology is understanding behaviour, cognition and emotion. Personality has long been suggested as a vehicle for understanding and explaining individual differences in behaviour, cognition and emotion. A number of measures of personality have been suggested, each with an underpinning theory. Perhaps the two most widely adapted theories are those by Eysenck (1953) and R. R. McCrae & Costa (1987). While Eysenck (1953) postulated that the three dimensions of Extraversion, Neuroticism and Psychoticism explained behaviour, more recently R. R. McCrae & Costa (1987) suggested that five dimensions were needed, namely Extraversion, Neuroticism, Openness, Conscientiousness and Agreeableness. However, the suggestion of a Type C (cancer-prone) personality was first raised by Kissen & Eysenck (1962) and implicated (high) Extraversion (low) Neuroticism. It was for this reason that the latest Eysenckian personality measure (the EPQ-R) was selected over a measure of the big 5 (Extraversion, Neuroticism, Openness, Conscientiousness and Agreeableness). These theories and dimensions are considered in more detail

in Chapter two.

The effects of psychological stressors such as cancer and the treatment of cancer are known to correlate with NI variables. This paradigm of considering psychological and NI variables as interrelated is termed psychoneuroimmunology (PNI) (R. Ader et al., 1991; R. Ader, 1983).

Segerstrom (2000) reviews four models that may explain the relationships between personality and NI. These are expanded upon in Chapter two but in brief may be a 'main effect' (*i.e.* personality is associated with immune system status), 'predispositional effect'; (*i.e.* personality is a risk factor for another variable), 'pathoplastic effect' (*i.e.* each variable affects the presentation of another variable), or 'common cause' effect (*i.e.* both variables share a common aetiology).

Cancer refers to diseases where there is a breakdown in the mechanisms which control cellular division, thereby allowing abnormal cells to divide and invade other tissues. Each year in the UK over 300,000 people in the UK are diagnosed with cancer (Cancer Research UK, 2013b) and approximately half die from the disease (Cancer Research UK, 2013d). Breast cancer is the most commonly diagnosed form of cancer in the UK accounting for 15% of all cancer diagnoses and 31% of cancer diagnoses in women (Cancer Research UK, 2013a).

As the average age of the population increases, due in part to the increasing success of health care initiatives and improvements in therapy, mortality rates and the impact on the NHS are unlikely to decrease. Therefore, better understanding the relationship between personality and the NI system of females with breast cancer may open the door to improvements in the treatment and care of women with breast cancer with the potential to improve outcomes (a UK government strategy) (Department of Health, 2011).

There is existing evidence that:

1. The humoral and cellular immune systems in humans have been well charecterised (Roitt et al., 2001).

2. The bidirectional influences of the brain and the immune system have been well documented and are becoming better defined (C. Ader, 2007; Vedhara & Irwin, 2005).

3. Reliable and valid (Cooper, 2002) measures of personality are available (P. T. Costa & McCrae, 1992; Eysenck & Eysenck, 1991), particularly measures of enduring personality constructs called traits such as Extroversion and Neuroticism (see Chapter two).

There is a need for well designed studies to indicate whether personality influences the immune system, for example, the extent to which a person scoring high on traits such as Neuroticism and Extraversion have impeded or improved immune function compared with their lower scoring counterparts. Existing literature focusses primarily on endpoints such as the incidence of cancer and death. However, samples and measures vary widely and reported results either supporting the presence or absence of such relationships are often open to critique of either the methods, analysis and/or interpretations (Chapters three to seven). These findings are of limited use in the understanding of relationships between personality and NI as most feature one or more of the four limitations below. Moreover, investigation of the personality variables that are or are not associated with immune response will inform further investigation.

Current research, summarised and discussed in Chapters three to seven, are often charecterised by:

1. Medical outcomes such as death or diagnoses of a cancer.
2. Heterogenous cancer types.
3. Non-standardised personality measures.
4. Lack of a longitudinal design.

Previous research has produced conflicting results, which may to some extent be explainable by the above limitations. Additionally, much associated research, not discussed within this thesis, has focussed upon the role of stressors on mood and how these impact on host defences (Maes, 2011; Dowlati et al., 2010; Agarwal & Marshall, 2001). These studies have undoubtedly informed the developing evidence of the role of psychological and NI variables in patients with a cancer but the systemic (Churchman, 1979, 1971) nature of PNI often makes it hard to distinguish between outcome and mechanism.

There is, therefore, a need for a well designed and controlled study to investigate one element of this systemic paradigm, specifically the relationship between personality and NI variables.

The potential role of personality and NI in cancer is under-investigated. Investigating the influence of personality variables on immunological response in recently diagnosed breast cancer patients is an important objective.

1.3 Cancer

The term 'cancer' refers to a heterogenous grouping of more than 200 different diseases (Cancer Research UK, 2013b), each a variation on the tissues and or cells effected

by the disease. However, all ytpes of cancer can be categorised asCancer Research UK (2013b):

- Carcinoma (originating in the skin or tissue covering internal organs).
- Sarcoma (originating in bone, cartilage, fat, muscle, blood vessels, *etc.*).
- Leukemia (originating in blood forming tissue).
- Lymphoma and myeloma (originating in the immune system).
- Central nervous system (CNS) (originating in the brain or spinal cord).

324,579 people in the UK were diagnosed with cancer in 2010 (Cancer Research UK, 2013b) and the lifetime risk of receiving a cancer diagnosis is more than one in three (Cancer Research UK, 2013f). In the same year 157,275 people died from cancer in the United Kingdom (Cancer Research UK, 2013d).

The population health implications of cancer make it a strong candidate for exploring the relationship between personality and NI anti-cancer response (how an anti-cancer response may be characterised is discussed below in this chapter). However, as cancer is a heterogenous term encompassing the five types listed above, it is perhaps too diverse a disease to meet the criteria for a well sample-controlled study as immunological responses to cancer are known to vary considerably.

1.4 Breast cancer

Breast cancer is the most commonly diagnosed form of cancer in the UK; 15% of all cancer diagnoses are breast cancer. However, given the gender imbalance in the incidence of breast cancer, it is not surprising that breast cancer accounts for 31% of cancer diagnoses in women, almost 50,000 in 2010, the last year for which information is available (Cancer Research UK, 2013a). There is an associated lifetime risk of developing breast cancer of 0.12% (1 in 868) for males and 6.22% (1 in 12.90) for females (Cancer Research UK, 2013f). Sadly, these figures are increasing in the UK (Cancer Research UK, 2013a), due in part to the increasing success of health-care initatiatives and improvement in therapy.

However, although breast cancer is the most prevalent cancer in females, it is not the most common cause of cancer-related female deaths; it accounts for 15% (11,556 deaths) of cancer-related deaths in females during 2010, compared with 21% for lung cancer (the most deadly cancer in females) (Cancer Research UK, 2013c). Positively, in the UK survival rates are improving: European age-standardised 3-year average mortality rates for females has decreased by 19% between 1999-2001 and 2008-2010 (Cancer Research UK, 2013c). This reflects improvements in medical and surgical treatments, as well as earlier diagnosis,

the introduction of a national screening programme and, possibly, public health initiatives to address lifestyle-related factors (such as physical inactivity, alcohol, smoking and diet).

Breast cancer forms in breast tissue making it a carcinoma (see section 1.3 above). Breast cancer is a disease characterised by inadequately controlled change and growth (proliferation) in normal cells creating a lump or tumour. Untreated, a tumour may spread into nearby tissue or spread to other parts of the body through the lymphatic system or bloodstream (metastasis).

The most frequently diagnosed type of breast cancer is ductal carcinoma (DC). DC accounts for between 70% and 80% of all breast cancer diagnoses (Cancer Research UK, 2013e). The remaining types of invasive breast cancer comprise invasive lobular, cribriform, inflammatory, malignant phyllodes medullary, metaplastic, mucinous, papillary, tubular and Paget's disease (Breast Cancer Care, 2013).

DC originates in the lining of the milk ducts (tubes that carry milk from the lobules of the breast to the nipple). Ductal Carcinoma In Situ (DCIS) occurs when cancerous cells are all contained inside the ducts and have not spread into the surrounding tissue. However, DCIS can progress to DC which, by definition, has spread into the surrounding breast tissue.

The extent of the spread for clinical purposes is summarised by using the TNM classification (Cancer Research UK, 2013g): size of the tumour (T), spread to the lymph glands/nodes (N), and metastases (M) .

The size of the tumour (T) is clinically categorised as[1]:

- Tx = cannot be assessed.
- Tis = DCIS, see above.
- T1 = $\leq$ 2cm.
- T2 = $>$ 2 and $<$ 5cm.
- T3 = $\geq$ 5 cm.
- T4 = spread to skin or chest wall.

Nodes (N) are clinically categorised as:

- Nx = cannot be assessed.
- N0 = no cancer cells in nearby nodes.
- N1 = cancer cells present in lymph nodes of the armpit but are not stuck to surrounding tissues.

[1] Various TNM categories have been excluded, and included categories are often further subdivided but such specificity is beyond the requirements of this thesis.

- N2 = cancer cells present in lymph nodes of the armpit but are not stuck to surrounding tissues or cancer cells present in the lymph nodes behind the breast bone detectable by scan or touch.
- N3 = cancer cells present in lymph nodes below the collarbone, in the armpit and behind the breast bone, or above the collarbone.

Metastases (M) are clinically categorised as:

- M0 = No sign of cancer spread (no metastases).
- M1 = Signs of cancer spread (metastases).

Breast cancer therefore offers an opportunity to increase our understanding of the influence of personality in a well classified disease of major population health relevance. Moreover, this understanding would be increased by investigating a homogenous group with respect to TNM stage (as we will see, this level of specificity may be important in detecting relationships in a complex (Waldrop, 1992) system (Churchman, 1979, 1971). Additionally, the standardised use of reliable and valid measures of personality would increase understanding of the most relevant personality variables. Although several personality factors have been associated with risk of cancer as well as disease progression (Type C personality - see chapter two), whether these are related to NI response is unknown. Combining carefully controlled personality and NI measures in a carefully conducted study could increase what is known about the possible relationship between personality and NI measures in breast cancer.

1.5 A brief overview of the immune system

1.5.1 Innate and adaptive immune systems. The primary function of the immune system is to eliminate infectious agents and to minimise any damage caused. Immune response involves identification of the pathogen (infectious agent or cause of disease) and a response to eliminate the pathogen. This two-stage process is undertaken by two integrated immune systems. The first is an innate (non-adaptive) immune system, and the second an adaptive immune system. The differences between these two systems are (1) specificity and (2) memory. That is the adaptive immune system is highly specific to a particular pathogen (for example *varicella zoster*) and, once encountered, subsequent response to the pathogen improves as the adaptive immune system 'remembers' the pathogen and provides, in the case of *varicella zoster virus* for example, life-long immunity by retaining the ability to re-call antigen, sometimes referred to as antigenic 'memory' (Szlosarek & Dalgleish, 2002).

1.5.2 Cells. The main source of immune response is leucocytes (white blood cells), of which there are two main types. The first type of leucocytes are *phagocytes* (neutrophil, eosinophil and mononuclear phagocytes, which bind to microorganisms, internalise and kill them as part of the innate immune response). Blood cells derived from mononuclear phagocytes are referred to as *monocytes.* Monocytes are particularly important as they engulf, internalise and destroy particles. Additionally within the body they can be found where they are most likely to encounter such a particle, and are all derived from stem cells in bone marrow. Monocytes move from blood to tissue where most needed and are excellent at presenting antigens to T lymphocytes. Polymorphonuclear neutrophils (sometimes referred to as PMNs or from here on *neutrophils*) are the most prominent phagocyte within the human body, and move into tissues, particularly during an inflammatory response. Unlike monocytes, the act of engulfing and destroying the particle is fatal to the neutrophil making them short lived in comparison to the monocytes (Roitt et al., 2001).

The second type of leucocytes, *lymphocytes*, are involved in the adaptive immune response and recognise specific pathogens. Lymphocytes can be further described as B lymphocytes (*B cells*), T lymphocytes (*T cells*) and *Large Granular Lymphocyte*s. B cells target pathogens outside of the host cell in the tissue or blood by releasing a molecule which specifically recognises and binds to a particular target molecule (antigen). This target molecule may either be a molecule on the surface of a pathogen, or a toxin produced by the pathogen. T cells have a broader role, some control B cell development and the production of antigen, others interact with phagocytic cells to assist in the destruction of pathogens, yet others recognise and destroy virus-infected cells. *B cells* are specific to particular antigens and once the paired antigen is recognised, the B cell multiplies and differentiates into plasma cells, producing its soluble mediator, a large glycoprotein antibody present in blood and tissue that is virtually identical to the originating B cell. As the connection between B cell (in its its antibody form) and antigen is maintained, the antibody can bind with the antigen (Roitt et al., 2001).

A T cell may take one of three forms :

- Type-1 helper (Th1) cells interact with mononuclear phagocytes to help them destroy intracellular pathogens (see figure 1).
- Type-2 helper (Th2) cells interact with B cells to help them to divide, differentiate and make antibody (see figure 2).
- T cytotoxic (Tc) cells destroy host cells infected by intracellular pathogen.

T cells impart an immune response either by releasing soluble mediators called cytokines or by direct cell-to-cell interactions. All three forms of T cell recognise antigens only when presented on the surface of the other cell by the major histocompatibility complex (MHC) molecules by means of a specific receptor called the T-cell antigen receptor (TCR) similar both functionally and structurally to the surface antibody used by B cells as antigen receptors (Roitt et al., 2001).

Large Granular Lymphocytes (LGLs) also recognise surface change to molecules, such as tumours. Unlike Tc cells, they are effective in identifying cells which have lost their MHC molecules. This is referred to as a natural killer (NK) response. Additionally LGLs can recognise and destroy some pathogens which become coated with a specific antibody (Roitt et al., 2001).

Auxiliary cells (basophil, mast cells and platelets) and other cells (tissue cells) are present in the immune system. Eosinophil polymorphs (*Eosinophils*) can damage large extracellular parasites by releasing granules in the vicinity of the parasite (Roitt et al., 2001).

Basophils and mast cells also have granules which, when triggered and released, produce inflammation via a variety of mediators. Both basophils and mast cells can also synthesise and secrete mediators which can control immune reactions. Basophils and mast cells differ in their range, mast cells can be found near blood vessels and in tissue whereas basophils circulate. Platelets, when activated, release inflammatory mediators.

Figure 1 depicts the components of the immune system discussed above and illustrates the components involved in adaptive immune response (green) and innate immune response (yellow) along with auxilliary cells (blue) and 'other' (magenta).

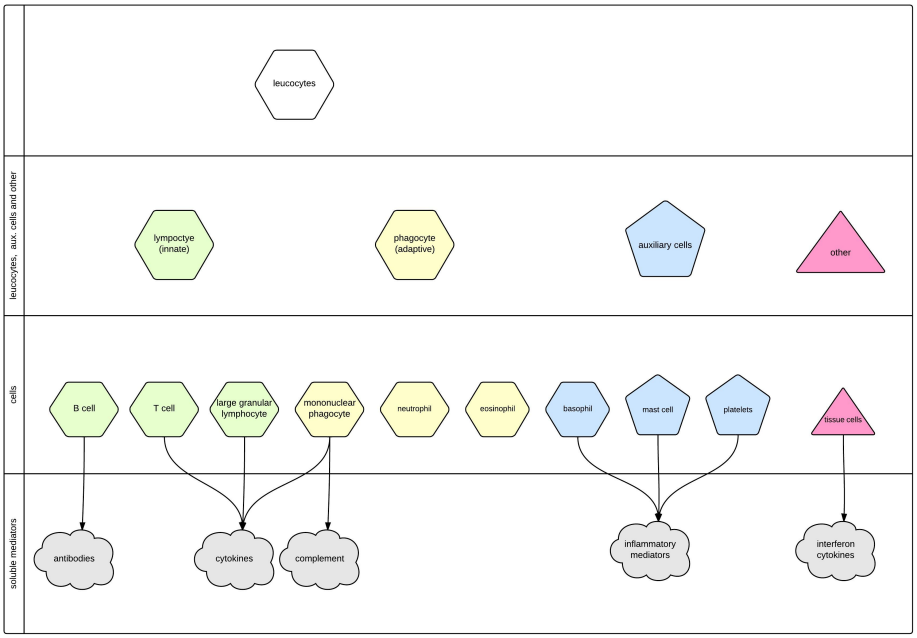

Figure 1. Components of the immune systems (adapted from Roitt et al. (2001), page 3).

While conceptually distinct, there is in practice considerable interaction between the lymphocytes and phagocytes. Therefore most immune responses to pathogens are both innate and adaptive. Early stage response is primarily innate but later stages feature lymphocyte-created adaptive responses to the pathogen thereby adding specificity and memory. Figure 2 depicts such interaction. The orange arrows show a scenario on which a phagocyte internalises an antigen and presents it to the T cell in a form it can recognise. Reciprocally, the T cell releases cytokines (soluble factors, see below), activating the phagocytes and resulting in the phagocytes destroying the pathogen they have internalised. In a second scenario (magenta line), B cells release antibodies allowing phagocytes to identify pathogens with greater accuracy. In a third scenario, (blue line) a sub-set of T cells controls B cell development.

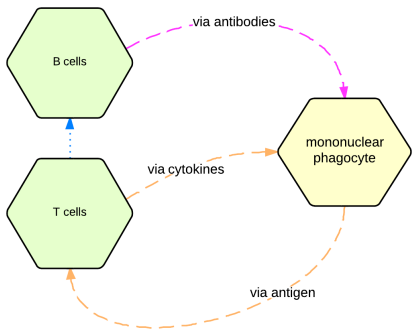

Figure 2. Interactions between and within the innate and active immune system. (adapted from Roitt et al. (2001), page 3).

Immune responses are controlled not just by the cells but also by the soluble molecules which they secrete. Figure 1 depicts the soluble mediators secreted by cells of the immune system.

1.5.3 Soluble mediators of immunity. As indicated in figure 1, a range of soluble mediators are involved in immune response and the concentration of these proteins in serum increases greatly during infection, which explains why they are sometimes referred to as acute phase proteins. *Antibody* (expressed by B cells) and *complement* (expressed by mononuclear phagocytes) promote phagoctytosis (the engulfing of an entity by a cell within a vacuole) and act as opsonins. Opsonins are deposited on an antigen promoting enhanced phagocytosis by improving the potential for binding (opsonisation) (Male, 2001).

The complement systems include around 20 serum proteins (Male, 2001) which interact with each other, mediate phagocytosis, control inflammation and interact with antibodies. Complement proteins cascade, that is to say each component has an effect of the previous component, *e.g.* (1) opsonisation prior to phagocytosis and intracellular killing (2) chemotaxis (the attraction of phagocytes to the infected site), (3) increased blood flow and permeability of capillaries to the infected site, (4) lysis (damage to the plasma membrane of a cell compromising its integrity), and (5) mast cells release further inflammatory mediators.

Cytokines are expressed by T cells, LGLs and mononuclear phagocytes. Cytokines are a large group of molecules which signal between cells during an immune response. The major divisions of cytokines are (Male, 2001):

- *Interferons* (IFNs): create an anti-viral resistance in unaffected cells. They are produced early in infection and are a first line of defense. IFNα and IFNβ are produced by cells which are virally infected. IFNγ is released by certain activated T cells.
- *Interleukins* (ILs): are cytokines produced mainly by T cells and which direct other cells to divide and differentiate (mononuclear phagocytes and tissue cells may also produce ILs).
- *Colony stimulating factors* (CSFs): direct the division and differentiation of bone marrow stem cells and the precursors of blood leucocytes.
- *Chemokines:* chemotactic cytokines direct cells around the body from blood to tissue.
- Other cytokines: Tumour necrosis factors *TNFa* and *TNFβ* and transforming growth factor-β (TGFTβ) have a variety of functions including the mediation of inflamma-

tion and cytotoxic reaction.

1.6 Psychoneuroimmunology (PNI)

The interdisciplinary study of the interactions between psychological processes and the nervous and immune systems of the human body, referred to as psychoneuroimmunology (PNI), involves collaborations between psychologists, immunologists, endocrinologists, neuroscientists, geneticists and other professions, with the shared aim of profiling the relationship between mental processes and health. Glaser and Kiecolt-Glaser (2005) summarised clinical and laboratory studies that indicate that the central nervous system (CNS) interacts bidirectionally with the endocrine and immune systems. Glaser & Kiecolt-Glaser (2005) point out that stress has been a focal point for PNI since the 1960s and has demonstrated that stress can induce immune dysregulation in a range of humoral and cellular immune responses.

In a seminal paper, Ader and Cohen (1975) reported that classical conditioning (Pavlov, 1927) techniques could be used to modify immune processes in rats in a similar manner to the way behaviorists such as Pavlov elicited conditioned responses in dogs. Ader and Cohen (1975) reported that if saccharin solution was associated with an immunosuppressive drug (cyclophosphamide) an immunosuppressive conditioned response to saccharin developed. Cessation of the drug with maintained saccharin solution resulted in avoidance to drinking the solution and death in some rats; the magnitude of the avoidance response was directly related to the volume of solution consumed. The implications of this classic study were clear - immune responses were modifiable by classical conditioning, and it therefore followed that (1) the brain and the immune system must be connected and (2) the brain could have a significant affect on physical functions that were previously believed to be independent. Almost 40 years later it is difficult to conceive of a contrary position. The term psychoneuroimmunology was first used by Ader in 1981 as the title to an edited book.

In a 10-year review of psychoneuroimmunology and cancer, Green McDonald et al. (2013) note that since a seminal issue of Brain, Behaviour and Immunity (as the title would suggest, a leading proponent of PNI) in 2003, 128 cancer-related PNI studies have been published in the journal compared with 12 articles published in the same journal before 2003. These bibliometric data suggest an increasing interest, and space, for PNI studies.

1.7 The immune system and cancer[2]

As outlined above, the immune system comprises cells and soluble factors. Cancer is not foreign to the immune system, being made up of host cells rather than substances external to the body, and this limits the immune response. However, mutations that cause a tumour to become malignant enable components of the immune system to identify cancerous cells and this mutated cell possesses unique tumour-specific antigens (TSA) and/or tumour-associated antigens (TAA). This change is believed to be enough to create a specific immune response (Szlosarek & Dalgleish, 2002).

Elements of the immune system which are known to have anti-cancer properties include the following, and each is described in turn below:

1. T lymphocytes.
2. Dendritic cells.
3. NK and LAK cells.
4. Cytokines.

1.7.1. T lymphocytes. Tumour infiltrating lymphocytes (TIL) (CD8+ and CD4+ T cells) are known to be found within a tumour and may be a good prognostic indicator of many cancer, such as B cell lymphoma. Some T-lymphocytes (T cells), such as CD8+ cytotoxic cells, have excellent tumour specificity and anti-tumour capabilities *in vitro*.

Both Th1 and Th2 cells amplify the effects of the immune response. Th2 cells assist B cells which respond by making antibodies against invading organisms; the success and speed of response is believed to be linked to whether or not the B cell has encountered the pathogen before (memory) or not (naive) (Szlosarek & Dalgleish, 2002). T cells only recognise antigens when presented on the surface of the other cell by major histocompatibility complex (MHC) molecules and elicit an effect either by releasing cytokines or by direct cell-cell interactions (Roitt et al., 2001).

Szlosarek and Dalgleish (2002) note that in patients with cancer the cell-mediated Th1 response is suppressed and the humoral Th2 response is enhanced, leading to the assumption that for a cancer to evolve, it must suppress components of the immune response. The Th1/Th2 balance is commonly considered significant in attempts to understand anti-cancer immune responses.

Research into xenogenic tumour models (human cancer tumours implanted in mice) has suggested IL-12+ tumour cells promote T cell movement into the tumour and T cell

[2]This section is based on a publication which I co-authored (L. G. Walker et al., 2005)

activation causing tumour regression. Moreover, Tumour Infiltrating Lymphocytes (TILs) comprise CD8+ and CD4+ T cells within the tumour and may be a good prognostic indicator in various types of cancer.

1.7.2 Dendritic Cells. Dendritic cells are similar to monocytes in that they also present antigen cells to T cells and can therefore be considered to be messengers between innate and adaptive immune systems. Like T cells and NK cells, dendritic cells are highly dependent on the 'correct' cytokine environment, but when the environment is correct, both *in vivo* and *in vitro* anticancer specific T cells are recruited by an increase in the quantity of MHC molecules and other co-stimulatory molecules (up-regulation) required for T cell activation .

1.7.3 NK Cells. NK cell involvement in response to malignant neoplasia has been well reported. As discussed, NK cells are CD16+ and CD56+ large granular lymphocytes (LGLs). NK cells only mediate damage to the plasma membrane of a cell (lysis) if it has lost its major histocompatibility complex (MHC) molecules - if present these inhibit NK signal.

Lymphokine activated killer (LAK) cells are IL-2 stimulated CD57+ NK cells and have been regularly shown to mediate tumour cell cytotoxicity. Moreover, *in vivo*, LAK is often suppressed in cancer patients.

1.7.4 Cytokines. CD4+ T cells include Th1 and Th2 cell populations. The Th1 response is commonly believed to be the dominant anti-cancer response. Th2 cells secrete cytokines responsible for a antibody specific immune response. A shift in the Th1:Th2 balance has been observed in many cancers. Studies on the IL12 and IL10 balance have clearly shown a prevalence of a Th2-like response especially in advanced tumours. However, it is not yet known if this is induced by the cancer or is the reason for some tumours progressing (Vedhara & Irwin, 2005).

1.8 Neuroendocrine systems[3]

An underlying assumption of the PNI model is that the neuroendocrine system can modulate the immune system, and there is considerable evidence in support of this (Vedhara & Irwin, 2005).

It is well known that the brain communicates with the immune system in various ways, including neuronal connections with organs such as the spleen and the adrenal

[3]Some parts of this section is based on a publication which I co-authored (L. G. Walker et al., 2005)

medulla (sympatho-adrenomedullary – the SAM axis) , and also via hormones released by the Hypothalamic-Pituitary-Adrenal (HPA) axis. The effects of both acute and chronic stress on these systems have been well documented (Kaye & Lightman, 2005), particularly following the pioneering work of Hans Selye in the 1930's which led him to develop the concept of the General Adaptation Syndrome (Selye, 1956).

The effects of neuroendocrine hormones on the immune system are wide-ranging. Various immune cells have been shown to have receptors for stress-related hormones, including growth hormone, prolactin, glucocorticoids, catecholamines (adrenaline and noradrenaline) and melatonin. Lymphocyte proliferation is stimulated by growth hormone and prolactin, whereas glucocorticoids have an inhibitory effect, and these three hormones have been shown to alter cytokine production in T cells (Dimitrov et al., 2004).

In terms of relevance to cancer, cortisol inhibits natural killer cell cytotoxicity whereas growth hormone increases cytotoxicity, and prolactin enhances both natural killer cell and lymphokine activated cell cytotoxicity. Glucocorticoids also induce lymphocyte apoptosis (programmed cell death), an effect that can be inhibited by prolactin. Genetically, hormones may influence the immune system. For example, prolactin regulates the expression of interferon regulatory factor 1 which mediates a range of immune responses (L. G. Walker et al., 2005).

It is well-known that the hormone oestrogen plays a very important role in the genesis and prognosis of breast cancer. Oestrogen down-regulates cell-mediated responses and enhances humoral immune responses, and oestrogen deficiency increases the production of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) (Aloysius et al., 2011). Interestingly, very recent evidence links high primary tumor glucocorticoid receptor expression (and associated increased glucocorticoid-mediated gene expression) to more rapid estrogen-independent breast cancer progression (Volden & Conzen, 2013).

In summary, therefore, there is good evidence that acute and chronic stress induce hormonal responses, and that some of these responses have significant effects on the immune system, including components relevant to the onset and progression of cancer.

1.9 Current healthcare for breast cancer in the UK: a place for PNI?

Treatment depends on a variety of factors, including TNM stage, oestrogen receptor status, herceptin receptor status, presence of a genetic abnormality (such as BRCA1, BRCA2 or Li Fraumeni syndrome) and age. Primary treatments for cancer are often provided in combination, and are normally one or more of surgery, chemotherapy (intravenous,

or less commonly oral, administration of cytotoxic or anti-neoplastic drugs) radiotherapy (ionizing radiation to control or kill malignant cells) and biological response modifiers (immunotherapy using substances that the human body produces naturally to improve the host's natural immune response to cancer, also referred to as BRM). Chemotherapy and radiotherapy target the rapidly dividing cancer cells which are thought to be particularly vulnerable to the effects of these treatments.

Ben-Eliyahu et al. (2007) noted that "Although the last decades have provided ample evidence for deleterious effects of stress on immunity and on cancer development and suggested mediating mechanisms, no psychoneuroimmunology (PNI)-related intervention has become a standard of care in conventional cancer treatment." (p.881). Possible explanations were presented, and the narrative was optimistic. However, despite continued research and interest in potential clinical implications such as depression (Irwin & Miller, 2007), cancer healthcare has not yet been influenced significantly by the PNI paradigm.

1.10 Epistemological Statement and the prospect of personality therapy

This thesis is epistemologically positivist and ontologically realist (Burrell & Morgan, 1979). That is to say that that the author believes that events may be explained and predicted by searching for causal relationships, and that the world is external to perception and present whether or not it is labelled or perceived.

As personality is a construct it cannot be directly observed. However, the effects of constructs are observable, and measures of behaviour, cognition and emotion are believed to be indicators of deterministic between-individual variance in personality.

In the context of this thesis, the personality debate is predicated on the extent to which personality may explain behaviour. Positivist causal relationships and regularities are believed to exist between trait personality (Chapter two) and variables such as behaviour (including NI behaviour, also Chapter two). The Situationism debate (Chapter two) questioned the contribution of personality to determining behaviour and that knowledge of the situation and (to a lesser extent personality) would allow accurate explanations of behaviour with reliable predictability.

Several personality theorists (Eysenck, 1987; Eysenck & Grossarth-Maticek, 1991) have suggested that personality may be amenable to interventions. . This is an intriguing and somewhat contradictory suggestion as personality is considered to be stable and emergent from both nature and nurture (Chapter two). The suggestion that personality may be amenable to intervention would suggest that the stability that is considered by many

to be the value of personality, is questionable. If personality is indeed modifiable, critics may challenge the concept of stable trait personality. Nevertheless, a framework in which personality is modifiable is clearly positivist, and to the extent that certain personality traits may be maladaptive (see, for example, Kissen & Eysenck, 1962). The suggestion that Psychologists could modify personality raises the potential of clinical intervention at a cognitive level (for example with Cognitive Behavioural Therapy).

Finally, The author suggests that the human body is a complex (Waldrop, 1992) biological system, existing within a network of cultural, environmental and other systems (Churchman, 1971) and has previously discussed variations of complexity theory in a Master's dissertation (A. A. Walker, 2001). This thesis takes a 'reductionistic complexity theory' stance following that of J. Cohen & Stewart (1994) in which complexity and reductionism are not incommensurable paradigms (Kuhn, 1970).

Chapter 2: Personality

2.1 Overview

This chapter introduces and justifies the concept of personality, specifically trait personality, as the focus for the thesis. The chapter concludes by establishing the importance of considering the wider psychological research of the known relationships between trait personality, and the associated psychological personality variables of affect, locus of control and emotional control and how they may all be related to immune response generally, and immune response to breast cancer specifically.

Theories about personality differences date back at least as far as Hippocrates, a physician of Ancient Greece (460BC - c.370). Hippocrates suggested that personality *type* is determined by the ratio of four humors (bodily fluid), namely blood, phlegm, black bile, and yellow bile. The names Hippocrates suggested for these four humor driven personalities are still in use today; they are sanguine (optimistic), phlegmatic (slow, lethargic), melancholic (sad, depressive), and choleric (angry, irritable).

2.2 Types and Traits

Theorists such as Allport (1937), Cattell (1970; 1946; 1943), Eysenck (1953; 1952), Eysenck and Eysenck (1975), Costa and McRae (1992; 1985) and McRae and Costa (1990) all have proposed that personality characteristics should be of interest to behavioural scientists and researchers as they are measurable, stable and predict behaviour in different settings. Personality disposes an individual to act or feel in a particular way in certain situations, with some evidence for cross-situational consistency (Mischel, 2004; Mischel & Shoda, 1995; Mischel, 1968).

Early exploration into personality began with the concept of 'types' as introduced in ancient Greek times in the section above, and later by the German psychiatrist Kretschmer and more recently the American physician, William H Sheldon. Sheldon suggested that three dimensions of physique correlated with the temperaments of those with the corresponding body types. Endomorphs, Sheldon suggested, were obese, and would be sociable, complacent, and capable of easy communication of feelings. The Mesomorph was athletic and strong, would be bold, competitive, aggressive and energetic. The Ectomporph was tall and thin with a large brain and sensitive nervous system, and would be inhibited, hypersensitive to pain and emotionally sensitive. (Sheldon et al., 1949). Sheldon considered a person to be the sum of all 3 body types, with each type being scored on a one to seven

point scale. Therefore, a person with a score of 1-4-7 would be low on Endomorphy, moderate on Mesomorphy, and high on Ectomorphy. Newer and more empirical and conceptual models have been proposed.

However, perhaps the most famous of typologies was that devised by Carl Jung (Stevens, 1994), a Swiss psychiatrist and psychoanalyst. Jung suggested that everyone could be considered as either introverted or extraverted. An introvert, Jung maintained, is withdrawn, especially in the context of exposure to stressful emotional conflict and is shy, preferring to be alone and avoiding others. Conversely, an extravert deals with stress by seeking company (becoming one of a crowd) and is attracted to social activities as the extravert is sociable and outgoing. The terms introverted and extroverted are still in use today.

Unlike typologies which assume discontinuities (or binary-like categories), traits are continuous dimensions. Therefore, a trait of extraversion would allow an individual to have a psychometrically derived score ranging from high extraversion to low extraversion (introversion) and this has advantages in terms of psychological measurement. Moreover, in many cases, most individuals have an intermediate amount of any given trait, with only a small percentage of individuals at either extreme. Operationally, Guilford (1959) defines a trait as "any distinguishable, relatively enduring way in which one individual varies from another" (page 6).

An important distinction should be made between traits and states. Both are constructs encompassing the perceived attributes of people, and both are derived from prototypes as ideal exemplars (Cantor & Mischel, 1979). The demarcation between traits and states is that traits are enduring, stable and internally caused. Conversely, prototypic states are transient and attributable to external causes (Chaplin et al., 1988).

Types and traits have a value beyond that of describing individual differences, and it is this second value that it of primary interest in this investigation. Some theorists, as will be shown later, promote the trait to hold explanatory value. That is to say, the trait is the quantum within an individual that explains his or her individual but relatively stable reactions to stimuli. The trait is no longer an adjective but an inferred construct capable of explaining, or perhaps even predicting behaviour. And with prediction comes the possibility of generating hypotheses.

Gordon Allport (1936; 1937) was a pioneer of trait personality and believed that traits are the psychological organisation of the structure of personality which accounts for

consistency of behaviour. Allport and Odbert (1936) noticed that, based on 17,953 words derived from Webster's Unabridged New International Dictionary that describe human behaviour, there was a considerable overlapping of words with a similar meaning. Allport (1937) went on to suggest that some people have general dispositions (cardinal traits) that influence most aspects of behaviour. For example, a person who pursued the attainment of excellence may be said to have a cardinal trait of attainment. Below cardinal traits in order of magnitude are central traits which are both generalisable and pervasive. Unlike cardinal traits, Allport believed that we all have central traits. Lastly, below central traits reside secondary dispositions or attitudes. Allport believed that this pattern of disposition (cardinal traits - central traits - secondary dispositions), or personality structure, explained why no two people are completely alike (as behaviour is determined by a particular personality structure) and by extension no two people respond identically to the same stimuli as, according to Allport, traits operate uniquely at the individual level. Allport, therefore, emphasised the individuality of each personality and believed that as personality structure is unique at the individual level, rather than shared between people or within a group, it cannot be studied by making comparisons at group level. However, Allport also suggested that due to the influence of shared experiences and common culture, many people develop broadly similar secondary dispositions on which they can be compared. Because of his emphasis on individual differences, Allport critcicised the statistical and quantitative methods of other trait theorists. Nevertheless, his influence is enduring and can be seen in the investigation of common "global" traits.

Like Allport, Raymond Cattell (1946) distinguished between types of traits. Common traits, he postulated, are possessed by all people whereas unique traits exist only at the individual level and do not exist in an identical way in any other individual. Moreover, Cattell hypothesised that surface traits are bodies of trait elements that group together. Source traits, on the other hand, are the causal entities which determining the surface manifestations of trait elements. Cattell obtained the adjectives identified by Allport (above) and after removing synonyms was left with a list of 171 words which factor analysis returned as 16 common traits which Cattell believed could be measured by the associated Sixteen Personality Factor Questionnaire (16PF) (Cattell et al., 1970).

Unlike Cattell who postulated a complicated model of traits (above), the British-based psychologist Hans Eysenck (1953; 1952; 1947) further developed the work of Jung, Allport and Cattell and extended the scope of research into personality to "normal" be-

haviour and "abnormal" (neurotic) personality. Eysenck developed the Jungian traits of introversion and extraversion by conceptualizing them as as a single dimensional trait. Like Cattell, Eysenck favoured factor analysis to derive descriptive dimensional traits and studied the association between the scores on such traits and a variety of other measures. Eysenck suggested that personality can be described in terms of three dimensions or traits briefly described below in terms of characteristics that would be expected of high scorers:

- Psychoticism (tough-mindedness): Solitary, troublesome, cruel and insensitive.
- Extraversion: Extraverts are sociable and outgoing, enjoy parties and other social activities, are impulsive and crave excitement. Introverts tend to be quiet, thoughtful, reliable and reserved, enjoying solitary pursuits.
- Neuroticism (emotionality): Anxious, worrying, frequently depressed.

Whereas Cattell argued for 16 factors, Eysenck believed that personality traits are determined mainly in terms of where a person falls along these three dimensions and can be measured using the Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975) or the Eysenck Personality Questionnaire - Revised (EPQ) (Eysenck & Eysenck, 1991).

2.2.1 A challenge to traits: Situationism. The greatest challenge to trait theories of personality is situationism. The person situation debate was prompted by Walter Mischel's 1968 book 'Personality and Assessment' in which he argued that behaviour is too inconsistent between situations to be accurately characterised in terms of personality traits (Mischel, 1968). Funder (1997) is critical of Mischel's findings and suggests that Mischel changed his position on fundamental issues (Mischel & Shoda, 1995), for example Mischel has claimed that that he did not intend to state that personality does not exist.

Mischel's situationist argument consists of three main points:

1. There is a small upper limit to how accurately we can predict what a person will do based upon any measurement of any aspect of that person's personality. Correlations between personality and behaviour in one situation and behaviour in another situation seldom exceed .30 (Nisbett revised this estimate upward to .40 (Nisbett, 1980)); Mischel (1968) referred to these as 'personality coefficients'.

2. Therefore, situations are more significant than personality traits in determining behaviour.

3. Therefore, we tend to see people as being more consistent across situations than they actually are.

The impact of Mischel's (1968) contribution was profound and "hit the field of personality

psychology in the early 1970s with surprisingly devastating force. Some personality psychologists, and even more psychologists outside the field of personality, concluded that a predictive limit corresponding to a correlation of .40 meant that personality did not exist" (Funder, 1997, page 65).

This challenge was addressed by emerging methodologies in the 1980s. Rather than attempting to predict single instances of (unreliable) behaviour, patterns of behaviour could be predicted by aggregating large numbers of observations (Epstein & O'Brien, 1985) increasing the strength of correlations between personality and behaviour (Funder, 1988).

In the aftermath of the situationist debate, a new theory of trait personality emerged and is currently the dominant approach. Building upon earlier work by Warren Norman (1963) and others, using factor analysis, McRae and Costa (1987) concluded that five traits are required to adequately capture personality. These five traits (often referred to as the Big Five) are:

- Neuroticism (versus emotional stability): Worrying, insecure, self-conscious and temperamental.
- Extraversion (surgency): Sociable, fun-loving, affectionate and friendly.
- Openness to experience: Original, imaginative broad interests and daring.
- Agreeableness (versus antagonism): trust and Machiavellianism (versus mistrustful, unsympathetic and stubborn).
- Conscientiousness: Governed by conscience or carful and thorough.

Like the three dimensions of Eysenck, these five traits are "orthogonal," implying that a high or low score on any one of these traits provides no information about a score on any of the others. However, some authors have suggested that the Big 5 may correlate with each other to some degree; for example in "many samples people who score high on extraversion tend to score low on neuroticism, for example" (Funder, 1997, page 144).

2.3 Personality and the immune system: 4 models

Authors such as Coe & Laudenslager (2007) suggest that the P (Psychological) component of PNI is often relatively neglected leading some critics to question whether PNI is more accurately the investigation of NI relationships - acknowledging the physiological brain-immune relationship and emphasising commonalities rather than individual differences. However, if psychological, neurological, or immunological variables are associated with personality, this would lend further weight to the paradigm of PNI by emphasising the potential for variance between persons with different personality types.

As personality endures, so may its influence on health through the immune system as a physiological pathway between personality and autoimmune health problems (Segerstrom, 2000).

Segerstrom (2000) reviews four types of model relating personality to the immune system.

1. Main effect; one variable (personality) is associated with immune system status. For example, repression or Neuroticism and mononuclear cell distributions such as T cells.

2. Predispositional effect; one variable (personality) is a risk factor for another variable (health). For example, personality predisposing stress induced immune response.

3. Pathoplastic effect; each variable affects the presentation of another variable. For example, cancer might be affected by and affect personality.

4. Common cause effect; both variables share a common aetiology. For example, cancer and a personality trait, such as neuroticism, might be the consequence of a shared genetic profile.

These four models are presented as a reference to allow interpretation of the existing literature on the relationship between cancer and personality below, and the studies presented and reviewed in chapters three to seven.

2.4 A cancer prone personality?

As long ago as the second century *A.D.,* Galen (*A.D.* 131-201) in *De Tumoribus* proposed that cancer was more frequent in "melancholic" than "sanguine" females. Much more recently, in 1962, Kissen and Eysenck reported on a 2x2 study of 116 lung cancer patients and 123 non-cancer controls (some of which had a psychosomatic disorder). Participants were asked to complete the Maudsley Personality Inventory (a precursor to the Eysenck Personality Questionnaire measuring Extraversion and Neuroticism, introduced above). Kissen and Eysenck tentatively reported that lung cancer patients scored higher on Extraversion and lower on Neuroticism than non cancer control participants.

Similar results were reported by Kissen et al. (1969); lung cancer patients had lower Neuroticism scores (as assessed by the Short Maudsley Inventory).

Other early contributions to the development of the Type C concept included work by Bahnson and Bahnson (1966) who, from a psychodynamic perspective, emphasised the importance of repression of feelings of guilt and hostility, and Le Shan (1959) who highlighted the importance of loss and depression. Summarising the literature, Eysenck (1994) reported that the main traits that had been suggested to be characteristic of the

Type C personality included "Being over-co-operative, appeasing, unassertive, over-patient, avoiding conflict, suppressing emotions like anger and anxiety, using repression and denial as coping mechanisms, self-sacrificing, rigid, predisposed to experience hopelessness and depression" (page 168). Others have suggested that Type C characteristics should be construed not in terms of personality characteristics predisposing to cancer but rather as a coping response to the diagnosis. For example, (L. R. Temoshok et al., 2008) state that "Type C coping is characterized by a failure to recognize internal physical or emotional cues, a lack of emotional expression and communication of emotions and needs, an external focus on the needs and feelings of others, and a facade of normalcy and mental health" (page. 782). They go on to theorise that "this maladaptive coping pattern keeps the individual in a chronic state of unrecognized and unaddressed stress, with concomitant dysregulation of homeostatic responses (Temoshok, 1990), including inappropriate physiological responses to stressors" (page 782). Temoshok originally identified Type C coping in patients with malignant melanoma and found that this was associated with poor prognostic indicators, immune mechanisms linked to a poorer prognosis in malignant melanoma, and poorer clinical outcomes (L. Temoshok et al., 1985; L. Temoshok, 1985). The empirical evidence relevant to Type C characteristics, both as predictors of cancer onset and prognosis, is reviewed later in this thesis, and issues regarding how best these characteristics might be measured are also addressed.

There would, therefore, appear to be some evidence for a Type C personality. A series of structured literature reviews were designed to test this hypothesis further. These literature reviews are presented in the following five chapters.

Chapter 3: Structured review of Eysenckian traits and risk of cancer

3.1 Overview

Following the overview of personality in Chapter 2, this chapter reports on a structured review of Eysenckian traits and risk of cancer and serves to:

1. Introduce the reader to the assumptions previously made, and research conducted, on Eysenckian trait personality and cancer.

2. Highlight the methodological flaws present in much of the reported research.

3. Set the scene for further structured reviews of less well known personality measures and subsequent research.

3.2 Background

If personality is associated with immune function, it may operate through pathoplastic or common effect mechanisms (Segerstrom, 2000). As discussed in chapter 2, personality has long been hypothesized to be related to the incidence, and to a lesser extent survival of cancer. However, personality traits associated with such predispositions have been measured and framed in a variety of ways over time, and often combined into multi-trait models.

Many studies have focussed on the personality traits of Extraversion and Neuroticism due to the long-standing interest in the Type C personality. Although, more recently, Costa and McCrae have included Extraversion and Neuroticism in the NEO-PI (P. T. Costa & McCrae, 1992) as two of five dimensions (Openness, Conscientiousness, Extraversion, Agreeableness and Neuroticism: OCEAN). However, the first personality trait theorist to develop a measure of extraversion and introversion was Hans Eysenck. The most recent version, Eysenck Personality Questionnaire -Revised (EPQ-R) (Eysenck & Eysenck, 1991), dates back to 1991 but its origins date back to the early 1950s in the form of the Maudsley Medical Questionnaire (MMQ), a measure of Neuroticism and has published reliability (P= 0.76, E=0.85, N=0.85 and L=0.79 in females) and test-retest reliability (P=0.81, E=0.89, N=0.81, L=0.80) (Eysenck & Eysenck, 1991)

Briefly, Eysenck suggested that three personality dimensions can be used to explain behaviour:

- Psychoticism (tough-mindedness): Solitary, troublesome, cruel and insensitive.
- Extraversion: Extraverts are sociable and outgoing, enjoy parties and other social

activities, is impulsive, and craves excitement. Introverts tend to be quiet, thoughtful, reliable and reserved, enjoying solitary pursuits.

- Neuroticism (emotionality): Anxious, worrying, frequently depressed.

It would be of interest, therefore to investigate to what extent an Eysenckian measure of personality has been used in studies involving participants with cancer, particularly given what has been suggested about the Type C personality (see chapter 2).

3.3 Review Methods

3.3.1 Description of the literature being reviewed . The literature reviewed is intentionally limited in two ways. First, it is all indexed within PubMed, and as such meets a particular standard for quality. Second, in order to minimise the risk of accidentally biasing the results by confusing terminology shared by theorists and measures (such as Extraversion), only personality traits assessed by Eysenck's two personality measures (and their derivatives) were included; namely the Eysenck Personality Inventory (EPI) and the Eysenck Personality Questionnaire (EPQ).

3.3.2 Objectives. Literature review had two objectives, derived from the potential background above, namely:

1. To review the evidence relating personality, cancer risk and progression in humans.
2. To identify the nature and quality of the evidence available on this topic.

3.3.3 Types of studies. All trial designs with humans participants were included.

3.3.4 Types of participants. Men and women over the age of 18 years with a diagnosis of cancer.

3.3.5 Types of outcome measures.

1. One or more measure of an Eysenckian personality trait.
2. Diagnosis of first cancer, recurrence or cancer related death.

3.3.6 Criteria for considering reviews for inclusion. The inclusion criteria for selection were:

1. Published in PubMed.
2. An original report of a study involving human adults (18 years of age or over).
3. Reports an Eysenckian personality trait obtained by either a reliable and valid EPI, EPQ or variant.
4. Does not combine more than one personality dimension or trait.

5. Outcome was diagnosis of first cancer, recurrence or cancer related death.
6. Written in English.

3.4 Search Methods for identification of literature

3.4.1 Data collection and analysis. Five independent searches of PubMed were conducted in October 2013. Each search focused in turn on (1) Eysenck, n=35, (2) Psychoticism, n=5 (3) Extraversion, n=20 (4) Neuroticism, n=36 and (5) Lie, n=5. The search criteria can be found in Appendix C. The results of these searches were merged resulting in 101 hits which after removing duplicates left 67 hits. The results were screened and visual inspection of title and abstract (together) excluded 41 obviously irrelevant[4] papers leaving 26.

The 26 abstracts (or titles where abstracts were unavailable) were assessed by the author against an *a priori* checklist based on definitions developed at the start of the review (criteria for considering reviews for inclusion), to identify potentially relevant studies for which full texts were obtained. Sixteen articles were excluded (table 1) and one study added (Augustine et al., 2009) identified from the structured review of positive and negative affect below, resulting in 11 studies in this review (table 2).

3.4.2 Data Extraction . Papers meeting the criteria for inclusion were reviewed for:

- Site of cancer.
- Measure of personality.
- Methodological quality.
- Outcomes and contentious discussion points

3.4.3 Study classification. Included studies were classified based upon

- Personality measure(s):
- Outcome(s)
- Sample size and cancer type(s)
- Outcome

[4] 'Obviously irrelevant' papers were those that from the reading of the title and abstract did not meet one or more of the inclusion criteria.

3.5 Results

Table 1:: Characteristics of excluded personality articles at full revision stage

Authors	*First inclusion criteria not met*[5]
Cardenal et al. (2012)	3
Lin et al. (2012)	5
Jiang et al. (2011)	4
Lemogne et al. (2010)	4
Ranchor et al. (2010)	2
Grov et al. (2009)	5
Nabi et al. (2008)	4
Stürmer et al. (2006)	5
Garssen (2005)	2
Surtees et al. (2003)	3
Lillberg et al. (2002)	3
Grossarth-Maticek et al. (2000)	3
Eysenck (1993)	2
Almada et al. (1991)	3
Priestman et al. (1985)	5
Scurry & Levin (1978)	5

3.5.1 Description of excluded literature. Cardenal et al. (2012) did not use a Eysenckian personality measure (criterion 3) and therefore did not meet all of the inclusion criteria. However, she did find that Anger Expression-in (suppression), Resignation, self-blame and conscientiousness (as measured using the NEO-FFI (P. T. Costa & McCrae, 1992)) predicted poor cancer outcome 2 years later. Further, compared to control participants (n=67), cancer patients (n=131) presented with higher neuroticism and lower extraversion, agreeableness and conscientiousness. The study was of relevance to the review on emotional control (chapter 6) and so will be be added to the review.

[5]1=Published in a PubMed. 2=An original report of a study involving human adults (18 years of age or over). 3=Reports an Eysenckian personality trait obtained by either a reliable and valid EPI, EPQ or variant . 4=Does not combine more than one personality dimension or trait. 5=Outcome was diagnosis of first cancer, recurrence or cancer related death. 6=Written in English.

Lin et al. (2012) reported on influence of personality on Quality of Life on 735 Esophageal cancer patients. The authors used the typology combinations of Extraversion and Neuroticism to create the four variants suggested by Eysenck (Eysenck & Eysenck, 1991) (namely "Sanguine" or stable extraverts (high Extraversion and low Neuroticism), "choleric" or unstable extraverts (high extraversion and high Neuroticism), "phlegmatic" (the authors in places refer to this as lymphatic) or stable introverts (low Extraversion and high Neuroticism), and "melancholic" or unstable introverts (low Extraversion and high Neuroticism). It is not reported which version or language of the EPQ was used or how it was administered. Type differences in Quality of Life were reported, but the recurrence or death (outcome) criterion was not met.

Jiang et al. (2011) reported on risk factors associated with 174 elderly colorectal patients (57 with a survival time of less than 2 years and 117 with a survival time of greater than 5 years). Neuroticism was assed by means of the EPQ-RSC (the Chinese version of the 48 item EPQ-Revised Short (EPQ-RS)). However, despite stating the the EPQ-RSC measures the two *dimensions* of Neuroticism and Extraversion the authors explicitly present a computed formula which locates both dimensions on the same continuum by summing the extraversion and neuroticism scores ($T = 50 + 10x(subjects\ scores - mean\ scores)/SD$). Extraversion =T$\geq$56.7 and Neuroticism = T$\leq$43.4. This variable "personality" was positively and significantly correlated to adverse prognosis in in univariate analysis (p=<.001 95%CI=3.688-18.034) and also positively significantly correlated with prognosis in a multivariate analysis (p=0.019 95%CI=5.943-27.687). Due to the irregular use of these dimensions, the study was excluded.

Lemogne et al. (2010) was reviewed in full and was found to contain no relevant data (although they claim to have measured the cancer-prone personality using the Grossarth-Maticek and Eysenck Personal Style Inventory (PSI)). However, a follow up of the same study is included (Lemogne et al., 2013) in this review. Cognitive hostility was the only personality measure associated with mortality after adjustment for depressive mood (R^2=1.97 95%CI = 1.39–2.77). The measurement criterion was not met.

Ranchor et al. (2010) contributed an invited commentary in the same journal, volume and issue as Nakaya et al. (2010) and considers whether it is time to "retire the hypothesis" that personality is a causal factor in cancer. Ranchor et al. (2010) is generous in his praise and some of his comments can be found in reviewing the Nakaya et al. (2010) study below. The authors are equally generous in their criticism of the Grossarth-Maticek studies and the

inclusion of the Grossarth-Maticek studies in meta-analysis. Even more strongly, Ranchor et al. (2010) concludes that while one reason for continuing to explore associations between personality and cancer is the potential for psychological programs to alter personality, no intervention study with an *a priori* endpoint of survival and controlled medical confounds has ever been reported.

Grov et al. (2009) reported on a cross-sectional study of 1,428 testicular cancer survivors (TCS) in Norway. Using the 18 item, non standard, EPQ 12% (n=176) of TCS scored high on Neuroticism and 88% (n=1252) scored low on Neuroticism (the authors used a summed score of 5 or 6 from a possible range 0-6 to infer 'high' Neuroticism). The authors reported significant differences in almost all variables measured including neurotoxic side effects, demography and life-style, and disease issues. However, the authors concluded, "many significant associations between self-reported somatic and mental morbidity, lifestyle, and health care consumption and neuroticism in TCSs. Neuroticism is a personality trait that should be considered in TCSs who at longterm have chronic and multiple somatic and mental complaints in spite of being cured of their cancer" (page 548). Recurrence or cancer related death was not reported and as such the outcome criterium was not met.

Nabi et al. (2008) followed up 14,455 participants (French gas and electric employees) aged between 39 and 54 years in 1993 from the GAZEL cohort. Participants completed one or more of the (a) Bortner Type-A scale, (b) Buss Durkee Hostility Inventory, and (c) Grossarth-Maticek Eysenck Personality Stress Inventory. Numerous positive personality relationships were found with all cause mortality (adjusted for age and gender) namely Type-A behaviour ($p=\leq.005$), total hostility ($p= \leq.001$), Neurotic hostility ($p=\leq.0001$), CHD prone Type 1 ($p=\leq.005$), Ambivalent Type 3 ($p=\leq.001$) and Anti-social Type 6 ($p=\leq.0001$). Moreover, all relationships significant at $p=\leq.001$ or $p=\leq.0001$ remained significant after adjusting for educational level and marital status. However, in cancer related mortality only Type A behaviour was positively significantly correlated with mortality from cancer (R^2 adjusted for age and gender = 0.59 95%CI =0.36-0.95, $p\leq0.05$). Interestingly Type 1 cancer-prone behaviour was never predictive. However, in terms of cancer-related death, it is well known that cancer mechanisms differ by cancer site and neither the forms of cancer reported nor their weightings are presented making the sample heterogeneous and difficult to interpret. The sample may also not have been representative, employment in gas or electric companies may be a source of bias. Positively, the effects of

smoking, alcohol consumption and BMI were adjusted for, and the authors conclude that the marginal 12% adjustment demonstrates the personality effect was not through these behaviours.

Stürmer et al. (2006) presented data from a follow-up of a population-based cohort with a sample of 4,267 male and female participants in Germany. Inadequate information on the personality measures used is reported. Moreover, the authors used factor analysis to derive five personality factors, one of which was termed 'Psychoticism' and concluded that Psychoticism was not associated with cancer. However, due to the methodological limitations of non-standardised measurement, analysis and interpretation, caution is advised when interpreting the results. The study was excluded for not meeting the measurement criterion.

Garssen (2005) authored a Comment in the Lancet entitled "No role for extroversion and neuroticism in cancer development" in which he references his own (2004) review and the review by Hansen et al. (2005) and concludes the title of the invited Comment, with the concession that, if such research should continue, it should focus upon helplessness, repression of negative emotions, and minimisation of disease for which he claims there is some evidence.

Surtees et al. (2003) reported on a large prospective study of 20,579 participants aged between 41 and 80 years from the European Prospective Investigation into Cancer (EPIC) - Norfolk Study in the United Kingdom. Although Neuroticism was measured using the personality deviance scales the authors did not include Neuroticism in their analysis of the cohort who died from cancer and as such the measurement criterion was not met.

Lillberg et al. (2002) reported that based upon a short version of a non-standardised in a sample of 12,499 Finnish Women. First in 1975 and again in 1981 (6 years later) measured Neuroticism by one or more of the (a) Abbreviated (non-standard) version of Eysenck Personality Inventory (EPI), (b) Bortner Type A scale or, (c) author constructed hostility scale and demonstrated equivalence in high and low scorers. Proportionate Hazard Models produced multivariable HRs of breast cancer for women with intermediate level (scores 3–6) and high level (7–9) of extroversion in 1975 were 1.18 95%CI = .87–1.60 and 0.97 95%CI .64–1.47, respectively, compared to those with low level (0–2). The authors concluded that "our findings do not support the existence of any substantial effect of personality on the risk of breast cancer. This is reassuring to those who have believed the contrary." (page 365). The lack of a repeatability caused by ambiguous outcome measure

was the cause of this trials exclusion.

Grossarth-Maticek et al. (2000) published a striking paper (posthumously after the death of Eysenck in 1997), reporting that breast cancer related death was predicted by (1) number of physical risk factors ($\leq 4 = 0.5\%$, 5-9 = 11.1%, between 10 and 14 29.9%, and $\geq$15= 68.6%) (2) number of psychosocial risk factors ($\leq 5 = 13.0\%$, 5-10 = 20.69%, and $\geq 11 = 60.2\%$) (3) interaction of (1) and (2) (low physical risk and stress = 0.4%, high physical risk and stress = 14%, low physical risk and no stress = 0.0%, high physical risk and no stress = 3.5% [error in original table], and (4) difference in between group survival (high stress and high physical risk participants is indicative of a causal relationship (63.9% autonomy training compared with 22.2% of controls, breast cancer related deaths 2.8% autonomy training compared with 19.4% of controls).

The most striking part of the reported results is that 0.3% of breast cancers in low physical risk scorers resulted in a cancer-related death, compared with 2.8% of middle scorers and 8.5% of high scores. Expressed in terms of percentage of breast cancer deaths, 60.2% of breast-cancer deaths occurred in those scoring high on psychical risk factors, 26.9% scoring in the central range of risk factors, and 13% scoring low on psychical risk. Pelosi & Appleby (1992) make the point more generally in terms of the body of work by Eysenck and Grossarth-Maticek; the descriptions of methods and analysis are unclear, the justification and lack of consistency for splitting the scores into groups is also unclear, as is whether such decisions were planned or made *post-hoc*.

Eysenck (1993) reviewed a number of studies conducted by Grossarth-Maticek including one large study in Yugoslavia and two in Hiedelberg, Germany. The criticisms presented on the Grossarth-Maticek studies and the subsequent follow-up studies and reanalyses are defended with spirited claims that while the criticism discrediting the body of research is "captious and irrational", other criticisms that do not invalidate the results are "valid" (page 513).

Almada et al. (1991) reported that Neuroticism was not significantly associated with risk of death from cancer, coronary disease, other cardiovascular disease and all other causes combined in a sample of 2,080 men recruited from the Western Electric study. This finding held when adjusted for cynicism, age, cigarette smoking, alcohol consumption, systolic blood pressure, and serum cholesterol. However the measure used was the MMPI and the study was therefore not included.

Priestman et al. (1985) reported an investigation into the association of stress with

breast cancer by comparing females with breast cancer, a benign lump, and healthy control). The participants completed the EPI and no difference in either Extraversion or Neuroticism was found between the participants with benign and malignant disease. Neither recurrence nor death was reported and as such the outcome criterion was not met.

In an early review, Scurry & Levin (1978) summarise and synthesis early research. As not a original report of a study, this article was excluded.

3.5.2 General characteristics of included literature.

- Personality measure: Six studies used the Eysenck Personality Inventory, three studies used the Eysenck personality Questionnaire, one study used the Revised Eysenck Personality Questionnaire and one study the Personality Stress inventory (PSI) .
- Outcome: Four studies reported an outcome of risk of cancer, two studies reported an outcome of death, three studies reported both risk of cancer and death. One study reported an outcome of age at surgery and one study reported recurrence and survival time.
- Sample size: Ranged from n=60 to n=59,548.
- Sample type: Seven studies recruited participants without a cancer diagnosis and four studies recruited participants with a cancer diagnosis.
- Results: Five studies reported a personality-related significant result and five studies did not report a significant personality result. One paper reported "no evidence" but contained two cancer-specific findings.

3.5.3 Review of included literature.

Please see table over the page.

Table 2:: Characteristics of included personality survival studies

Author	Personality measure(s)	Outcome(s)	Sample size and cancer type(s)	Cancer related significant finding(s)[6]
Lemogne et al. (2013)	Personality Stress Inventory (PSI)	Risk of cancer.	n=13,768	Type 1 personality associated with decreased risk of breast cancer (HR per SD=.081 95%CI .068-.097, p=.02) Type 5 personality associated with "other cancers" excluding prostate, breast, colorectal and smoking related (HR per SD=1.17 95%CI 1.04-1.31, p=.01)
Osthus et al. (2011)	Eysenck Personality Questionnaire (EPQ) Neuroticism scale	Death.	n=139 Head and neck	none
Nakaya et al. (2010)	Abbreviated (non-standard) version of Eysenck Personality Inventory (EPI)	Risk of cancer. Death.	n= 59,548	(1) High Extraversion associated with lung cancer: unadjusted HR =1.08 95%CI = 1.03-1.13, p < 0.01); multivariate HR=1.06 95%CI 1.01-1.10, p = 0.01) (2) high Neuroticism associated with lung cancer: unadjusted HR=1.10 95%CI 1.06-1.14, p < 0.01); multivariate HR =1.05 95%CI 1.01-1.10, p=0.01). (3) low Neuroticism associated with liver cancer unadjusted HR=0.92 95%CI 0.85-0.98, p=0.02); multivariate HR =0.91 95%CI 0.85-0.98, p=0.01). However the authors report "In multivariate analyses, Extraversion and Neuroticism were not significantly associated with risk of cancers at all sites (Extraversion: hazard ratio = 0.99, 95% confidence interval: 0.98, 1.01; Neuroticism: HR = 1.00, 95% confidence interval: 0.99, 1.02)" (p377).

[6]Key. HR=Hazard Ratio. SD=Standard Deviation. RR=Relative Risk

Table 2:: Characteristics of included personality survival studies

Augustine et al. (2009)	Eysenck Personality Questionnaire (EPQ) Behavioral Activation/Behavioral Inhibition Scale (BAS/BIS)	Age at which participants underwent surgery	n=203 non small-cell lung cancer	A difference of 4.33 years for Neuroticism and 3.12 years at 1 SD above versus 1 SD below the mean suggesting a negative associated with age at time of surgery (higher in these constructs associated with earlier onset of illness: younger at surgery).
Shipley et al. (2007)	Eysenck Personality Inventory (EPI)	Death.	n=5,424	none
Nakaya et al. (2006)	Abbreviated (non-standard) version of Eysenck Personality Inventory (EPI)	Risk of cancer. Death.	n=1, 020	High Neuroticism associated with risk of all cause death (HR=2.3 95%CI 1.1–4.7, p_{trend}=0.04) but not between extraversion and risk of death (HR=0.9 95%CI 0.4–1.7, p_{trend}=0.34). Similar results were found when using cancer-related death. Stratification by gender revealed a strong positive association between Neuroticism and risk of death among women (p_{trend}=0.03).
Canada et al. (2005)	Eysenck Personality Questionnaire (EPQ)	Recurrence of cancer and survival time	n=60 Stage I malignant melanoma	none
Hansen et al. (2005)	Abbreviated (non-standard) version of Eysenck Personality Inventory (EPI)	Risk of cancer.	n=29,595	none
Nakaya et al. (2003)	Eysenck Personlity Questionnaire - Revised (EPQ-R) Short Form, Japanese version.	Risk of cancer.	n=29,606	Multivariable Risk Ratios for all cancer; Lie RR= 0.9 95%CI 0.7-1.0; p_{trend}=.19); Neuroticism RR=1.2 95%CI 1.0-1.4, p_{trend}=.06). Neuroticism was positively, linearly associated with prevalent cancer at baseline (p_{trend}<.001) and incident cancer cases diagnosed within the first 3 years of follow-up (p_{trend} = .03); however, no association with cases diagnosed during the fourth through the seventh years of follow-up (p_{trend} = .43)

Table 2:: Characteristics of included personality survival studies

Aarstad et al. (2002)	Eysenck Personality Inventory (EPI)	Risk of cancer.	n=139 (78 newly diagnosed head and neck and 61 benign head and neck disease)	Cancer patients had higher Neuroticism scores than non-cancer patients (10.7 ± 0.5 compared with 8.3 ± 0.6, p=<0.01). Lie Score predicted disease-sepcifc death (p=0.02)
Schapiro et al. (2001)	Abreviated (non-standard) version of Eysenck Personality Inventory (EPI)	Risk of cancer. Death.	n=1,023	none

In a large (n=13,768) 16-year longitudinal study of French national gas and electric workers, Lemogne et al. (2013) reported that Type 1 personality (charecterised by suppressed emotional expression in the context of interpersonal relationships) was associated with decreased risk of breast cancer (HR per SD=.081, 95%CI .068-.097, p=.02), and Type 5 personality (anti-emotional tendencies) associated with the onset of "other cancers", excluding prostate, breast, colorectal and smoking related (HR per SD=1.17, 95%CI 1.04-1.31, p=.01).

Osthus et al. (2011) investigated Health Related Quality of Life (HRQL) in 139 Norwegian male and female patients followed up for 75±4 months. Little information is provided other than that the Neuroticism scale of the EPQ was completed. Neuroticism was largely used to explain variance in HRQL. A regression analysis of general symptoms identified Neuroticism (β=.454, p≤.0001), T-stage (β=.037) and smoking status (β=.192) as significant, collectively accounting for 34.1% of the total variance. In terms of functional score, Neuroticism was the most significant (β=-.387, p≤.0001), but the model also included avoidance focussed coping (β=-.244), T-stage (β=-.176), and alcohol consumption (β=-0.227). Based on the extend of variance explained by Neuroticism, the authors checked to see if Neuroticism predicted survival but reported no predictive value, even when adjusted for HRQL scores. The authors adjusted for alcohol, tobacco and self-reported heart and lung disease. A cited strength of study was that the mean time between diagnosis and study inclusion was 67 months and, because mortality caused by reoccurrence often occurs within 36 months, risk of recurrence was low. However only successfully treated and cognitively functioning participants were included which limits the generalisability of the findings.

Nakaya et al. (2010) reported on a prospective study of the largest trial included in this review, 59,548 Finish and Swedish participants identified through either (a) the Finnish twin cohort registry (same-sex twin pairs (n=29,720)) or (2) the Swedish twin registry (twins (n=29,828)). Participants were asked to complete the EPI short form and recorded the potential confounders of education, parity, weight, height, smoking status and alcohol consumption because, on the basis of previous studies, these factors are thought to play a role in the causal pathway between personality traits and cancer risk and survival. The lifestyle factors in particular were considered potential mediators and that any personality effect may be through such mediators and not independent. Follow-up identified a total of 4,631 cases of cancer (Swedish cohort n=1,898, Finnish cohort n=2,733).

The authors reported that neither Extraversion nor Neuroticism was significantly

associated with risk of cancers at all sites as measured by Hazard Ratio (HR) (Extraversion: HR=1.00, 95%CI 0.99-1.01, p_{trend}=.66; Neuroticism: HR=1.01, 95%CI 1.00-1.02, p_{trend}=.06) both when unadjusted and after adjustment for potential mediators. Importantly, Nakaya et al. (2010) and colleagues found that by looking at specific forms of cancer (site), significant positive HR were noted between Extraversion and lung cancer (HR=1.08, 95%CI 1.03-1.13, p_{trend}< 0.01) and between Neuroticism and lung cancer (HR =1.10 95%CI 1.06-1.14, p_{trend}< 0.01). A significant hazard ratio was observed between Neuroticism and liver cancer (HR= 0.92, 95%CI 0.85-0.98, p_{trend}= 0.02). Again, these remained unchanged when unadjusted and after adjustment for potential confounders. Finally, unadjusted analysis of the combined effect of Extraversion and Neuroticism also showed no significant associations (HR for persons with levels of low Extraversion and high Neuroticism, high Extraversion and low Neuroticism, and high Extraversion and high Neuroticism compared with persons with levels of low Extraversion and low Neuroticism were 1.02, 1.03, and 0.94, respectively). Once more, these remained unchanged when unadjusted and after adjustment for potential confounders.

In terms of survival reported by Nakaya et al. (2010), the 4,631 cancer incidents resulted in 1,548 deaths. No significant associations between either Extraversion or Neuroticism and risk of death were found either when cancer sites were combined or considered separately by site in either unadjusted or multivariate analyses. Moreover, unadjusted analyses of the combined effect of Extraversion and Neuroticism also showed no significant associations; the hazard ratios for persons with levels of low Extraversion and high Neuroticism, high Extraversion and low Neuroticism, and high Extraversion and high Neuroticism compared with persons with levels of low Extraversion and low Neuroticism were 1.04, 1.08, and 0.96, respectively. Again, these results remained unchanged after adjustment for confounders.

Nakaya et al. (2010) concluded that their results offer no support for the hypothesis that personality traits are direct risk factors for cancers at all sites. Moreover, they concluded that the confounding effect of smoking on the hazard ratio for personality and lung cancer explains most of the observed effect and that with better accuracy no independent personality effect would be expected. In terms of the lung cancer findings, hazard ratios were not mediated by alcohol, but the number of cancer cases was small, which may have resulted in a chance finding. Moreover, no significant associations between personality and risk of immune-related cancers was found these findings is somewhat at odds with other

studies presented in this chapter (Nakaya et al., 2003; Hansen et al., 2005; Nakaya et al., 2006).

The non-standardised used of the EPI is curious and unexplained, as is the choice of sample used in that it appears to be neither random nor stratified as participants came from two cohorts of twins. Moreover, although the authors comment on zygosity and report it was not associated with either exposure or outcomes, and therefore not treated as a covariate, it is impossible to assess the extent to which the findings can be generalised to individuals who are not twins. Nevertheless, Ranchor et al. (2010) commend the trial for its large sample size, choice of analysis, interpretation of results and use of controlling variables (including zygosity, and time since baseline assessment) and considers the results to be effectively conclusive.

Augustine et al. (2009) reported a difference at time of surgery of 4.33 years for Neuroticism and 3.12 years at 1 SD above versus 1 SD below the mean, suggesting a negative association at time of surgery (higher in these constructs associated with earlier onset of illness: younger at surgery) in a group of 203 head and neck cancer patients recruited during treatment for lung cancer and post surgery to resect stage I or II non-small-cell lung cancer. Smoking was assessed and included in analysis; partial correlation between age at time of surgery and all other measures for Neuroticism (p=-.20* including smoking and p=-.14* when including smoking and gender) "suggesting perhaps that those with heightened trait negative affect might not possess the immunological resources needed to resist the progression of a lung cancer infection" (Augustine et al., 2009, page 7).

Shipley et al. (2007) reported on the UK Health and Lifestyle Survey (HALS), a sample of 5,424 participants followed up for 21 years. A comprehensive assessment by both an interviewer and nurse in the participants' home included the full 57 item EPI. Sociodemographic factors, health behaviours, psychological measures, mental status and vital status were all assessed. As is the standard in such reviews, Cox proportional regression analysis was used to determine hazard ratios.

Three models were tested; model one included age and gender, model two included age and gender with the addition of education, occupational social class, health, physical activity, alcohol and smoking, and model three consisted of age, gender and GHQ status. The authors suspected that being male was associated with increased Extraversion and mortality, and being female with increased Neuroticism but this was not supported statistically (p=.94 and p=.85 respectively) and was therefore not included in the models. Of

the 5,424 participants, 614 women and 721 men died during follow-up.

The authors found that a one SD increase in Neuroticism (as measured by the EPI) contributed a HR of 1.09 (95%CI 1.03-1.11) to increased risk of mortality in all ages from all causes in model one. However model two and model three were not significant (HR=1.05, 95%CI .99-1.11) and (HR=1.03 95%CI .96-1.10) respectively. Similarly, a one SD increase in Neuroticism contributed a HR of 1.12 (95%CI = 1.03-1.21) to death from cardiovascular disease in model one, and this remained significant in model two (HR=1.10, 95%CI 1.00-1.21) but not in model three (HR 1.09 95%CI .98-1.21). In participants aged between 40 and 59, model significantly predicted risk of cardiovascular disease (HR=1.20 95%CI 1.02-1.42) and was protective of risk of respiratory disease in an all-age analysis using model one (HR=.89 95%CI .76-1.06).

Significantly in the context of this thesis, Neuroticism was not associated with risk of lung cancer, other cancers (nor for completeness stroke or respiratory disease). Extraversion, however, was found to be protective of death from respiratory disease (HR=0.84 95%CI .70-1.00).

The authors concluded that as no single co-variate accounted for a significant amount of variance, the findings suggest mortality and Neuroticism is mediated by sociodemographic, health behaviour or physiological factors. The authors hypothesise that low mood or psychiatric illness may play a mediating role. Moreover, a genetic model is hypothesised with a correlation between Neuroticism and GHQ cited as .91, the inference being that either Neuroticism or genetics may have some effect, other than on mood, and that adjusting for GHQ may be an over adjustment. The role of extraversion on cause-specific mortality is attributed to chance. The authors conclude that future studies of the role of Neuroticism and Extraversion should examine possible genetic mechanisms and the mediating effect of low mood.

The sample was analysed in its entirety and in groups of 20-39, 40-59 and ≥60 years but due to power limitations, the younger sample could not be analysed separately. Although there was no difference in GHQ score between the three groups, the younger sample was notable due to (1) being from a higher occupational social class, (2) higher educational attainment than the older population, (the middle aged sample were equivalent), (3) engaging in more unhealthy behaviours than the oldest (the middle group were equivalent), and (4) being healthier than the other two groups (lower BMI, better BP and respiratory function). This may have been a source of bias. Another major limitation of the study

was that the cancers were classified as lung (n=96) and non lung (n=279).

Nakaya et al. (2006) reported on a sample of 1,020 persons born in 1936 and living in four municipalities of Copenhagen. They were asked to complete the EPI and participate in a social-psychiatric interview. Participants were followed up from the date of the social-psychiatric interview, until (a) the date of first cancer diagnosis (other than non-melanoma skin cancer), (b) death (c) emigration or (d) 31/12/2002 whichever occurred first. A total of 189 cancer diagnosis were identified and this sub-cohort was then followed-up for death from the date of cancer diagnosis until (a) death (b) emigration, or (c) end of the study period (31/01/2005). The following variables were considered as *a priori* confounders (an asterisk denotes significant association in the univariate Cox proportional hazard model): gender*, age*, cancer site*, clinical stage*, length of education in years, marital status, social class, smoking status at baseline*, alcohol consumption at baseline* and psychiatric status at time of interview (normal, neurotic, or deviant/psychotic), those described as neurotic showed an increased but borderline significant (P_{trend}=0.053) risk of death from all causes compared to normal subjects.

Controlling for age, gender, cancer site, clinical stage, smoking status, and alcohol consumption at baseline, did not alter the effect of Extraversion on risk of death (HR=.8 95%CI .4–1.7, p_{trend}= 0.33) and the addition of psychiatric status as a confounder also made little difference (p_{trend}=.34). Excluding the 19 persons who were diagnosed as having cancer within the first 3 years from the baseline also had little effect (p_{trend}= 0.38). Finally, when looking exclusively at cancer-related death, no significant effect of Extroversion was observed (HR=.6 95%CI .3–1.3, p_{trend}=.12).

Turning to Neuroticism, and risk of deaths from all causes, age and gender showed no significant HR. However, the multivariable adjusted HR showed a significant association between Neuroticism and the risk of death from all causes (HR=-2.6 95%CI 1.4–5.0; p_{trend}=<.01). The addition of psychiatric status as a confounder remained significant (p_{trend}=.02). A further multivariate adjusted HR excluded persons diagnosed as having cancer within the first 3 years from the baseline (as the symptoms may have affected their response), but this only made a small difference (p_{trend}=0.04).

With cancer mortality as the end point, a similarly significant positive HR between Neuroticism and risk of death was observed (P_{trend}=.04). However, intriguingly, Neuroticism in females was strongly associated with cancer survival in a multivariate adjusted HR (p_{trend}=.03). A similar pattern was noted by Nakaya et al. (2006) in males, although not

significant. It is worthy of note that further statistical modeling (including interactions between gender and Neuroticism, banding age, and cut-off points for the personality scales from tertiles to quartiles) did not have an effect which suggest statistical robustness.

Nakaya et al. (2006) rightly state as as methodological strength that personality was assessed before the cancer diagnosis. This is significant, because assessing personality after the cancer diagnosis may have been influenced by the psychological reactions to the diagnosis or brought about by the treatment. This goes some way to refute the cautious interpretations of the findings on Neuroticism cited below (Nakaya et al., 2003) and supports the finding. The authors also acknowledge limitations of the methodology, perhaps most significantly that the confidence intervals for the multivariable analyses of Neuroticism in females were broad, and therefore the potential role of chance cannot be ignored. Finally, no information was available about the health behaviours after the cancer diagnosis or on treatment compliance both of which may affect survival.

Hansen et al. (2005) followed up 29,595 Swedish twins from the national Swedish Twin Registry. Participants were followed up from 01/01/1974 until (a) death (b) emigration, or (c) end of the study period (31/01/2005) whichever occurred first. Personality was assessed using a nonstandard 18 item version of the Eysenck Personality Inventory. Cancer groups were typed (hormone-related solid cancers, virus-related and immune-related cancers, digestive organ cancers (excluding liver), respiratory organ cancers, other cancer sites and all cancer sites). Again a Cox proportional hazards model (95%CIs) estimated HRs for Extraversion and Neuroticism, separately and together. Environment and genetic factors were accounted for by a nested case-control logistical regression model in twin groups (in which one twin had a cancer diagnosis and the other did not).

Analysis did not find any significant associations. The authors do not report the statistical data, but they state that no significant associations between Neuroticism and Extroversion were found when the personality scales were treated as linear measures. When dichotomised (low 0-4; high 5-9), non-significant effects of low Extraversion (age adjusted HR=1.00, 95%CI not-given), high Extraversion (age adjusted HR=1.03, 95%CI .92-1.15), high Neuroticism (age adjusted HR=1.00, 95%CI not-given) and low Neuroticism (age adjusted HR=1.02, 95%CI =.90-1.17) on all cancer sites was found.

Larger effects were found when the analysis was restricted to virus-related and immune-related cancers; low Extraversion (age adjusted HR = 1.00 95%CI not given) high extraversion (age adjusted HR=1.38, 95% CI=.92-2.06); multivariable HR = 1.36, 95%

CI= .90-2.03); high Neuroticism (age adjusted HR=1.00 95%CI not-given), low Extraversion (age adjusted HR=1.12, 95%CI .71-1.78; multivariate HR=1.10, 95%CI .69-1.76). The authors conclude that they have found no evidence of personality affecting cancer, even when accounting for risk behaviours and that the direction of predicted risk for Neuroticism and Extraversion was not consistently demonstrated. Post-hoc analysis excluding the first 3 years, and a separate analysis including only the first 3 years of follow up, did not change the results, unlike the earlier study by Nakaya et al. (2003).

When considered together and dichotomised, the joint effects of Extraversion and Neuroticism were also not significant in all cancer types, including in individuals with high Extraversion and low Neuroticism, which were *a priori* assumed to be high risk based on Eysenck's theories (see Chapter 2). However the largest joint effect was found in high Extraversion and low Neuroticism in virus and immune related cancers (age adjusted HR = 1.45 95%CI =.77-2.70; multivariable HR=1.40 95%CI .74-2.65)

Canada et al. (2005) followed up 60 men and women for 10 years from time of surgery as part of larger Randomised Control Trial. The authors concluded that there was no relationship between personality and either recurrence or survival (from the time of original surgical intervention through 10-year follow-up) in a group of malignant melanoma patients. Using personality as a single predictor of outcome univariate, Psychoticism, Extraversion, Neuroticism and Lie were not predictive of recurrence (X^2=1.01, p=.316, X^2=.05, p=.829, X^2=2.04, p=.153, X^2=.09, p=.765) or death (X^2=.31, p=.579, X^2=.15, p=.697, X^2 = .88, p=.349, X^2=.05, p=.818) respectively. Multivariate analysis found that only Breslow Depth predicted outcome.

The authors acknowledged as a limitation that the original study had a small sample size and was not designed to determine the effects of the intervention, or of personality, on recurrence and survival rates and consequently any generalisations are limited. Moreover, Canada et al. (2005) reported that, as a consequence of excluding eight participants for whom psychological data were not available, the 10-year follow-up study concluded that participation in a psycho-educational group was predictive of longer survival but multivariate analysis did not replicate this finding indicating that power may have been an issue.

In a study of 29,606 residents of 14 municipalities of Miyagi Prefecture in rural northern Japan, Nakaya et al. (2003) assessed personality by the completion of the EPQ-R short form. Using a multivariate Cox proportional hazards model the Relative Risks

(RR) for Extraversion and Neuroticism and cancer incidence were not significant. However, Neuroticism was a statistically significant positive linear RR with existing cancer at baseline ($p_{trend}<.001$), and the 320 cancer cases diagnosed within the first three years of follow-up ($p_{trend} = .03$).

The RR for Neuroticism was not significant for the 666 cancer's diagnosed during the follow-up from four to seven years ($p_{trend}= .43$). In addition, no statistically significant associations between any of the personality sub-scales and the risk of the four most common cancers (stomach, colorectum, lung, and breast) were discovered, and personality scales and cancer at sites defined according to whether or not they are associated with smoking were also not significant. Nakaya et al. (2003) concluded that the data did not support the hypothesis that personality is a risk factor for cancer incidence and suggest that the RR between Neuroticism and prevalent cancer may be an effect, rather than a cause, of cancer diagnosis or indeed symptoms. This prospective study benefits from the recruitment of subjects from the general population and control of potentially confounding variables.

Nakaya et al. (2003) concede that, while the sample is representative, and demonstrative of higher incidence of cancer in those with higher smoking and alcohol consumption, cancer site is heterogeneous and therefore may have lacked statistical power for detecting small changes in the risk of cancer at individual sites associated with personality scales, particularly the case for hormone-related cancers (such as breast) which are less prevalent in Japan than in Western countries. Nevertheless, Nakaya et al. (2003) conclude that their findings support the hypothesis that personality does not play a major role in the causation of cancer.

Aarstad et al. (2002) investigated whether personality assessed by the full 57 item EPI was associated with the risk and prognosis of head and neck squamous cell carcinoma (HNSCC) in 78 males with HNSCC and 61 males with benign head and neck disease. Cancer patients were primarily statistically associated with alcohol consumption and to a lesser extent with higher Neuroticism (10.7 ± 0.5 vs 8.3 ± 0.6; $p <.01$), the conclusion being neuroticism is related to alcohol consumption and alcohol consumption related to HNSCC. Interestingly, low Lie score predicted disease-specific death ($p=.02$). The study controlled for smoking, drinking and education.

Schapiro et al. (2001) reported a 20 year follow-up of 1,031 Danish participants who took part in a Danish health survey in 1976-1977 and who completed the EPI. This prospective design was investigated the Kissen and Eysenck hypothesis of cancer-prone

personality, that high Extroversion and/or low Neuroticism is associated with an increased risk of cancer. The trial is commendable as it adjusted for age, gender, calendar period, alcohol, smoking, marital status, social class and psychiatric illness as assessed by an interviewing doctor and found no significant relative risk for personality or cancer site.

However, personality was assessed using a non standard 18 item version of the EPI (which to the authors' credit for acknowledging, is included as an appendix, curiously labelled the EPI-Q). Even more curiously, and again to the authors' credit, a scoring system for missed questions on the EPI was constructed which compensated by over rating scores of two or more when seven items were completed and five or more when 8 questions were answered. Consequently, a score of 6 could be worth six points when all items completed on the scale, a score of seven when eight items were completed or a score of eight when seven items were completed (all with a scoring range of 0-9). The Extraversion and Neuroticism scales were then dichotomized and assigned into groups based on hypothesized risk of cancer (Extraversion; background risk 0-3, low risk 4-5, medium risk 6-7 and high risk 8-9) (Neuroticism; background risk 6-9, low risk 4-5, medium risk 2-3, high risk 0-1). EPI data was available for 1,023 participants (Extraversion) and 1,024 participants (Neuroticism). 1,020 participants were included in the multivariate analysis, due to missing values in one or both scales.

Follow-up was from day of interview to either (1) emigration, (2) a cancer diagnosis, (3) death, or (4) end of trial on the 31/12/1996 whichever occurred first. Copenhagen county incidence dates were used to determine the expected number of cancers and this was multiplied by person years of observation

Both personality dimensions predicted social class (High Extraversion and High Neuroticism associated with white-collar), smoking (High Extraversion and High Neuroticism associated with former smokers), psychiatric group (High Extroversion and High Neuroticism with Neurotic diagnosis). Additionally, high Neuroticism was positively associated with marital status and high Extraversion with decreased alcohol consumption. However, compared with 114.3 predicted, 113 cancers were observed (standardized incidence ratio (SIR)=.99 95%CI .81-1.19) Neither a trend nor link between personality and cancer was observed, and this was maintained when stratified for gender. Moreover, no trend or link was confirmed when analysis was restricted to one type of cancer (Hormone related cancers including breast, for example, were reported as total SIR=.88 (95%CI .58-1.28); High Extraversion/risk SIR=.93 (95%CI .53-1.51); Low extraversion/risk=.83 (95%CI .41-

1.48); high Neuroticism/risk SIR=.94 (95%CI .57-1.45); and low Neuroticism/risk SIR=.81 (95%CI .33-1.66) although only 27 cases were included in the analysis. The authors accounted for significant differences in the distribution of lifestyle and socioeconomic status in the multivariate analysis and explain its significance in terms of widely heterogenous groupings. It would seem that the terms blue-collar and white-collar were binary terms intended to capture all employment status', including no employment, and therefore making interpretation of the results difficult and therefore its inclusion as a variable questionable. The authors, however, did collect and include known cancer risk factors in their models, which they themselves point out, before they cite the use of EPI rather than a more inclusive model such as the NEO-Personality Inventory.

3.5.4 Summary of main results. Of the 11 papers included (Lemogne et al., 2013; Osthus et al., 2011; Nakaya et al., 2010; Augustine et al., 2009; Shipley et al., 2007; Nakaya et al., 2006; Canada et al., 2005; Hansen et al., 2005; Nakaya et al., 2003; Aarstad et al., 2002; Schapiro et al., 2001), 6 reported significant results (Lemogne et al., 2013; Nakaya et al., 2010; Augustine et al., 2009; Nakaya et al., 2006, 2003; Aarstad et al., 2002) for trait personality and cancer and five did not (Osthus et al., 2011; Shipley et al., 2007; Canada et al., 2005; Hansen et al., 2005; Schapiro et al., 2001).

Seven significant findings were reported:

1. High Extraversion was associated with risk of lung cancer, but not when all cancers were combined (Nakaya et al., 2010).

2. Low Neuroticism was associated with risk of lung cancer and liver cancer, but not when all cancer types were combined (Nakaya et al., 2010).

3. High Neuroticism was associated with lower age at surgery for lung cancer (Augustine et al., 2009), incidence of all cancer (Nakaya et al., 2003, 2006; Aarstad et al., 2002), risk of all cancer (Nakaya et al., 2003, 2006), death from lung cancer (Nakaya et al., 2006) and all cause death, particularly in females (Nakaya et al., 2006).

4. Low Lie was as associated with risk of cancer (Nakaya et al., 2003) .

5. Low Lie was associated disease specific death (Aarstad et al., 2002).

6. Type 1 personality was associated with decreased risk of breast cancer (Lemogne et al., 2013) and Type 5 with 'other' cancers (Lemogne et al., 2013).

7. BIS was negatively associated with age at surgery for lung cancer (Augustine et al., 2009).

3.6 Discussion, Limitations and Implications

The structured review revealed 11 studies that met the inclusion criteria. Given the only source of data collection used was PubMed and the forced search terms of 'risk', this would seem a reasonable hit-rate. The studies ranged greatly in size and methodological sophistication but the overall picture is that as many studies reported a significant result (n=5) as did not report a significant result (n=6), indeed one study tentatively reported a finding and then explained it away. A second observation was that where a result was found, this tended to be in an analysis restricted to cancer site (only two studies combining results reported a significant finding, and these were by far the largest with up to 59,548 participants). Moreover, many of the studies included complicated and numerous multi-factorial models adjusting for a wide range of known confounds, and it was often such models that were the reported abstract figures. An assessment of bias and review of the suggested relationship between personality and outcome would also be informative, as many authors rightly suggest that other risk factors controlled for in the studies may or do explain the between group difference more than personality does.

All sources that met the criteria for inclusion were given equal weighting. The space taken in the above Chapter and in review Chapters four to seven which follow, reflect the 'Data Extraction' sections of Chapters three to seven, in this case, 'site of cancer', 'measure of personality', 'methodological quality', and 'outcomes and contentious discussion'. The weighting of studies could perhaps have been improved by undertaking a quality review, and this is discussed further later in this section.

A further observation is the consideration given by many authors about the timing of the personality measures, and the potential for asymptomatic and undiagnosed cancers to effect response. Several trials adjusted for this statistically, and in one trial this made a significant result non-significant, but this may have been for other reasons.

Given what is believed to be known about Type C personality, the finding by Nakaya et al. (2003) that high Lie scores protected against risk of cancer would seem to be counter to the expected direction, as if Lie scales are a measure of social conformity, this would be much like the "Being over-co-operative, appeasing, unassertive, over-patient, [and] avoiding conflict" definition suggested (Chapter 2) for Type C personality. However, conversely, the Aarstad et al. (2002) study found a relationship the direction supporting a Type C personality; higher Lie, greater disease depth.

The traits of being High in Extraversion and Low in Neuroticism (together or in-

dependently) are often cited as indicators of a Type C personality, the genesis being the widely cited Kissen & Eysenck (1962) study. It should be noted, however, that in the Kissen & Eysenck (1962) study, Eysenck predicted the high Neuroticism and High Extraversion would be the most significant. The study by Nakaya et al. (2010) produced the only evidence of these findings, but this was the study in which the authors discounted their own results as chance. Indeed three studies including one by the Nakaya group found evidence that high Neuroticism was a risk factor as predicted but not found by Kissen and Eysenck.

Considering the included literature above, Lemogne et al. (2013) investigated a French sample, Osthus et al. (2011) a Norwegian sample, Nakaya et al. (2010) a Finish and Swedish sample, Augustine et al. (2009) an American sample, Shipley et al. (2007) a British sample, Nakaya et al. (2006) a Danish sample, Hansen et al. (2005) a Swedish sample, Canada et al. (2005) undisclosed (data from a RCT), Nakaya et al. (2003) a Japanese sample, Aarstad et al. (2002) a Norwegian sample and Schapiro et al. (2001) a Danish sample. Given the cross-cultural use of the trait-based personality measures, it is important to determine the validation of associated measures.

The psychometric structure of the Eysenck Personality Questionnaire (EPQ) has been reproduced successfully in over 25 countries (Barrett & Eysenck, 1984). The revised EPQ has been translated to a number of languages including Hindi (Tiwari et al., 2009) reporting Extraversion, Neuroticism, Psychoticism and Lie scales at Chronbach's alpha 0.77, 0.77, 0.24, 0.62, respectively; Turkish (Karanci et al., 2007) Kuder-Richardson alpha coefficients at 0.78, 0.65, 0.42, and 0.64, respectively; and German (Francis & Lewis, 2006) alpha coefficients 0.86, 0.81, 0.44, 0.64 respectively. The construct validity of the translated questionnaires can therefore be considered to be good, although interestingly the low reliability of the Psychoticism when translated reflects the validity challenges to the scale presented earlier.

It is clear that there remains sustained interest in a Type C personality, perhaps even if the current empirical evidence does not seem to sustain it. It would be interesting to expand the literature reviews included in this thesis (this Chapter and those that follow in Chapters four to seven) by identifying material from a wider range of online databases. PubMed is maintained by The United States National Library of Medicine (NLM) at the National Institutes of Health and indexes references and abstracts on life sciences and biomedical literature, whereas Scopus, Web of Science, and Google Scholar cover most

scientific fields. A paper by Falagas et al. (2008) differentiates the academic literature databases by suggesting that, "Scopus offers about 20% more coverage than Web of Science, whereas Google Scholar offers results of inconsistent accuracy. PubMed remains an optimal tool in biomedical electronic research. Scopus covers a wider journal range, of help both in keyword searching and citation analysis, but it is currently limited to recent articles (published after 1995) compared with Web of Science. Google Scholar, as for the Web in general, can help in the retrieval of even the most obscure information but its use is marred by inadequate, less often updated, citation information."

Therefore, it would be interesting to subject the literature yielded from querying the above databases to a more systematic COCHRANE style review of trait personality (specifically Extraversion and Neuroticism), perhaps including other well validated and reliable measures such as the NEO-PI. However, if the studies included above are typical, caution would be needed in interpreting the results as computed scales and non-standardised measures seem wide-spread. Considering risk of bias would allow for the strengths and weaknesses of the various studies presented in this Chapter and those in Chapters four to seven to be made explicit and, perhaps, the potential for meta-analysis. It is unlikely that Eysenck would have agreed with such a strategy (Eysenck, 1994). Perhaps to soften the blow, such a review could include subject specific criteria such as mode of measure delivery, as Eysenck suggested that, “Measurement using personal contact (interview methods) is significantly more likely to give positive results than simply handing out questionnaires” (Eysenck, 1994, 204). Certainly the studies reviewed above employed a variety of modes of delivery, unsurprisingly the larger prospective observational epidemiological studies opting for postal questionnaires.

Chapter 4: Structured review of positive and negative affect and risk of cancer

4.1 Overview

This chapter reports on a structured review of positive and negative affect and risk of cancer to:

1. Introduce the reader to the assumptions previously made, and research conducted, on positive and negative affect and risk of cancer and cancer.

2. Highlight the methodological flaws present in much of the reported research.

3. Set the scene for further such structured reviews of less well known personality measures and subsequent research.

4.2 Background

Two general factors typically labeled Positive Affect (PA) and Negative Affect (NA) have consistently been proposed as the dominant dimensions of emotional experience. The two factors of affect are distinct, like Eysenck's Psychoticism and Neuroticism dimensions, and it is therefore possible to be high (or low) on either or both PA and NA. Affect has been found to be stable over time and context (Naragon & Watson, 2009). PA has been suggested to correspond with Extraversion (D. Watson & Clark, 1984) and NA with Neuroticism.

One well known measure of affect, the Positive and Negative Affectivity Schedule (PANAS) (M. Watson & Greer, 1983), is a twenty item measure of both PA and NA.

4.3 Review Methods

4.3.1 Description of the literature being reviewed. The literature reviewed is intentionally limited in two ways. First, it is all indexed within PubMed, and as such meets a particular standard for quality. Second, in order to minimise the risk of accidentally biasing the results by confusing terminology shared by theorists and measures (such as affect), only personality traits relating to positive or negative affect were included.

4.3.2 Objectives. The structured literature reviewed had two objectives, derived from the potential background above, namely:

1. To review the evidence relating positive and negative affect, cancer risk and progression in humans.

2. To identify the nature and quality of the evidence available on this topic.

4.3.3 Types of studies. All trial designs with humans participants were included.

4.3.4 Types of participants. Men and women over the age of 18 years with a diagnosis of cancer.

4.3.5 Types of outcome measures.

1. One or more measure of positive or negative affect.
2. Diagnosis of first cancer, recurrence or cancer-related death.

4.3.6 Criteria for considering reviews for inclusion. The inclusion criteria for selection were:

1. Published in PubMed
2. An original report of a study involving human adults (18 years of age or over).
3. Reports positive or negative affect.
4. Does not combine affect.
5. Outcome was diagnosis of first cancer, recurrence or cancer related death.
6. Written in English.

4.4 Search Methods for identification of literature

4.4.1 Data collection and analysis. A search of PubMed were conducted in October 2013. The search criteria can be found in appendix D. The search resulted in 34 hits. The results were screened and visual inspection of title and abstract (together) excluded 31 obviously irrelevant[7] papers leaving three.

The three abstracts (or titles where abstracts were unavailable) were assessed by the author against an *a priori* checklist based on definitions developed at the start of the review (criteria for considering reviews for inclusion), to identify potentially relevant studies for which full texts were obtained.

4.4.2 Data Extraction. No result met all of the criteria for inclusion

[7] 'Obviously irrelevant' papers were those that from the reading of the title and abstract did not meet one or more of the inclusion criteria.

4.5 Results

Table 3:: Positive and negative affect and cancer risk: Characteristics of excluded articles at full revision stage

Authors	Inclusion criteria not met
Augustine et al. (2009)	3
Steptoe et al. (2009)	2
Garssen (2004)	2

4.5.1 Description of excluded literature. Augustine et al. (2009) reported on "personality predictors of the time course for lung cancer onset". Neuroticism as measured by the EPQ , BIS as measured by the Behavioral Activation/Behavioral Inhibition Scale, anger, hostility, verbal aggression and total aggression as assessed by the Buss-Perry aggression questionnaire, anxiety as assessed by the State-Trait Anxiety Inventory, and depression as assessed by the Beck Depression Inventory were negatively related to age at time of surgery; higher (vs. lower) scoring in these constructs showed an earlier onset of illness indicated by being younger at surgery. Finally, coping behavior (both adaptive and less adaptive) was negatively related to age at time of surgery, such that those who engage in more coping showed an earlier onset of illness (younger at surgery) even when controlling for gender. As Augustine et al. (2009) did not measure PA or NA as defined in this review, the study was included in the Eysenckian personality review in chapter two due to its use of the EPQ.

Steptoe et al. (2009) presented an interesting review article of affect in a range of disease populations which do not include cancer, and concluded that at a biological level, expressed cortisol has consistently been shown to be lower in individuals reporting PA, and favorable associations with heart rate, blood pressure, and pro-inflammatory cytokines such as IL-6 have also been described. Moreover, the reported relationships were said to be independent of NA and depressed mood, which Steptoe et al. (2009) suggests may indicate that PA may have distinctive biological correlates.

In a review of "psychological factors and cancer development: Evidence after 30 years of research" Garssen (2004) reviews the evidence for a range of psychological factors in cancer development. While PA is not directly discussed, negative emotions are and are handled with the umbrella term "distress". Garssen (2004) reports on 33 studies:

in summary he found 6 positive, 16 absent and 11 negative (progression studies) and 1 positive, 6 absent and 7 negative (initiation studies) where a positive finding is one that reports negative emotions predict a more favourable outcome. Garson notes, "What strikes the eye, however, is the large number of studies that failed to find a relationship: 22 of the 47 studies (47%)" (page 323). This may be due to the unspecified and presumably homogenous cancer types and measures of negative emotion/distress assessed.

4.6 Discussion and Implications

No cancer survival and risk studies assessed by a dedicated measure of either PA and/or NA were returned from PubMed when the search criteria, outlined above and re-created in full in Appendix D, was run. This may because the search terms "personality" was forced so as to limit results to a manageable number. It would be interesting to undertake a more comprehensive literature review with more refined search criteria intended to yield cancer studies that use a measure such as the PANAS (M. Watson & Greer, 1983) to determine if there is (1) an evidence base for Affect being distinct from negative emotions or distress, and (2) to what extent, if any, measuring both Affect and Eysenckian personality traits adds predictive value over either alone.

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Chapter 5: Structured review of locus of control and risk of cancer

5.1 Overview

This chapter reports on a structured review of locus of control and risk of cancer and serves to:

1. Introduce the reader to the assumptions previously made, and research conducted, on locus of control and cancer.

2. Highlight the methodological flaws present in much of the reported research.

3. Set the scene for further such structured reviews of less well known personality measures and subsequent research.

5.2 Background

Health Locus of Control (HLC) is widely used in the planning of health education programs (Kuwahara et al., 2004), and can be defined as the perception of what controls a persons own health (Wallston et al., 1978).

5.3 Review Methods

5.3.1 Description of the literature being reviewed. The literature reviewed is intentionally limited in two ways. First, it is all indexed within PubMed, and as such meets a particular standard for quality. Second, in order to minimise the risk of accidentally biasing the results by confusing terminology shared by theorists and measures, only measures of locus of control were included.

5.3.2 Objectives. The structured literature reviewed had two objectives, derived from the potential background above, namely:

1. To review the evidence relating locus of control, cancer risk and progression in humans.

2. To identify the nature and quality of the evidence available on this topic.

5.3.3 Types of studies. All trial designs with humans participants were included.

5.3.4 Types of participants. Men and women over the age of 18 years with a diagnosis of cancer.

5.3.5 Types of outcome measures.

1. One or more measure of locus of control
2. Diagnosis of first cancer, recurrence or cancer related death.

5.3.6 Criteria for considering reviews for inclusion. The inclusion criteria for selection were:

1. Published in PubMed.
2. A original report of a study involving human adults (18 years of age or over).
3. Reports a measure of locus of control.
4. Does not combine more than one personality dimension or trait.
5. Outcome was diagnosis of first cancer, recurrence or cancer related death.
6. Written in English.

5.4 Search Methods for identification of literature

5.4.1 Data collection and analysis. A search of PubMed were conducted in October 2013. The search criteria can be found in appendix E. The search resulted in 11 hits. The results were screened and visual inspection of title and abstract (together) excluded six obviously irrelevant[8] papers leaving five.

Five abstracts (or titles where abstracts were unavailable) were assessed by the author against an *a priori* checklist based on definitions developed at the start of the review (criteria for considering reviews for inclusion), to identify potentially relevant studies for which full texts were obtained.

5.4.2 Data Extraction. Papers meeting the criteria for inclusion were reviewed for; site of cancer, measure of personality, methodological quality, outcomes and contentious discussion points were extracted. Data excluded for not meeting the afore mentioned criteria, including other reviews, are presented below under description of excluded literature. One paper P. Taylor et al. (1988) could not be obtained.

5.4.3 Study classification. Included studies were classified based upon

- Personality measure(s):
- Outcome(s)
- Sample size and cancer type(s)
- Outcome

[8] 'Obviously irrelevant' papers were those that from the reading of the title and abstract did not meet one or more of the inclusion criteria.

5.5 Results

Table 4:: Locus of Control and cancer risk: Characteristics of excluded articles at full revision stage

Authors	Inclusion criteria not met
Stürmer et al. (2006)	3
Garssen (2004)	2
De Boer et al. (1999)	2

5.5.1 Description of excluded literature. Garssen (2004) previously discussed in chapters three and four reviews emotional control under the heading "repression of emotion" and reports several studies using several different measures, often together. The results are difficult to interpret without knowledge of the measures used, the participant characteristics and potential confounding factors, but the narrative gives a sense of the suggestion of a weak evidence base.

Stürmer et al. (2006), first presented in this thesis in chapter 3, reports no significant findings on internal locus of control and cancer morbidity and mortality. However, as with personality, inadequate information is presented on how the measures collected were factor analysed to include within the review.

De Boer et al. (1999) presents a well structured review of the psychosocial correlates of cancer relapse and survival from 1979 to 1995. A number of studies relevant to the other reviews within this thesis were identified, but regrettably due to the time constraints available could not be included. Nevertheless, they conclude "Factors most frequently evaluated with respect to their association with survival and/or relapse were depression, anxiety, hopelessness/helplessness, hostility, marital status and social involvement, mainly inconsistent results were found" (De Boer et al., 1999, page 226). The authors list a number of methodological problems which may account for the inconsistent findings, and these have been presented earlier under the personality review chapter (Chapter two) but are briefly, sample size, heterogenous cancer types and stages, and non-consistent outcome measures. Additionally, prospective longitudinal design with short follow up, statistical analysis and the lack of theoretical models are suggested as limitations.

5.5.2 Review of included literature.

Table 5:: Characteristics of included studies and cancer related significant findings

Author	Locus of Control measure(s) / means of administration	Outcome(s)	Sample size / cancer type(s)	Cancer related significant finding(s)
Price, Tennant, Smith, et al. (2001)	Locus of Control of Behaviour (LCB) scale	between-group difference	n=288 / Breast cancer and control	none

(Price, Tennant, Smith, et al., 2001) report on a semi-prospective study of 2,224 older women recalled for assessment in a breast screening program. Designed to examine the three domains of Temoshok's "cancer prone personality", the subjects completed a self-report measure of defense style, locus of control, emotional expression and control, self-esteem, trait anxiety, and state anxiety and depression while waiting for examination. Despite the potentially anxiety provoking context, no differences were detected between breast carcinoma subjects and controls (benign tumours) which the authors suggest is supported by the findings of Bleiker et al. (1996).

5.5.3 Summary of main results. Zero of the two papers included (B. C. Taylor et al., 1992; Price, Tennant, Smith, et al., 2001) reported significant results.

5.6 Discussion and Implications

It is reasonable to agree with Garssen (2004) that "most empirical findings failed to demonstrate a relationship between personality in general, and locus of control in particular, and cancer initiation or cancer progression" (page 328).

Chapter 6: Structured review of emotional control and risk of cancer

6.1 Overview

This chapter reports on a structured review of emotional control and risk of cancer and serves to:

1. Introduce the reader to the assumptions previously made, and research conducted, on emotional control and cancer.

2. Highlight the methodological flaws present in much of the reported research.

3. Set the scene for further such structured reviews of less well known personality measures and subsequent research.

6.2 Background

Anti-emotionality has been linked with immune change (Bleiker et al., 1996; van der Ploeg et al., 1989). The Courtauld Emotional Control Scale (CECS) was developed by (M. Watson & Greer, 1983) as a measure of emotional control, specifically the extent to which individuals self report controlling anger, anxiety and depressed mood.

6.3 Review Methods

6.3.1 Description of the literature being reviewed . The literature reviewed is intentionally limited in two ways. First, it is all indexed within PubMed, and as such meets a particular standard for quality. Second, in order to minimise the risk of accidentally biasing the results by confusing terminology shared by theorists and measures, only measures of emotionalcontrol were included.

6.3.2 Objectives. The structured literature reviewed had two objectives, namely:

1. To review the evidence relating locus of control, cancer risk and progression in humans.

2. To identify the nature and quality of the evidence available on this topic.

6.3.3 Types of studies. All trial designs with humans participants were included.

6.3.4 Types of participants. Men and women over the age of 18 years with a diagnosis of cancer.

6.3.5 Types of outcome measures.

1. One or more measure of locus of control
2. Diagnosis of first cancer, recurrence or cancer-related death.

6.3.6 Criteria for considering reviews for inclusion. The inclusion criteria for selection were:

1. Published in PubMed.
2. An original report of a study involving human adults (18 years of age or over).
3. Reports a measure of locus of control.
4. Does not combine more than one personality dimension or trait.
5. Outcome was diagnosis of first cancer, recurrence or cancer related death.
6. Written in English.

6.4 Search Methods for identification of literature

6.4.1 Data collection and analysis. A search of PubMed was conducted in October 2013. The search criteria can be found in Appendix F. The search resulted in four hits. The results were screened and visual inspection of title and abstract (together) excluded three obviously irrelevant[9] papers leaving one.

The one abstract was assessed by the author against an *a priori* checklist based on definitions developed at the start of the review (criteria for considering reviews for inclusion), to identify potentially relevant studies for which full texts were obtained.

6.4.2 Data Extraction. The paper meeting the criteria for inclusion were reviewed for; site of cancer, measure of emotional control, methodological quality, outcomes and contentious discussion points were extracted. Data excluded for not meeting the afore mentioned criteria, including other reviews, are presented below under description of excluded literature.

[9] 'Obviously irrelevant' papers were those that from the reading of the title and abstract did not meet one or more of the inclusion criteria.

6.5 Results

Table 6:: Locus of Control and caner risk: Characteristics of excluded articles at full revision stage

Authors	**Inclusion criteria not met**
Stürmer et al. (2006)	3
Garssen (2004)	2
De Boer et al. (1999)	2

6.5.1 Description of excluded literature. The review articles by Garssen (2004), Stürmer et al. (2006) and De Boer et al. (1999) are now familiar, having been identified in at least one earlier review presented in this thesis. No previously unreported discussions are relevant here.

6.5.2 Review of included literature. No articles reviewied were included.

Please see table over the page.

Table 7:: Characteristics of included studies and cancer related significant findings

Author	Emotional control measure(s) / means of administration	Outcome(s)	Sample size / cancer type(s)	Cancer related significant finding(s)
Price, Tennant, Butow, et al. (2001)	Locus of Control of Behaviour (LCB) scale	between-group difference	n=288 / Breast cancer and control	none

The study by (Price, Tennant, Smith, et al., 2001) has been discussed above in chapter 5, but, briefly a study of 2,224 older women recalled for assessment in a breast screening program did not show a relationship between emotional control and the diagnosis of breast cancer. The measure used was the Emotional Expression and Control (EEC) scale, developed from the Watson and Greer's (1983) Courtauld Emotional Control scale which is a self-report measure of expression and control of anger, anxiety, and depression. The study was well controlled, including age, surgical removal of benign breast tissue, oral contraceptive use, current use of HRT, daily alcohol consumption, and body mass index on the basis of significant group differences. Age at the onset of menopause, family history of breast carcinoma, first birth after age 29 years, and parity were included as well documented correlates.

6.6 Discussion and implications

The one study included in this review did not report any significant associations between emotional control and cancer diagnosis, despite being well controlled for possible confounders. Moreover, no studies reviewed addressed the issue of emotional control and prognosis.

Chapter 7: Structured review of personality and immunology in participants with cancer

7.1 Overview

This chapter reports on a structured review of the relationship between personality and NI factors and risk or progression of cancer, this chapter serves to:

1. Introduce the reader to the assumptions previously made, and research conducted, on personality and immunology in cancer.

2. Highlight the methodological flaws present in much of the reported research.

7.2 Background

In order to set the context for an exploratory study of the relationship between personality and NI variables, it is important to (1) establish that the research question has not already been answered, (2) review the methodologies used by others in exploring relationships between personality, immunology and cancer and (3) review the various measures of personality used.

7.3 Review Methods

7.3.1 Description of the literature being reviewed.

7.3.2 Objectives. The structured literature reviewed had two objectives, namely:

1. To review the existing literature on the relationship between personality and NI variables in subjects with a diagnosis of cancer.

2. To identify the nature and quality of the evidence available on this subject.

7.3.3 Types of studies. All study designs were included. As the review focuses upon relationships between immunology and personality, articles were included if they contained immunological data and the use of a measure of personality. Reviews in which the dependent variable was a behaviour, mood state or coping style were excluded, despite possible relationships, unless personality and immunology were also measured. The term personality is most widely used to refer to normal ranges of stable individual differences in humans. While individual differences have been identified in non humans and linked with immunity, this review will focus upon human participants.

7.3.4 Types of participants. Men and women over the age of 18 years with a diagnosis of cancer.

7.3.5 Types of outcome measures.

1. Personality measures
2. Immunological measures
3. Indicators of stability of personality
4. Indicators of stability of immunology

7.3.6 Criteria for considering reviews for inclusion. The inclusion criteria for selection were:

1. Written in English
2. Published in a peer reviewed journal
3. Being a research study
4. Involved human participants with a cancer
5. Included a measurement of personality using a standardised measure
6. Included a measurement of immunology using a standardised measure
7. Written in English

7.4 Search Methods for identification of literature

7.4.1 Data collection and analysis. All searches were up to date as of midday on the 23rd March 2012.

(1) The Cochrane Database of Systematic Reviews was searched ("personality and cancer and immunology" in Cochrane Database of Systematic Reviews) and 9 irrelevant results were identified.

(2) OVID was used to search (i) Embase (from 1974), (2) OVID MEDLINE (from 1946) and PsychINFO (from 1806). 44 results were identified. The search criteria can be found in appendix G, but in brief were:

1. personality
2. individual differences
3. 1 or 2
4. immunology
5. cancer
6. 3 and 4 and 5
7. Limit 6 to English Language

(3) PubMed was searched and 511 results were identified. The search criteria can be found in appendix H.

The results of all searches were compared and duplicates were discarded leaving 540 unique references. The results were screened and visual inspection of title and abstract (together) excluded 521 obviously irrelevant[10] papers leaving 19.

The 19 abstracts were assessed by the author against an *a priori* checklist based on definitions developed at the start of the review (criteria for considering reviews for inclusion), to identify potentially relevant studies for which full texts were obtained.

Articles were obtained and the author determined which studies met the criteria for inclusion by comparing the title and abstract (if available) with the inclusion criteria. Articles that did not meet the criteria were excluded, and reasons for exclusion were noted in Table 8 (Characteristics of excluded trials). The remaining trial is summarised in Table 9 (Characteristics of included trials) to enable an evaluation of their type and focus.

7.4.2 Data Extraction. The paper meeting the criteria for inclusion were reviewed for; methods, participants, personality measures, mono-nuclear cell distributions, cytokines, outcomes, and assessment points. Data excluded for not meeting the afore mentioned criteria, including other reviews, are presented below under description of excluded literature.

7.5 Results

One article remained for discussion.

7.5.1 Description of excluded literature.

[10] 'Obviously irrelevant' papers were those that from the reading of the title and abstract did not meet one or more of the inclusion criteria.

Table 8:: Personality and immunology: Characteristics of excluded immunology articles at full revision stage

Authors	**Reason for exclusion**	**Exclusion criteria not met**
(Zozulya et al., 2008)	review article	3
(Coe & Laudenslager, 2007)	review article	3
(Segerstrom, 2005)	review article	3
(Lutgendorf, 2003)	review article	3
(Kiecolt-Glaser et al., 2002)	review article	3
(Segerstrom, 2002)	review article	3
(Segerstrom, 2000)	review article	3
(Hosaka et al., 1999)	reliability paper	3
(Gruzelier et al., 1998)	review article	3
(Meyer et al., 1998)	not cancer participants	4
(Bryla, 1996)	review article	3
(Biondi & Kotzalidis, 1990)	review article	3
(O'Leary, 1990)	review article	3
(Andrianopoulos, 1990)	letter to editor and reply	3
(Fox et al., 1987)	no immunology	6

Table 8:: Personality and immunology: Characteristics of excluded immunology articles at full revision stage

(Wellisch & Yager, 1983)	opinion	3
(Mastrovito et al., 1979)	no immunology	6
(Scurry & Levin, 1978)	review article	3

The literature review revealed a substantial amount of narrative review papers largely focused upon immunology with some investigating the possible role of personality and are excluded from the analysis. One instrument reliability paper was identified (Hosaka et al., 1999).

In an early trial Fox et al. (1987) suggested that Type C behavior (passive, appeasing, suppressive of negative emotions, and possibly with a tendency to helplessness) was a subset of Type B behaviour and as such, those who exhibited Type C behavior would be at higher risk of developing cancer. However, Fox et al. (1987) concede that the possibility is "quite speculative" and the reported trial design and analysis is weak. Indeed conflicting arguments are made for the risk of Type A and Type B behavior on risk of cancer. This article was excluded from further critique due to the focus on behavior rather than personality, the inferred nature of Type B behavior being the absence of Type A and a plausible sub-population of Type B and the lack of immunological measures.

Meyer et al. (1998) used a modification of the Freiburg Personality Inventory (FPI) to assess nervousness, aggressiveness, depression, excitability, sociability, calmness, dominance, inhibitedness, frankness, extraversion, emotionality and self-perception in healthy volunteers. Meyer et al. (1998) acknowledge limitations in their understanding of the relationship between personality and immunology and, therefore, describe their use of statistical analysis as exploratory. Of the 69 volunteers (the gender split is not explicitly stated; of the 28 females and 41 males initially recruited, 11 participants were excluded), 31 were dominant and 15 submissive based on standard nine (stanine) scores. Statistically significant differences (using Welsch's t-test) were found between mean values of dominant and submissive participants in leukocytes, CD4, CD13 and HLA-DR. CD20, CD 14, and the soluble IL-2 α receptor chain (sIL-2R) approached a significant difference. A case comparison of extreme participants suggested that dominant individuals (number of stanine >=8) have a more active immune system than submissive participants (number of stanine <=3) with higher T helper cells (CD4) and monocytes (CD13 and CD14) in blood, and more activated immunological parameters (HLA-DR, IL-2 and sIL-2R). They claim to have demonstrated a correlation between personality traits and immunological parameters in normal subjects for the first time. It is implied that the other scales were completed, although no reference to the results are made. There is significant risk of volunteer bias in this trial and the lack of presenting gender split results is a considerable omission.

An early study by (Mastrovito et al., 1979) included 288 patients with a suspected

diagnosis or presumed diagnosis of gynecological cancer of which 180 later received a confirmed diagnosis. Specific site of cancer in decreasing order of prevalence were Cervix, Uterus, Ovary, Vagina/Vulva, trophoblastic disease, other. An adjective Checklist was used with 200 candidate items and participants were asked to mark the adjectives that he or she felt self-descriptive. The authors conclude that the results support the cancer-prone personality models. "The core of these findings is consistent with the concept that cancer patients are emotionally inhibited and in general have a diminished capacity for emotional discharge, particularly aggressive impulses and feelings." (page 284).

7.5.2 Review of included literature.

Please see table over the page.

Table 9:: Characteristics of included immunology and personality studies

	Messina et al. (2010)
Methods	Correlational
Participants	30 consecutive cancer patients, 8 forms of cancer (including 11 breast cancer patients)
Personality Measures	Rorschach: 10 cards
Mono-nuclear cell distributions	T-helper ($CD4^+$) and T-cytotoxic/suppressor ($CD8^+$) cells, Natural Killer (NK) cells ($CD16^+CD56^+$), T Lymphocytes ($CD3^+$) and Regulatory T cells ($CD4^+CD25^+$)
Cytokines	none
Outcomes	(1) Increased $CD4^+CD25^+$ in group with self punishment significantly higher than than those without self punishment (11/18 vs. 3/12 (25%) $p<0.05$). (2) The percentage of patients with abnormally low $CD4^+/CD4^+CD25^+$ ratios were significantly higher in those with self punishment (16/18 vs. 4/12 $p<0.01$). (3) Mean regulatory T cell lymphocytes in the self punishment group significantly higher than no self-punishment ($314\pm319/mm^3$ vs. $173\pm27mm^3$, $p<0.05$). (4) Mean $CD4^+/CD4^+CD25^+$ ratio in the self punishment group significantly lower than no self-punishment (2.6 ± 0.2 vs. 5.2 ± 0.8, $p<0.025$). (5) No significant difference in mean number of $CD4^+$ lymphocytes.
Time points	one

In a correlational study of 30 heterogenous cancer patients, Messina et al. (2010) found (1) $CD4^+CD25^+$ in a self-punishing group (assessed with the 10 card Rorschach test) was significantly higher than than those who did not self punish (11/18 vs. 3/12 (25%) $p<0.05$). (2) the percentage of patients with abnormally low $CD4^+/CD4CD25^+$ ratios were significantly higher in those with self punishment (16/18 vs. 4/12 $p<0.01$). (3) Mean regulatory T cell lymphocytes in the self punishment group were significantly higher than no self-punishment ($314\pm319/mm^3$ vs. $173\pm27mm^3$, $p<0.05$). (4) Mean $CD4^+/CD4^+CD25^+$ ratio in the self punishment group significantly lower than no self-punishment (2.6 ± 0.2 vs. 5.2 ± 0.8, $p<0.025$). (5) No significant difference in mean number of $CD4^+$ lymphocytes. The authors concluded that that self-punishment may suppress the production of an effective anti-cancer immune response by stimulating the activation and proliferation of regulatory T cell lymphocytes which stimulate tumor spread by suppressing anti-cancer immunity (in other words regulatory T cell lymphocyte count is correlated with self-punishment). As between group differences in other lymphocyte sub-sets (NK, CD3 and CD8) were not significant, Messina et al. (2010) suggested that regulatory T cell lymphocyte activity represents a specific immune alteration of cancer patients related to self-punishment. However, Messina et al. (2010) do not acknowledge that the direction of causality can not be determined.

Moreover, Messina et al. (2010) report that while 18 of 30 of all participants were self-punishers, interestingly nine of the 11 participants with breast cancer were self-punishers, a finding that Messina et al. (2010) do not bring to the readers attention to and that which be indicative of the the need for homogeneity of cancer type in studies. Other cancer types had small samples with the exception of lung cancer which was evenly distributed (5:4 self punishment).

Messina et al. (2010) studied a mixed cohort of cancer types and while describing type, did not report staging. Immunological and personality time points were assessed at one time point and therefore the temporal stability of the data is unknown.

7.6 Discussion and implications

The paucity of good quality research investigating the relationship between personality and NI provides clinicians with little incentive to assess personality and differentiate treatment accordingly. The existing literature does not provide evidence of whether personality makes a differnce to the chance of acquiring a cancer, an existing cancer progression, or whether a patient's immune response can be predicted by knowing his or her

personality. However, the demonstration of high self punitiveness being associated with an increased numbers of regulatory T cells is consistent with the literature on type C reviewed in Chapter 2.

It is clear that remarkably little is known about the relationship between personality and the immune system in patients with cancer, and clearly there is considerable scope for further research.

Chapter 8: Study one - the relationships between personality and neuroendocrinological-immunological variables in women with early breast cancer

Abstract: 183 women were assessed 6 weeks post-surgery for early breast cancer using the revised Eysenck Personality Questionnaire (EPQ-R), the Positive and Negative and Affect Schedule (PANAS), the Multidimensional Health Locus of Control Scale (MHLCS) and the Courtauld Emotional Control Scale (CECS). Blood samples were collected for neuroendocrinological and immunological (NI) analyses. Based on structured literature reviews hypotheses were generated regarding personality and NI relationships. Following normalisation of distributions as required, the relationship between personality variables and NI variables were computed using Pearson's Product-Moment Correlation coefficients. As Psychoneuroimmunological (PNI) relationships may be affected by age, multiple linear regression was used to establish the extent to which significant relationships remained. At least one NI measure correlated significantly with at least one personality dimension. Five immunological variables were predicted by two or more personality variables. (1) Psychoticism and Extraversion both correlated significantly with the Th1-like response CD4/IL10. When entered simultaneously with age, Psychoticism and Extraversion accounted for 7.1% of the variance, better than either trait alone. (2) Neuroticism, Positive Affect (PA) and Anger correlated significantly with the Th1-like response CD4/IFNγ, together accounting for almost 10% of the variance, again greater than any single variable alone. (3) Neuroticism, Negative Affect (NA), Internal Locus of Control (ILOC) and Chance Locus of Control (CLOC) were all significantly correlated with the Th1-like response CD8/IL2 and collectively accounted for almost 10% of the variance, greater than any one variable alone. However, only CLOC was a significant independent predictor of percentage of CD8/IL2. (4) CLOC and Powerful-other Locus of Control (PLOC) correlated with NK cell activity, but were less predictive than each individual dimension alone, and (5) Anxiety combined with Depressed mood correlated with percentage cells expressing CD2, but was less predictive than each individual dimension alone. The direction of the relationships are not always easy to reconcile with the existing literature on host defences and prognosis on the one hand, and personalty and survival on the other. This could be due to the particular characteristics of the participants, a very well adjusted group of women with early breast cancer six weeks post surgery, or it may reflect

the subtlety of how the many components of the immune system interact to produce an effective anti-cancer response.

8.1 Introduction/Overview

From the reviews presented in chapters 3-7 it is evident that there is a need to design and conduct a study to investigate at (1) a homogeneous group, (2) with a homogenous diagnosis (3) receiving homogenous treatment, (4) in a large cohort, (5) using established, valid and reliable measures of personality (6) with data missing at random, and (7) quality assurance for psychological measures and immunological and endocrinological assays, (8) ideally with multiple time point data. This chapter, and the next, report two studies that have attempted to address this need.

8.1.1 Aims. The aims of study one were (1) to examine the direction and magnitude of correlations between personality variables and NI variables, (2) to explore these relationships in more detail, taking into account age as a possible confounder, and (3) to investigate the extent to which combining personality variables which correlated significantly with the same NI variable improves prediction.

8.1.2 Hypotheses. Based on the the review of cancer-related NI responses in Chapter 1, NI response may be grouped as follows:

- A Th1-like response is charecterised by increased CD3/IL2, CD3/IFNγ, CD4/IL2, CD4/IFNγ, CD8/IL2 and CD8/IFNγ. CD3, CD4 and CD8 are T cell markers. IL2 is a cytokine produced by T cells which also targets T cells with the aim of increasing T cell proliferation and differentiation and activation of cytotoxic lymphocytes and macrophages. IFNγ is a cytokine produced by T cells and NK cells which targets leucocytes, tissue cells, and Th2 cells and has, amongst other functions, MHC induction and macrophage activation.

- A Th-2 like response is charecterised by increased CD3/IL4, CD3/IL10, CD4/IL4, CD4/IL10, CD8/IL4 and CD8/IL10. CD3, CD4 and CD8 are T cell markers. IL4 is a cytokine produced by T cells which targets B cells and T cells and enhances B-cell growth factor, amongst other functions.

(An increased Th1-like response, and a decreased Th2-like response are considered beneficial in breast cancer (Chapter 1)).

- An anti-cancer NK response is charecterised by increased percentages of CD16, CD56 and increased NK and LAK cell activity. CD16 and CD56 are NK cell markers. NK

cells mediate lysis. LAK cells (IL-2 stimulated NK cells expressing CD57) mediate tumour cell cell cytotoxicity.

- An anti-cancer hormonal response is charecterised by increased prolactin, increased growth hormone, decreased cortisol and the same direction for their respective receptors; prolactin receptor, growth hormone receptor and glucocorticoid receptor.

Using the above four groupings, and the concepts and studies reviewed in chapters 1-8, a number of relationships between personality and NI responses were hypothesised. These are:

1. Psychoticism - no hypothesis.

2. Extraversion (outgoingness, socialness and sensation seeking) will correlate positively with a Th1-like response, anti-cancer NK response and anti-cancer hormone response, and negatively with a Th2-like response. This would be consistent with the Type C literature (Kissen & Eysenck, 1962), and suggestions that greater Extraversion is associated with CD3-CD16+CD56+ counts and lower CD4+/CD8+ ratios (Bouhuys et al., 2004) and lower Extraversion associated with lower NK cell cytotoxicity (Miller et al., 1999)

3. Neuroticism (anxiety and worry) will correlate negatively with a Th1-like response, an anti-cancer NK response and anti-cancer hormone response, but positively with a Th2-like response. Again, this would be consistent with the Type C literature (Kissen & Eysenck, 1962) suggesting that increased Neuroticism is associated with increased stimulated IL-6 production in a depressed elderly population (Bouhuys et al., 2004) and increased circulation of IL-6 and C-reactive protein (Marsland et al., 2008; Terracciano, 2003).

4. The Lie scale (social conformity) Eysenck (1994) will correlate negatively with a Th1-like response and an anti-cancer NK response and anti-cancer hormone response, but positively with a Th2-like response. This would be in accordance with the reports of Ratcliffe et al. (1995) and L. G. Walker (2004) who found that high EPI L-scores are associated with much poorer survival in patients with Hodgkin's disease and non-Hodgkin's lymphoma.

5. Positive Affect (PA) will correlate positively with a Th1-like response, anti cancer NK response and anti-cancer hormone response, and negatively with Th2-like response. This would be consistent with the Type C literature (Kissen & Eysenck, 1962).

6. Negative Affect (NA) will correlate negatively with a Th1-like response, an anti-cancer NK response, anti-cancer hormone response and positively with a Th2-like response as this is considered to be conceptually similar to neuroticism.

7. Internal locus of control will correlate positively with a Th1-like response and anti-cancer NK response and an anti-cancer hormone response, and negatively with a Th2-like response. This would be consistent with the literature linking "fighting spirit" to survival in women with breast cancer (Greer et al., 1990).

8. Chance locus of control will correlate negatively with a Th1-like response, anti-cancer NK response and an anti-cancer hormone response, and positively with a Th2-like response. This would be consistent with the literature which indicates that the belief that events are uncontrollable are more stressful psychobiologically.

9. Powerful Other locus of control - no hypothesis.

10. Control over emotional reactions (anger, anxiety and depression) will be negatively correlated with a Th1-like response, an anti cancer NK response and an anti-cancer hormone response, but positively with a Th-2 like response in keeping with the the Type C literature which identifies emotional suppression as a key component (Eysenck, 1994; Bahnson, 1980).

8.2 Design/Method

8.2.1 Description of participants.

8.2.1.1 Inclusion criteria (medical criteria and care pathway assessed at MDT). In order to achieve a high level of homogeneity for the reasons indicated above, the combined inclusion/exclusion criteria for study one were:

1. Female

2. Received a recent diagnosis of histologically established early breast cancer (that is Tis, T1, T2 or T3:N0:M0)

3. Received breast surgery

4. No previous malignancy other than basal cell carcinoma.

5. No clinically significant cognitive impairment or dementia

6. NHS post-operative treatment planned

8.2.1.2 Exclusion criteria (capacity and co-enrollment assessed by a specialist oncology nurse).

1. Under 18 years of age at the time of providing written informed consent

2. Unable to provide written informed consent

3. Enrolled on either a Clinical Trial of Investigational Medicinal Products (CTIMP) or a non-CTIMP trial other than the host study (Sharp et al., 2010)

4. Unable to complete self-report questionnaires

8.2.1.3 Rationale

. *Clinical criteria.* In order to avoid the methodological weaknesses of other trials reported in chapters four to eight, a homogenous cancer site was required. As reported in chapter 1, breast cancer is the single most commonly diagnosed form of cancer in the UK, and therefore a study of breast cancer in females could be considered to be of considerable interest. As previously described (chapter 1) breast cancer can be categorised using the TMN classification system. In order to reduce variation in the sample early breast cancer was selected, operationally defined as Tis, T1, T2 or T3; M0; N0. Finally, eligible participants should have received breast surgery, in keeping with standard clinical practice.

To reduce the chance of any spurious NI findings, persons with a previous cancer (other than basal cell carcinoma) were excluded.

Research criteria. All participants provided written informed consent in keeping with Good Clinical Practice (*Research Governance Framework for Health and Social Care, 2nd edition*, 2005; *MRC Guidelines for Good Clinical Practice in Clinical Trials*, 1998). All participants were over 18 years of age were and able to provide written informed consent. As the study design involves self-report, the ability to complete self-report questionnaires was required. Co-enrollment was not supported.

8.2.1.4 Recruitment. Patients were recruited between 11 June 2002 and 15 February 2005 and identified at a weekly breast multidisciplinary team (MDT) group meeting. Participants were approached for recruitment between four to six weeks post surgery either by telephone or when they attended their first oncology outpatient clinic.

A consecutive series of 243 subjects were assessed for eligibility and of these 242 were eligible. 51 participants declined to take part and 183 were enrolled into the study. The reasons for non enrollment can be found in Figure 3, a CONSORT (Schulz et al., 2010) style statement for study one (the CONSORT statement is intended for the use of parallel group randomised controlled trials, but the model is reproduced below as best practice).

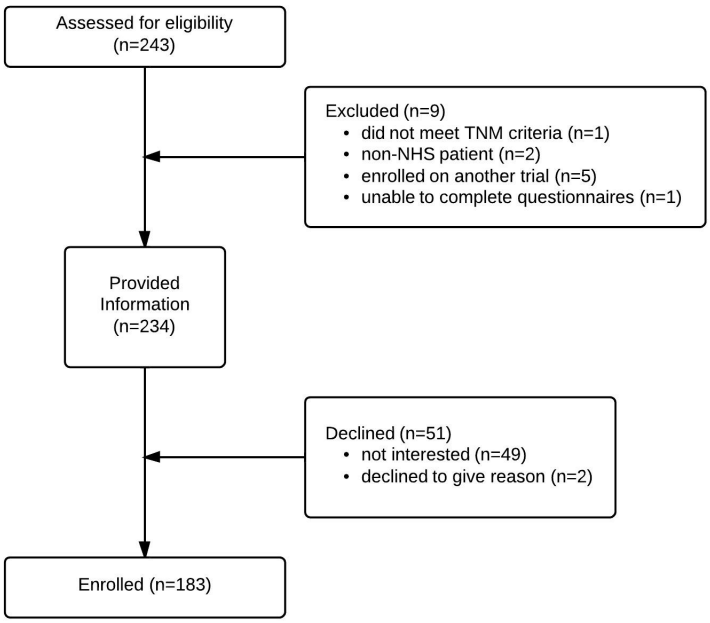

Figure 3. CONSORT diagram of enrollment into study one

Table 10:: Demographic and clinical profile of included partcipants: study one

		Total (n=183)
Age		
	mean age (years)	58.78
	SD	10.31
	range	32-81
Ethnicity		
	Caucasian	183
ER status		
	Positive	164
	Negative	18
	Unknown	1
PR status		
	Positive	150
	Negative	30
	Unknown	3
T stage		

Table 10:: Demographic and clinical profile of included partcipants: study one

	Tis	3
	T1	124
	T2	52
	T3	4
Breast surgery		
	Wide local excision	144
	Quadrantectomy	1
	Mastectomy	26
	Mastectomy + reconstruction	12
Radiotherapy planned		
	Yes	149
	No	34
Chemotherapy planned		
	Yes	30
	No	153

8.2.2.5 Demographic and clinical profile of included participants.

8.3 Materials

8.3.1 Choice of psychological measurements

. **Psychoticism, Extraversion and Neuroticism**

As presented in Chapters 2 and 3, many of the studies discussed above have focussed on the personality traits of Extraversion and Neuroticism due to the long-standing interest in the Type C personality. Although, more recently, Costa and McCrae have included Extraversion and Neuroticism in the NEO-PI (P. T. Costa & McCrae, 1992) as two of five dimensions (Openness, Conscientiousness, Extraversion, Agreeableness and Neuroticism: OCEAN), as discussed in chapter two, the first personality trait theorist to develop a measure of extraversion and introversion was Eysenck. Eysenck and Eysenck (1991) published a set of Personality scales including the revised Eysenck Personality Questionnaire (EPQ-R). The genesis of the EPQ-R was the Maudsley Medical Questionnaire (MMQ), a measure of Neuroticism. The Maudsley Personality Inventory (MPI) replaced MMQ in

1952 extending the range of measurement to include Extraversion-Introversion. In 1964 the Eysenck Personality Inventory (EPI) added the Lie scale as a measure of dissimulation and included improvements in language, reliability, and independence of scales. In 1975 the EPI was replaced by the Eysenck Personality Questionnaire (EPQ) and included a scale to measure Psychoticism and was updated in 1991 with an improved measure of Psychoticism.

Of Eysenck's three personality scales, the P scale has been particularly challenged, and Eysenck himself has acknowledged that the P scale has shortcomings (Eysenck & Eysenck, 1991). The original P scale as featured in the EPQ (Eysenck & Eysenck, 1975) included 25 items and Eysenck claimed reliability of 0.74 for males and 0.68 for females. The revised P scale in the EPQ-R claims reliability of 0.77 for males and 0.81 for females (although this may be 0.78 and 0.76 respectively as the text and table are inconsistent (Eysenck & Eysenck, 1991)). Eysenck explains this relatively low reliability as due to the P scale including more facets than the other scales (including hostility, cruelty, lack of empathy *etc.*) but Eysenck concludes the reliabilities are 'acceptable' (Eysenck & Eysenck, 1991, 19). Low range of scoring on the original EPQ P scale (means of 3.78 +-3.09 males 2.63 +- 2.36 females) and the revised EPQ-R P scale (means of 7.18 +-4.60 males and 5.73 +- 3.85 females) has also been discussed (Eysenck & Eysenck, 1991) as a weakness of the P scale. Finally the P scale is both positively skewed and leptokurtic. The non-normal distribution is explained by Eysenck as reflecting the non-normally distributed facets it measures, which "inevitably, by its very nature, constitute some departure from normality" (Eysenck & Eysenck, 1991, 19).

The EPQ-R manual (Eysenck & Eysenck, 1991) contains age norms and standard deviations, reliability (P= 0.76, E=0.85, N=0.85 and L=0.79in females), test-retest reliability (P=0.81, E=0.89, N=0.81, L=0.80) and inter-correlation scores for the four scales. A relatively recent statistical bootstrapping approach has suggested the the EPQ-R does not suffer from gender differences in reliability (Miles et al., 1999).

Affect

As presented in Chapter 4, two general factors, typically labeled Positive Affect (PA) and Negative Affect (NA), have consistently been proposed as the dominant dimensions of emotional experience. D. Watson et al. (1988) developed the Positive and Negative Affect Schedule (PANAS) to measure affect in two 10-item scales for PA and NA respectively. Crawford & Henry (2004) published a comprehensive analysis of the measure and based

on a UK study of over 1,000 participants concluded that the PANAS has good reliability (Cronbach's α was .89 for PA and .85 for NA) and good construct validity.

Locus of Control

The Multidimensional Health Locus of Control (MHLC) was designed by Wallston et al. (1978) to measure the construct of Locus of Control (LOC). The MHLC contains three sub-scales: Internal, Powerful others and Chance. Each sub-scale measures an individual's tendency to believe that health outcomes are due mainly to his/her own behavior, powerful others (such as medical professionals or family) or to chance. The former can be classified as internal belief, and the latter external belief. Wallston (2005) has more recently suggested that there; "is ample evidence in the literature that the MHLC scales validly assess health locus of control beliefs" (page 623). Moreover, recent validity data (for Form A) has been published in version translated into Japanese Kuwahara et al. (2004). Form A will be used.

Emotional control

Anti-emotionality has been linked with immune change (Bleiker et al., 1996; van der Ploeg et al., 1989). The Courtauld Emotional Control Scale (CECS) was developed by M. Watson & Greer (1983) as a measure of emotional control, specifically the extent to which individuals self report controlling anger, anxiety and depressed mood. Based upon a sample of hospital employees, Watson and Greer report reliability of anger ($r=0.86$, $p<0.001$), (anxiety $r=0.84$, $p<0.01$), depressed mood ($r=0.89$, $p<0.001$) and total score ($r=0.95$, $p<0.001$) (M. Watson & Greer, 1983). In terms of validity, Watson and Greer report a number of comparison with other measures including the finding that, in patients awaiting heart surgery, the Bortner Type A behaviour scale and all sub-scale of the CECS correlated inversely (Anger $r=-0.34$, $p<0.05$, Anxiety $r=-0.42$, $p<0.01$, Depressed Mood $r=-0.57$, $p<0.001$, Total score $r=-0.052$, $p<0.01$). This was interpreted as supporting the hypothesis that those scoring lower on emotional control score higher on Type A behaviour.

8.3.2 Summary of measures of personality selected for use. The variables of personality measured and analysed in study one are presented with the abbreviations used hereafter in Table 11.

Table 11:: Summary of measures of personality, scales and abbreviations

Measure	Scale	Abbreviation
Eysenck Personality Questionnaire-Revised		EPQ-R

Table 11:: Summary of measures of personality, scales and abbreviations

	Psychoticism	P
	Extraversion	E
	Neuroticism	N
	Lie	L
Positive and Negative Affect Scale		PANAS
	Positive Affect	PA
	Negative Affect	NA
Multi Health Locus of Control Scale		MHLC
	Internal	I
	Chance	C
	Powerful other	P
Courtauld Emotional Control Scale		CECS
	Anger	Ag
	Depressed mood	D
	Anxiety	Ax
	Total	Total

8.3.3 Choice of NI measurements

. **Choice of variables**

The immunological measures were chosen because of their relevance to breast cancer (see summary above in chapter 1 sections 1.7 and 1.8). Therefore, to characterise the Th1-like response IL2 and IFNγ were chosen. IL1 and IL10 were selected to characterise the Th2-like response. Functional activity was assessed using NK cell activity and LAK cell activity. Widely used cluster of differentiation (CD) profiles were also determined as indicators of the following; CD2 (total T cells), CD3 (activated T cells), CD4 (T helper cells), CD8 (T suppressor cells), CD14 (Monocytes), CD16 (a subset of NK cells), CD19 (a marker for B cells), CD25 (Activated lymphocytes/regulatory T cells), CD 56 (a subset of NK).

The NI variables obtained and analysed in study one are presented in their NI grouping and with the abbreviations used hereafter in Table 12. The relationship of the CD markers and cytokines to the immunology presented in chapter 1 can be found in Appendices I and J.

Table 12:: Summary of measures of NI response and abbreviations

Grouping	**Variable (units)**	**Abbreviation**
Th1-like response		
	CD3 cells expressing IL2 (mean %)	CD3/IL2
	CD3 cells expressing IFNγ (mean %)	CD3/IFNγ
	CD4 cells expressing IL2 (mean %)	CD4/IL2
	CD4 cells expressing IFNγ (mean %)	CD4/IFNγ
	CD8 cells expressing IL2 (mean %)	CD8/IL2
	CD8 cells expressing IFNγ (mean %)	CD8/IFNγ
Th2-like response		
	CD3 cells expressing IL4 (mean %)	CD3/IL4
	CD3 cells expressing IL10 (mean %)	CD3/IL10
	CD4 cells expressing IL4 (mean %)	CD4/IL4

Table 12:: Summary of measures of NI response and abbreviations

	CD4 cells expressing IL10 (mean %)	CD4/IL10
	CD8 cells expressing IL4 (mean %)	CD8/IL4
	CD8 cells expressing IL10 (mean %)	CD8/IL10
Killer cell structure and function		
	K562 cell death induced by NK at 5:1 (mean %)	NK
	Daudi cell death induced by LAK at 5:1 (mean %)	LAK
	Cells expressing CD16 (mean %)	CD16
	Cells expressing CD56 (mean %)	CD56
T cell phenotypes		
	Cells expressing CD2 (mean %)	CD2
	Cells expressing CD3 (mean %)	CD3
	Cells expressing CD4 (mean %)	CD4
	Cells expressing CD8 (mean %)	CD8
	Cells expressing CD25 (mean %)	CD25
Neurohormones		
	Cortisol concentration (ng/ml)	Cortisol
	Expression of Glucocorticoid receptor (mean %)	Gluc-R
	Prolactin concentration (ng/ml)	Prolactin
	Expression of prolactin receptor (mean %)	PRL-R
	Growth hormone concentration (μIU/ml)	Growth hormone
	Expression of growth hormone receptor (mean %)	GH-R
Others		

Table 12:: Summary of measures of NI response and abbreviations

	Cells expressing CD14 (mean %)	CD14
	Cells expressing CD19 (mean %)	CD19

8.4 Procedure

Study one is a single measurement point, single group, correlative design using correlation and stepwise logistical regression.

8.4.1 Personality assessment. Personality measures were completed within the Oncology Health Centres, Hull and East Yorkshire NHS Trust. The measures were arranged in a predefined order and attached to a clipboard, explained and administered by by trained specialist oncologist nurses. Measures were self-completed in a quiet room, without distraction from either family or health professionals.

Following the collection of immunological measures, all psychological self-report measures were checked for completeness by a specialist oncology nurse and where omissions noted, passed back to the participant for completion.

8.4.2 Collection of immunological samples. Following completion of the self-report measures, immunological samples were collected in the same room. Samples of blood and saliva were collected from participants by specialist oncology research nurses in the Oncology Health Centres. Samples were delivered to the Centre for Biomedical Research at the University of Hull for analysis.

8.4.3 Identifying NI variables. This information below summarises the collection of NI variables. Detailed information on the specialised analysis of the samples is presented in full in Green et al. (2010) which the present author co-authored.

8.4.3.1 Biological assays: Peripheral blood mononuclear cell (PBMC) isolation and serum separation

50ml of venous blood was collected in syringes containing 1,250 IU heparin for PBMC analysis and 8ml of venous blood for serum separation was transported to the Centre for Biomedical Research at the University of Hull.

8.4.3.2 Immunotyping of peripheral blood mononuclear cells

Prepared (see Green et al., 2010) PBMCs were labelled with 5 µl (0.1 mg/ml) of one of a panel of fluorescein isothiocyanate (FITC)-conjugated monoclonal antibodies specific

for the surface markers: CD2 and CD3 (T cells), CD4 (T helper cells), CD8 (T cytotoxic cells), CD16 and CD56 (NK cells), CD14 (monocytes), CD19 (B cells) and CD25 (activated lymphocytes/regulatory T cells).

8.4.3.3 Th1/Th2 cellular determination

PBMCs were prepared (see Green et al., 2010) and incubated with 5 µl (0.1 mg/ml) of FITC labelled monoclonal antibody specific for the surface markers CD3 or CD8. After incubation, the cells were washed and permeabilised with leucoperm B before being incubated with 5 µl r-phycoerythrin (rpe)-labelled anti-cytokine antibody [IL2, IFNγ, IL4, IL10 0.1 mg/ml]. Stimulated lymphocytes produced Th1 (IL2/IFNγ) and Th2 (IL4/IL10) cytokines. CD3 was used as a total lymphocyte marker. The CD4 element was determined by subtraction of the percentage of CD8+ cells.

8.4.3.4 NK and LAK cell cytotoxicity

Cytotoxic activity of both NK and LAK cells within the PBMC population was determined using log-phase growing target cells [erythroleukaemic cell line (K562) for NK and Burkitt lymphoma cell line (daudi) for LAK pre-labelled with a green fluorescent membrane dye (diOc18(3), 30 µM) and incubated in complete RPMI medium with or without recombinant IL2 (500 U/ml; Abd Serotec) to stimulate LAK formation and for NK determination respectively. Following washing, viable effector cells were enumerated using trypan blue exclusion, and $1.5x10^5$ cells were added to $3x10^4$ target cells to give a 5:1 ratio in a total volume of 140 µl.

8.4.3.5 Hormone receptor measurements

Following activation of PBMCs (described above), cells to be used for the detection of the prolactin receptor (PRL-R) and the glucocorticoid receptor (GLUC-R) were permeabilised. PBMCs were then incubated (see Green et al., 2010) to determine: Growth Hormone receptor (GH-R) unconjugated, Glucose receptor (GLUC-R-FITC) conjugated and prolactin receptor (PRL-R Ab1 (B6.2)prL-r Ab-1 (B6.2)) unconjugated.

8.4.4 Data quality and entry. All data were anonymised. Data was entered from the paper-based Case Report Form (CRF) and self-report measurements of personality by the author and into the Statistical Package for the Social Sciences (SPSS) version 13. A volunteer from the University of Hull between the first and second year of her undergraduate psychology course visually verified all entries and raised any data queries with the author. NI data was entered into SPSS by colleagues at the Centre for Biomedical Research at the University of Hull also using SPSS version 13. The datasets were combined for the

purpose of this PhD by Dr Eric Gardner, Statistician Clinical Psychology department, at the University of Hull.

8.4.5 Data preparation and exploring assumptions of normal distribution. The measures of personality and immunology were explored to test assumptions of normal distribution. SPSS descriptive statistics were run (histograms, stem and leaf plots, Kolmogorov-Smirnov test, Shapiro-Wilk test, Q-Q plot and box plot). Data were visually inspected independently by the present writer and his supervisor. All data were normalised as required using log transformations ($log(X_i)$), square root transformations ($\sqrt{X_i}$) and reverse score transformations ($1/X_i$). It was agreed that several scales had a significant positive skew and should be 'reflected' by subtracting the highest score from the observed score on each variable, thus producing negative skew, prior to log transformation (which always produced the best normalisation compared with the other options) and then re-mirroring the data (by subtracting the maximum log-score from each transformed log score per variable, and in doing so restoring the original direction of variables and the minimised positive skew). Details of the transformations can be found in Appendices K and L for psychological and NI data respectively.

All transformations, and subsequent analyses, were completed using version controlled SPSS syntax files.

8.5 Statistical Methodology

8.5.1 Analysis one. In order to to examine the direction and magnitude of correlations between each of the personality and NI variable, Pearson's product–moment correlations were computed and correlations significant at $p \leq 0.05$ (two-tailed) were identified (Table 13 and Appendix M).

8.5.2 Analysis two. Each of the significant correlations identified in analysis one were analysed further using multiple linear regression to explore these relationships in more detail, taking into account age as a possible confounder. In accordance with the recommendations of (Kinnear & Gray, 2010), the stepwise method of multiple linear regression was used.

All regressions were evaluated to ensure underlying assumptions of multiple linear regression were met (see Field, 2009). The text proceeding each Table identifies any significant problems with collinearity (*i.e.* tolerance which is the correlation between the predictor variables and/or variance inflation factor (VIF) - the reciprocal of tolerance).

The text also documents variance explained by the model (R^2) and the significance of the improvement upon intercept-only prediction of the dependent variable (F ratio).

Tables were constructed from the SPSS 18 output and show;

1. B: the slope of the regression line,

2. SE B: the Standard Error of B,

3. β: the Beta coefficient(s). This is a standardised B coefficient(s) and gives a measure of the contribution of each variable to the model, and

4. p: an indication of the significance of each predictor variable.

Each table also contains the constant, which is the value on the y axis where it is intercepted by the regression line.

8.5.3 Analysis three. To investigate the extent to which combining personality variables which correlated significantly with the same immunological variable improves prediction, where more than one personality variable was identified for a particular dependent variable, all of these personality variables were analysed together with age in a multiple linear regression. Where possible, the stepwise method was used as in step 1. However, because the ratio of subjects to independent variables for stepwise regression should be at least 40:1 (Tabachnick & Fidell, 1996), simultaneous entry of variables was used where this criterion could not be met. Biological data at baseline were available for between 69-181 participants which meant that between 1 and 4 independent variables could be used for stepwise regression. When the stepwise method could not be used due to a failure to meet the ratio criterion, simultaneous entry of variables was used. For this latter method, the ratio of subjects to independent variable should be no less than 50+8k where k equals the number of independent variables, or 104 + k if the significance of individual variables is of interest (Tabachnick & Fidell, 1996).

Regressions were evaluated and tabulated as in analysis two.

8.5.4 Power. As noted in the prefix, this thesis in set in the context of a Randomised Controlled Trial (RCT). The RCT protocol (unpublished) stated "Power calculations have been carried out using nQuery. We consider that a 10% difference in the primary outcome measure (FACT-B) would be clinically meaningful. With 60 patients in each group, there will be 95% power to detect a 10% difference in scores (a difference between means of 120 and 132, assuming a common standard deviation of 18)." Therefore, the sample size for this study was limited by the RCT.

8.6 Results

8.6.1 Analysis 1. Table 13 summarises all the significant Pearson's product-moment correlation coefficients ($p \leq$ to 0.05 (two-tailed)) for each of the personality and NI variables. The complete correlation matrix is included as Appendix M and shows the number of patients included for each correlation.

Table 13:: Summary of significant correlations

Measure and scale	**NI**	$\mathbf{r_{xy}}$
EPQ-R Psychoticism		
	CD3/IL10	.227*
	CD4/IL10	.221*
EPQ-R Extraversion		
	CD4/IL10	.185*
EPQ-R Neuroticism		
	CD4/IFNγ	.218*
	CD8/IL2	.212*
	CD4/IL4	-.239*
	CD8/IL4	.210*
EPQ-R Lie		
	CD14	.189*
PANAS Positivity		
	CD3/IL2	-.180*
	CD4/IL2	-.183*
	CD4/IFNγ	-.200*
PANAS Negativity		
	CD8/IL2	.216*
	CD4	-.193*
MHLC Internal		
	CD8/IL2	-.190*
MHLC Chance		
	CD8/IL2	-.203*
	NK	-.200*

Table 13:: Summary of significant correlations

MHLC Powerful other		
	NK	-.448**
CECS Anger		
	CD4/IFNγ	.186*
CECS Depressed Mood		
	CD2	.192*
	prolactin	-.155*
CECS Anxiety		
	CD2	.228**
CECS Total		
	CD2	.206*

8.6.2 Analysis two. All of the correlations shown in table 13 were analysed further using the stepwise multiple regression procedure described above.

EPQ- R P and CD3/IL10 EPQ-R P correlated .227 (p=.007) and Age (p=-.141, ns) with CD3/IL10. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,114}$ =6.191, p =.014) and gave an adjusted R^2 of .043. EPQ-R P was a small significant independent predictor of CD3/IL10.

Table 14:: Stepwise regression of EPQ-R P and CD3/IL10

	B	**SE B**	**β**	**p**
Constant	.185	.046		<.0005
EPQ-R P	.025	.010	.227	.014*

EPQ-R P and CD4/IL10 EPQ-R P correlated .221 (p=.009) and Age -.179 (p=.027) with percentage of CD4/IL10. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,111}$= 5.692, p =.019) and gave an adjusted R^2 of .040. EPQ-R P was a significant independent predictor of CD4/IL10 .

Table 15:: Stepwise regression of EPQ-R P and CD4/IL10

	B	SE B	β	p
Constant	.140	.047		.004
EPQ-R P	.025	.010	.221	.019*

EPQ-R E and CD4/IL10 EPQ-R E correlated -.185 (p=.025) and Age -.179 (p=.027) with percentage of CD4/IL10. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,111}$= 3.936, p =.050) and gave an adjusted R^2 of .026. EPQ-R E was a significant independent predictor of CD4/IL10.

Table 16:: Stepwise regression of EPQ-R E and CD4/IL10

	B	SE B	β	p
Constant	.146	.051		.005
EPQ-R E	.200	.101	.185	.050*

EPQ-R N and CD4/IFNγ EPQ-R N correlated .218 (p=.010) and Age -.116 (p=.105, ns) with CD4/IFNγ. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,113}$= 5.622, p =.019) and gave an adjusted R^2 of .039. EPQ-R N was a significant independent predictor of CD4/IFNγ.

Table 17:: Stepwise regression of EPQ-R N and CD4/IFNy

	B	SE B	β	p
Constant	.0944	.045		<.0005
EPQ-R N	.008	.003	.218	.019*

EPQ-R N and CD8/IL2 EPQ-R N correlated .212 (p=.011) and Age -.014 (p=.442, ns) with CD8/IL2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,113}$ = 5.320, p =.023) and gave an adjusted R^2 of .037. EPQ-R N was a significant independent predictor of CD8/IL2.

Table 18:: Stepwise regression of EPQ-R N and CD8/IL2

Table 18:: Stepwise regression of EPQ-R N and CD8/IL2

	B	SE	β	p
Constant	.360	.052		<.0005
EPQ-R N	.009	.004	.212	.023*

EPQ-R N and CD4/IL4 EPQ-R N correlated -.239 (p=.005) and Age -.074 (p=.214, ns) with CD4/IL4. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,112}$= 6.785, p =.010) and gave an adjusted R^2 of .049. EPQ-R N was a significant independent predictor of CD4/IL4.

Table 19:: Stepwise regression of EPQ-R N and CD4/IL4

	B	SE B	β	p
Constant	.588	.078		<.0005
EPQ-R N	-.014	.006	-.239	.010*

EPQ-R N and CD8/IL4 EPQ-R N correlated .210 (p=.012) and Age -.155 (p=.047) with percentage of CD8/IL4. Stepwise regression produced a model excluding age which was statistically significant ($F_{1,113}$ = 5.211, p =.024) and gave an adjusted R^2 of .036. EPQ-R N was a significant independent predictor of CD8/IL4.

Table 20:: Stepwise regression of EPQ-R N and CD8/IL4

	B	SE B	β	p
Constant	.178	.063		.006
EPQ-R N	.010	.005	.210	.024*

EPQ-R L and CD14 EPQ-R L correlated .189 (p=.015) and Age .053 (p=.270, ns) with CD14. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,130}$= 4.790, p =.030) and gave an adjusted $R^2$of .028. EPQ-R L was a significant independent predictor of CD14.

Table 21:: Stepwise regression of EPQ-R L and CD14

Table 21:: Stepwise regression of EPQ-R L and CD14

	B	SE B	β	p
Constant	.666	.086		<.0005
EPQ-R L	.015	.007	.189	.030*

PANAS P and CD3/IL2 PANAS P correlated -.180 (p=.025) and Age .084 (p=.180, ns) with CD3/IL2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,117}$ =3.929, p =.050) and gave an adjusted R^2 of .024 (Table *). PANAS P was a small significant independent predictor of CD3/IL2.

Table 22:: Stepwise regression of PANAS P and CD3/IL2

	B	SE B	β	p
Constant	25.099	1.812		<.0005
PANAS P	-.8.929	4.503	-.180	.050*

PANAS P and CD4/IL2 PANAS P correlated -.183 (p=.023) and Age .100 (p=.142, ns) with CD4/IL2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,116}$ =4.038, p =.047) and gave an adjusted R^2 of .025. PANAS P was a small significant independent predictor of CD4/IL2.

Table 23:: Stepwise regression of PANAS P and CD4/IL2

	B	SE B	β	p
Constant	22.759	1.673		<.0005
PANAS P	-8.356	4.158	-.183	.047*

PANAS P and CD4/IFNγ PANAS P correlated .-200 (p=.015) and Age -.116 (p=.105, ns) with CD4/IFNγ. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,116}$ = 4.841, p =.030) and gave an adjusted R^2 of .032. PANAS P was a significant independent predictor of CD4/IFNγ.

Table 24:: Stepwise regression of PANAS P and CD4/IFNy

Table 24:: Stepwise regression of PANAS P and CD4/IFNy

	B	**SE B**	β	**p**
Constant	1.104	.033		<.0005
PANAS P	-.179	.081	-.200	.030*

PANAS N CD8/IL2 PANAS N correlated .216 (p=.009) and Age -.014 (p=.442, ns) with CD8/IL2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,116}$ = 5.685, p =.019) and gave an adjusted R^2 of .038. PANAS N was a significant independent predictor of CD8/IL2.

Table 25:: Stepwise regression of PANAS N and CD8/IL2

	B	**SE B**	**β**	**p**
Constant	.091	.161		.574
PANAS N	.306	.129	.216	.019*

PANAS N and CD4 PANAS N correlated -.193 (p=.012) and Age (p=-.139, ns) with CD4. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,133}$ = 5.152, p =.025) and gave an adjusted R^2 of .030. PANAS N was a small significant independent predictor of CD4.

Table 26:: Stepwise regression of PANAS N and CD4

	B	**SE B**	**β**	**p**
Constant	.375	.062		<.0005
PANAS N	-.113	.050	-.193	.025*

MHLC I *and CD8/IL2* MHLC I correlated -.190 (p=.020) and Age -.014 (p=.442, ns) with CD8/IL2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,116}$ = 4.326, p =.040) and gave an adjusted R^2 of .028. MHLC I was a significant independent predictor of CD8/IL2.

Table 27:: Stepwise regression of MHLCS I and CD8/IL2

	B	**SE B**	**β**	**p**
Constant	.703	.113		<.0005
MHLC I	-.009	.004	-.190	.040*

MHLC C and CD8/IL2 MHLC Chance correlated -.203 (p=.014) and Age -.014 (p=.442, ns) with CD8/IL2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,116} = 4.970$, p =.028) and gave an adjusted R^2 of .033. MHLC C was a significant independent predictor of CD8/IL2.

Table 28:: Stepwise regression of MHLCS C and CD8/IL2

	B	**SE B**	**β**	**p**
Constant	.614	.067		<.0005
MHLC C	-.007	.003	-.203	.028*

MHLC C and NK MHLC C correlated -.200 (p=.024) and Age correlated -.150 (p=.070, ns) with NK. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,97} = 4.046$, p < .047) and gave an adjusted R^2 of .030. MHLC C is a small, but significant, independent predictor of NK.

Table 29:: Stepwise regression of MHLCS C and NKCA

	B	**SE B**	**β**	**p**
Constant	1.018	.154		<.0005
MHLC C	-.0.15	.007	-2.00	.047*

MHLC P and NK MHLCS P correlated -.448 (p<.0005) and Age correlated -.150 (p=.070, ns) with NK. Stepwise regression produced a model which excluded Age and which was statistically significant ($F_{1,97} = 24.366$, p < .0005) and gave an adjusted R^2 of .193. MHLC Pis a highly significant independent predictor of NK.

Table 30:: Stepwise regression of MHLCS P and NKCA

	B	**SE B**	**β**	**p**
Constant	1.313	.127		<.0005
MHLCS P	-.030	.006	-.448	<.0005*

CECS Ag and CD4/IFNγ CECS A correlated .186 (p=.022) and Age -.116 (p=.105 ns) with CD4/IFNγ. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,115}$ = 4.136, p =.044) and gave an adjusted R^2 of .026. CECS A was a significant independent predictor of CD4/IFNγ.

Table 31:: Stepwise regression of CECS A and CD4/IFNy

	B	**SE B**	**β**	**p**
Constant	.917	.065		<.0005
CECS A	.007	.004	.186	.044*

CECS D and CD2 CECS D correlated .192 (p=.013) and Age correlated -.040 (p=.320, ns) with CD2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,132}$ =5.056, p =.026) and gave an adjusted R^2 of .030. CECS D is a small, but significant, independent predictor of CD2.

Table 32:: Stepwise regression of CECS D and CD2

	B	**SE B**	**β**	**p**
Constant	66.503	4.624		<.0005
CECS D	.563	.250	.192	.026*

CECS D and Prolactin CECS D correlated -.155 (p=.019) and Age -.117 (p=.059, ns) with prolactin. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,178}$= 4.406, p =.037) and gave an adjusted R^2 of .019. CECS D was a significant independent predictor of prolactin.

Table 33:: Stepwise regression of CECS PRL-R

	B	**SE B**	**β**	**p**
Constant	.968	.088		<.0005
CECS D	-.010	.005	-.155	.037*

CECS Ax and *CD2* CECS Ax correlated .228 (p=.004) and Age correlated -.040 (p=.320, ns) with CD2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,132}$ =7.254, p =.008) and gave an adjusted R^2 of .045. CECS Ax is a small,

but significant, independent predictor of CD2.

Table 34:: Stepwise regression of CECS Ax and CD2

	B	SE B	β	p
Constant	64.857	4.494		<0.0005
CECS Ax	.664	.246	.228	.008*

CECS Total and CD2 CECS T correlated .206 (p=.009) and Age correlated -.040 (p=.320, ns) with CD2. Stepwise regression produced a model excluding Age which was statistically significant ($F_{1,132}$ =5.833, p =.017) and gave an adjusted R^2 of .035. CECS T is a small, but significant, independent predictor of CD2.

Table 35:: Stepwise regression of CECS Total and CD2

	B	SE B	β	p
Constant	66.082	4.894		<.0005
CECS T	.219	.091	.206	.017*

8.6.3 Analysis three. Analysis two identified five immunological variables, each of which was predicted by two or more personality variables. The details of these five regressions are shown below.

Predictors of CD4/IL10 EPQ-R P and EPQ-R E were entered simultaneously into a regression. The model was statistically significant ($F_{3,109}$ = 3.850, p=.012) and gave an adjusted R^2 of .071. Only EPQ-R P was a significant independent predictor of percentage of CD4/IL-10.

Table 36:: Simultaneous regression of EPQ-R P, EPQ-R E and CD4/IL10

	B	SE B	β	p
Constant	.350	.167		.038
Age	-.004	.003	-.160	.085
EPQ-R P	.022	.010	.198	.034*
EPQ-R E	.137	.101	.126	.179

Predictors of CD4/IFNγ EPQ-R N, PANAS P and CECS A were entered simultaneously into a regression. The model was statistically significant ($F_{4,110} = 3.056$, p=.020) and gave an adjusted R^2 of .067 (Table 37). None of the variables was a significant independent predictor of percentage of CD4/IFNγ.

Table 37:: Simultaneous regression of CECS Ag, PANAS P, EPQ-R N and CD4/IFNy

	B	SE B	β	p
Constant	1.076	1.35		.000
Age	-.003	.002	-.140	.132
EPQ-R N	.005	.003	.148	.122
PANAS P	-.117	.088	-.131	.184
CECS Ag	.005	.004	.135	.164

Predictors of CD8/IL2 EPQ-R N, PANAS N, MHLCS I and MHLCS C were entered simultaneously into a regression. The model was statistically significant ($F_{5,109} = 3.433$, p=.006) and gave an adjusted R^2 of .096. Only MHLC C was a significant independent predictor of percentage of CD8/IL2.

Table 38:: Simultaneous regression of MHLCS I, MHLCS C, PANAS N, EPQ-R N and CD8/IL2

	B	SE	β	p
Constant	.434	.268		.108
Age	.001	.002	.051	.578
EPQ-R N	.007	.005	.174	.134
PANAS N	.169	.165	.119	.308
MHLC I	-.006	.004	-.122	.186
MHLC C	-.009	.003	-.251	.008*

Predictors of NK MHLC C and MHLC P were entered simultaneously into a regression. The model was statistically significant ($F_{3,95} = 8.020$, $p < .0005$) and gave an adjusted R^2 of .177. MHLC P was a highly significant independent predictor of NK.

Table 39:: Simultaneous regression of MHLCS C, MHLCS P and NKCA

	B	SE B	β	p
Constant	1.253	.271		<.0005
Age	.001	.004	.012	.903
MHLC C	.003	.008	.042	.698
MHLC P	-.031	.008	-.474	<.0005*

Predictors of CD2 CECS Ax, CECS D and CECS T were entered simultaneously into a multiple linear regression, along with age. Diagnostic tests revealed that collinearity was a problem (VIF>10; Tolerance<0.1). CECS Total was therefore omitted and the analysis was carried out again. This produced a model which was statistically significant ($F_{3,130}$=2.762, p=.045) and gave an adjusted R^2 of .038. CECS D was an independent predictors of CD2.

Table 40:: Simultaneous regression of CECS Ax, CECS D and CD2

	B	SE B	β	p
Constant	59.772	13.526		<.0005
Age	-.003	.191	-.002	.988
CECS Ax	-.192	.583	-.061	.744
CECS D	1.058	.521	.374	.049*

8.7 Discussion

A diagnostically homogenous group of women, all of whom had received surgery six weeks earlier and were not receiving adjuvant treatment or taking any immunosuppressive drugs such as systemic corticosteroids, were investigated using a cross-sectional design.

The first aim of study one was to examine the direction and magnitude of correlations between each of the personality variables and each of the NI variables.

1. As Psychoticism has not been investigated in cancer in any of the literature discussed above, and in the absence of known immunological correlates in breast cancer, no *a priori* hypotheses were made.

However, Psychoticism correlated positively with CD3/IL10 (r_{xy}=.227, p=.007) and

CD4/IL10 (r_{xy}=.221, p=.009), two of the possible six Th-2 like responses. This suggests that higher levels of Psychoticism are associated with a Th2-like response as charecterised by CD3/IL10 and CD4/IL10, but not by cells expressing IL4. To the best of our knowledge, this is the first time that this has been documented in breast cancer. No evidence of an effect on Th1-like response (0/6 correlates), NK killer cells and function (0/4 correlates), or neurohormones (0/6 correlates) were found.

2. It was hypothesised that Extraversion would correlate positively with a Th1-like response, anti-cancer NK response, and anti-cancer NK response, and negatively with a Th2-like response.

Extraversion correlated positively with CD4/IL10 (r_{xy}=.185, p=.025). This suggests that higher levels of extraversion are associated with a Th2-like response, one of the possible six Th2-like responses. To the best of our knowledge, this is the first time that this has been documented. Nakaya et al. (2010) reported that extraversion was positively correlated with risk of lung cancer, although this finding was not maintained in breast cancer or cancers combined. Moreover, it dealt with risk rather than prognosis.

No evidence of a Th1-like response (0/6 correlates), anti-cancer NK response (0/4 correlates) or anti-cancer hormonal response (0/6 correlates) were found in support of the hypotheses.

The results are also consistent with Bouhuys et al. (2004) who found Extraversion was not related to total CD3+ or CD8+ counts, and are at variance with Miller et al. (1999) who found lower Extraversion was associated with reduced NK cell cytotoxicity in a relatively large sample of healthy young to middle-aged adults. The different clinical and sociodemographic characteristics may go some way to explaining the divergent findings.

3. It was hypothesised that Neuroticism would correlate negatively with a Th1-like response, anti-cancer NK response and anti-cancer hormonal response, but positively with a Th2-like response.

Four NI variables correlated significantly with Neuroticism. CD4/IFNγ and CD8/IL2 correlated positively (r_{xy}=.218, p=.010 and r_{xy}=.212, p=.011 respectively) suggesting a Th1-like response opposite to the predicted direction (two of the possible six significant correlates of a Th1-like response).

CD4/IL4 correlated negatively (r_{xy}=-.239, p=.005), which is counter to the hypothesised Th2-like response. However CD8/IL4 correlated positively (r_{xy}=.210, p=.012) as predicted (2/6 correlates: 1/6 in the anticipated direction).

No evidence of an anti-cancer NK response (0/4 correlates) or anti-cancer hormonal response (0/6 correlates) were found in support of the hypotheses. The failure to support the hypotheses regarding a Th1-like response might be explained by Eysenck's Inoculation Theory (Eysenck, 1983). Based on animal studies that showed an inhibitory effect of chronic stress on tumour cell proliferation, he argued that the process of adapting to chronic stress had an "inoculation" effect on the organism. In support, he cites Sklar and Anisman(1981); "Acute stress results in depletion of catecholamines and increased ACh, increased synthesis and secretion of hormones, and immune suppression. Adaptation to these biological mechanisms is observed with chronic stress, such that normal levels of functioning or alteration opposite to those induced by acute stress are apparent." (p.391) Nakaya et al. (2006) found that high Neuroticism predicted poor prognosis from lung cancer. It may be that the PNI of breast cancer and lung cancer differ with respect to Neuroticism.

4. It was hypothesised that the Lie scale would correlate negatively with a Th1-like response, anti-cancer NK response and anti-cancer hormonal response, but positively with a Th2-like response.

Lie scores correlated positively with CD14 (r_{xy}=.189, p=.015). No evidence of an Th1-like response (0/4 correlates), Th-2 like response(0/4 correlates), anti-cancer NK response (0/4 correlates) or anti-cancer hormonal response (0/6 correlates) were found.

CD14 is a marker molecule expressed by monocytes, macrophages and granulocytes. This is the first time that a positive correlation with Lie has been documented and this interesting relationship is worthy of further research.

5. It was hypothesised that PA would also correlate positively with an Th1-like response, anti-cancer NK response, and anti-cancer hormonal response, but negatively with a Th2-like response.

PA correlated negatively with CD3/IL2, CD4/IL2 and CD4/IFNγ (r_{xy}=-.180, p=.025, r_{xy}=-.183, p=.023, and r_{xy}=-.200, p=.015 respectively) a Th1-like response in the direction counter to the hypothesis (3/6 correlates: 0/6 in the anticipated direction). This is a consistent pattern which suggests that high PA (high energy, full concentration, and pleasurable engagement) is associated with a reduced Th1-like response, whereas low PA (sadness and lethargy) is associated with an enhanced Th1-like response. No evidence of a Th2-like response (0/6 correlates), anti-cancer NK response (0/4 correlates) or anti-cancer hormonal response (0/6 correlates) was found.

There has been little research on the relationship between PA and Th1-like and Th2-like responses. Most of the research has focussed on pro-inflammatory cytokines such as IL1 and IL6 and has addressed susceptibility to infections.

6. It was hypothesised that NA would correlate negatively with a Th1-like response, anti-cancer NK response and anti-cancer hormonal response, and positively with a Th2-like response.

NA was positively correlated with CD8/IL2 (r_{xy}=.216, p=.009), a Th-1 like response in the opposite direction to the hypothesis (1/6 correlates: 0/6 in the predicted direction). NA also correlated negatively with CD4 (r_{xy}=-.193, p=.012). No evidence of a Th2-like response (0/6 correlates), anti-cancer NK response (0/4 correlates) or anti-cancer hormonal response (0/6 correlates) was found.

Although contrary to prediction, the positive correlation between NA and CD8/IL2 is consistent with the positive correlation between CD8/IL2 and Neuroticism reported above. It would appear that the predicted relationship between NA and Neuroticism was justified as they behave similarly. The explanation proposed above for the positive relationship between Neuroticism and CD8/IL2 may also be valid for NA.

7. It was hypothesised that Internal locus of control (LOC) would correlate positively with a Th1-like response, anti-cancer NK response and anti-cancer hormonal response, and negatively with a Th2-like response.

Internal LOC correlated negatively with CD8/IL2 (r_{xy}=-.190, p=.020), indicating an unpredicted negative correlation with a Th1-like response (1/6 correlates: 0/6 in the predicted direction). No evidence of a Th2-like response (0/6 correlates), anti-cancer NK response (0/4 correlates) or anti-cancer hormonal response (0/6 correlates) was found.

8. It was hypothesised that Chance locus of control would correlate negatively with a Th1-like response, anti-cancer NK response and anti-cancer hormonal response, but positively with a Th-2 like response.

LOC Chance correlated negatively with NK cell activity (r_{xy}=-.200, p=.024) as hypothesised. This is consistent with the considerable literature demonstrating that the belief that events are uncontrollable renders these events more psychobiologically stressful. No evidence of a Th1-like response (0/6 correlates), Th2-like response (0/6 correlates) or anti-cancer hormonal response (0/6 correlates) was found.

9. No hypothesis was made due to the absence of empirical evidence or a conceptual framework with respect to powerful other locus of control.

MHLC P correlated strongly negatively with NK activity (r_{xy}=-.448, p=<.0005). This would suggest that the belief that Powerful others determine health state is associated with a non beneficial PNI outcome in terms of the anti-cancer NK hypothesis. This is the first time that this relationship has been documented. No evidence of a Th1-like response (0/6 correlates), Th2-like response (0/6 correlates) or anti-cancer hormonal response (0/6 correlates) was found.

10. It was hypothesised that control over emotional reactions would be negatively correlated with a Th1-like response, anti-cancer NK response and anti-cancer hormonal response, but positively correlated with a Th2-like response.

Anger correlated with CD4/IFNγ (r_{xy}=.186, p=.022), suggesting that anger suppression is associated with a Th2-like response in keeping with the hypothesis (1/24[11] correlates: 1/24 in the predicted direction). This finding therefore is consistent with the literature suggesting that patients with Type C characteristics have a poorer prognosis (Garssen, 2004; Bahnson, 1980, 1969).

Depressed mood correlated negatively with prolactin (r_{xy}=-.155, p=.019) in keeping with the hypothesis. Prolactin is a polypeptide hormone which is produced by the anterior pituitary gland and has a number of immuno-stimulatory properties. Prolactin has been shown to increase CD4/IFNγ, CD8/IFNγ, and CD8/IL2 in healthy humans (Dimitrov et al., 2004). The finding suggests that high levels of emotional control with respect to depressed mood is associated with reduced prolactin.

Depressed Mood, Anxiety, and Total scores correlated positively with percentage of cells expressing CD2 (r_{xy}=.192, p=.013, r_{xy}=.228, p=.004 and r_{xy}=.206, p=.009). CD2 is only expressed by T cells, and T cells are believed to impart an immune response either by releasing soluble mediators (cytokines) or by direct cell-to-cell interactions, although their relevance to breast cancer immunology is unclear.

No evidence was found for a Th1-like response (0/24 correlates), anti-cancer NK response (0/24 correlates) or anti-cancer hormonal response (0/24 correlates).

The first aim of study one was to examine the direction and magnitude of correlations between each of the personality variables and each of the NI variables and, in total, 22 correlations were significant at p ≤.05. The second aim of study one was to explore these relationships in more detail, taking into account age as a possible confounder. When these correlations were analysed further using stepwise regression, age was not significant in any

[11] each of the 3 scales and the total could each have up to 6 correlates

case. The lack of correlation was not due to having a restricted age range as ages ranged from 32 to 81 years (mean 58.78 years, SD 10.31). We can only conclude, that in this population of females with early breast cancer, age did not act as a significant confounder.

The third aim of study one was to to investigate the extent to which combining personality variables which correlated significantly with the same immunological variable improved prediction. In five cases, it was possible to evaluate this.

Psychoticism and Extraversion both correlated significantly with CD4/IL10. When entered simultaneously with age into a regression only Psychoticism was a significant independent predictor. The adjusted R^2 for Psychoticism without Extraversion was .040 and for Extraversion on its own the adjusted $R^2$was .026. When entered simultaneously, with age, the model gave an adjusted R^2 of .071, which is an improvement on either the EPQ-R variable alone, as together they account for 7.1% of the variance.

Three personality variables correlated significantly with CD4/IFNγ, namely Neuroticism, PA and Anger. When these, with age, were entered into a simultaneous multiple linear regression, none was a significant independent predictor of CD4/IFNγ. The adjusted $R^2$for stepwise regressions were Neuroticism: R^2= .039, PA: R^2 =.032 and Anger: R^2 = .026. When these three variables were entered together, with age, the model gave an adjusted R^2 of .067 indicating that, collectively, they accounted for 6.7% of the variance and represent a worthwhile improvement over the individual personality variables.

Neuroticism, NA, ILOC and CLOC were all significantly correlated with CD8/IL2. When entered simultaneously, with age, only CLOC was an independent significant predictor. The overall adjusted R^2 for the model was .096 indicating that, collectively, the variables account for almost 10% of the variance. Again, this represents a useful improvement on the predictive value of the individual variables (Neuroticism adjusted R^2 = .049, PA adjusted R^2 = .025, Internal LoC adjusted R^2=.028 and CLOC adjusted R^2 = .033).

CLOC and PLOC correlated significantly with NK. Both LOC scores were entered simultaneously into a regression, with age, and PLOC emerged as a highly significant independent predictor of NK. In the stepwise analysis CLOC gave an adjusted R^2 of .030 and PLOC an adjusted R^2 of .193. In the simultaneous entry model they give an adjusted R^2 of .177, accounting for 17.7% of the variance. The combined model, therefore, is a less good predictor of PLOC alone.

Anxiety, Depressed mood and Total score all correlated significantly with CD2 and were entered simultaneously into a multiple linear regression, along with age. Diagnostic

tests revealed that collinearity was a problem (VIF>10; Tolerance<0.1). The Total score was therefore omitted and the analysis was re-run. Depressed mood was a significant independent predictors of CD2 and the statistically significant model gave an adjusted R^2 of .038. The stepwise regressions gave adjusted R^2 as follows; Depressed mood =.030, Anxiety =.045, Total=.035. Therefore, CECS Anxiety alone, adjusted for age, accounted for a higher percentage of variance (4.5%) than the combined model (3.8%).

The variance explained by the personality variables is statistically significant but is never-the-less low and this is somewhat at odds with the literature that suggests that internal coping and PA are associated with better outcomes in breast cancer.

8.8 Conclusion

Study one investigated the relationship between personality, psychological and NI variables using Pearson's Product-Moment Correlation coefficients. The study benefited from a good sample size (n=183 women) relative to published similar studies. A wide range of personality, psychological and NI measures were employed. At least one NI measure correlated significantly with at least one personality dimension, however this may have been due chance and the number of possible correlations.

When personality and psychological measures were combined in linear models, five immunological variables were predicted by two or more variables however, the direction of the relationships are not always easy to reconcile with the existing literature on host defences and prognosis on the one hand, and personality and survival on the other. The reason for this is unclear, but again may have been due to chance.

An alternative explanation is that the particular characteristics of the participants, a very well adjusted group of women with early breast cancer six weeks post surgery may have explained the lack of findings. Only 10.4% of participants had a positive Structured Clinical Interview for Diagnosis (SCID) using DSM-TR 4 criteria Sharp et al. (2010). In a large population based study of 3,491 women between the ages of 25 and 65 (Breeman et al., 2014), 19.0% scored ≥ 11 which is the generally accepted cut-off for clinically significant anxiety. As the incidence of anxiety is known to decrease in the elderly (L. G. Walker et al., 1998) the prevalence of 14.2% found in participants in this study indicates that the man levels of anxiety were comparable to the community based norms. It may well be that individuals who score high on Neuroticism, for example, and are therefore predisposed to high levels of state anxiety show more marked PNI responses and the effect of a restricted range would be to reduce the magnitude of obtained correlations.

Alternatively, the absence of findings in keeping with the literature may reflect the subtlety of how the many components of the immune system interact to produce an effective anti-cancer response. The complexity (Waldrop, 1992) and systemic (Churchman, 1979) nature of the human body has been discussed elsewhere in this thesis, and the fundamentals of complexity and systems thinking in A. A. Walker (2001).

Chapter 9: Study two - predictive value of high and low scores of personality variables on neuroendocrinological-immunological responses

Abstract: Study two was designed to investigate the stability of personality and NI correlations over 18 weeks, and to investigate interactions between NI and higher and lower scorers on various measures of personality. 62 women with early breast cancer were studied. Personality was assessed 6 weeks post-surgery using the revised Eysenck Personality Questionnaire (EPQ-R), the Positive and Negative and Affect Schedule (PANAS), the Multidimensional Health Locus of Control Scale (MHLCS) and the Courtauld Emotional Control Scale (CECS). Blood samples were collected at 6, 18 and 24 weeks post surgery for NI analysis. Pearson's product-moment correlations were computed for each personality variable and each NI measure to identify variables that produced statistically significant correlations at more than one time point, thereby indicating a significant degree of longitudinal stability. In order to identify possible differences between above and below average scorers on the personality variables (interaction effects), median values were derived for each of the personality variables and these were used to create groups of above and below median scorers. Personality and NI relationships were examined across the three time points by ANOVA. A statistically significant interaction between extraversion and CD19 was obtained for T1 and T2 ($F=9.496$, $p=.004$) and T1 and T3 ($F=5.037$, $p=.030$) indicating that in lower scorers CD19 decreased significantly over time whereas in higher scorers it was relatively stable. This is a novel finding which deserves further study. A number of interesting statistically non-significant interesting effects were observed for EPQ-R Lie and CD8/IL10, EPQ-R Lie and LAK, Positive Affect (PA) and LAK, Negative Affect (NA) and PRL-R, NA and Cortisol, NA and Growth Hormone, NA and GH-R, CLOC and Growth Hormone, and PLOC and PRL-R.

9.1 Introduction/Overview

Study one found that certain personality traits (Psychoticism, Extraversion and Neuroticism), affect (positive and negative) and locus of control (internal and chance) correlated with certain NI variables, but many relationships were not significant and in the opposite direction to what was hypothesised. Study two was designed to investigate the stability over time of any underlying personality and NI associations, and to investigate the

potential for an interaction effect between NI and higher and lower scorers on a measure of personality over time. In order to protect against claims of selective reporting only relationships significant at baseline were analysed and all relationships are reported.

9.1.1 Aims. The aim of study two was to investigate the NI profile over time of different personality subtypes in order to test whether different personality characteristics are associated with differential NI responses.

9.1.2 Hypotheses.

1. Negative and positive tails of the distribution of personality variables will be associated with significantly different immunological profiles over time.

2. Related to 1, above, different personality variables will be effected differentially by the immunosuppressive effects of cancer treatment (anticipated to be most evident at the second time point, T2) over time.

9.2 Design/Method

9.2.1. Procedure. Study two is a longitudinal, repeated-measures design using Analysis of Variance (ANOVA).

Please see the timeline of the three measurement point over the page.

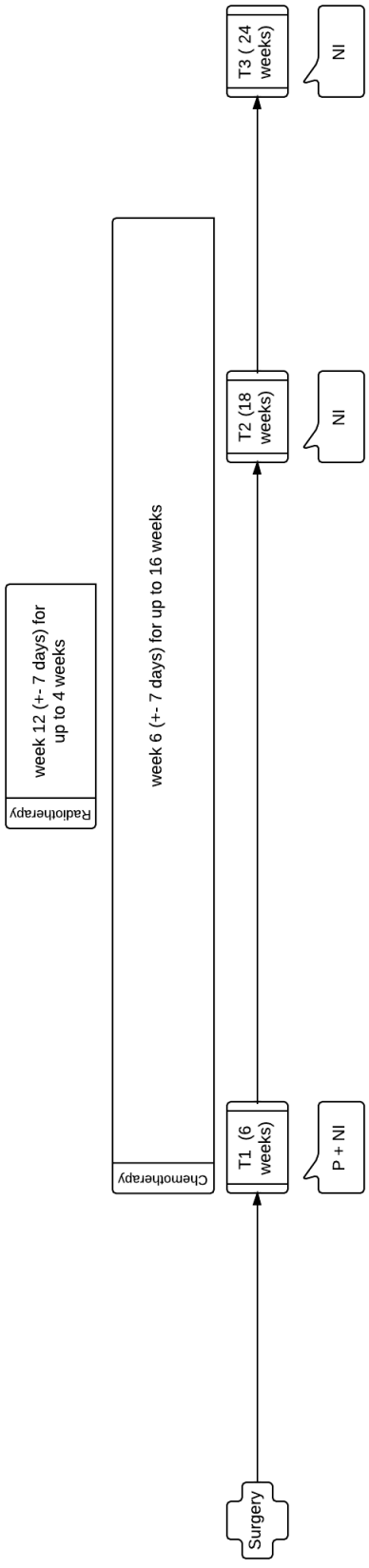

Figure 4. Timeline of the three measurement points: T1 (6 weeks post surgery), T2 (18 weeks post surgery) and T3 (24 weeks post surgery) alongside chemotherapy and/or radiotherapy. Measurements are also plotted (P = personality measurement, NI = neuroendocrinological-immunological measurement).

9.2.2 Description of participants.

9.2.2.1 Inclusion and exclusion criteria. All participants included in study one were eligible for study two. One third of the women (n=62) were selected at random for longitudinal follow-up.

Patients were randomised by a specialist oncology nurse six weeks (± one week) post breast surgery, before study one data were collected. Randomisation was produced by Graph-Pad (http://www.graphpad.com) to create permuted blocks (concealed blocks of 8) stratified for (1) menopausal status, (2) chemotherapy, and (3) radiotherapy. Randomisation was carried out manually by pre-approved and trained personnel at the Institute of Rehabilitation, University of Hull.

Table 41:: Demographic and clinical profile of included partcipants: study two

		Total (n=62)
Age		
	mean age (years)	59.36
	SD	10.23
	range	36-77
Ethnicity		
	Caucasian	62
ER status		
	Positive	55
	Negative	7
	Unknown	0
PR status		
	Positive	51
	Negative	11
	Unknown	1
T stage		
	Tis	1
	T1	41
	T2	19

Table 41:: Demographic and clinical profile of included partcipants: study two

	T3	1
Breast surgery		
	Wide local excision	51
	Quadrantectomy	0
	Mastectomy	7
	Mastectomy + reconstruction	4
Radiotherapy planned		
	Yes	47
	No	15
Chemotherapy planned		
	Yes	9
	No	53

9.2.2.2 Demographic and clinical profile of included participants. In summary, the group of participants selected at random to be followed-up are representative of the 183 females in study one.

9.3 Materials

All of the materials used in study two have already been presented in study one.

9.4 Procedure

The procedure for obtaining and analysing data at T2 and T3 were identical to that at T1, presented in study one.

9.4.1 Rationale for using baseline personality measures vs temporal personality measures. The decision was made to use baseline personality measures as the dependent variable at all three time points. The rationale for this was (1) personality is believed to be stable over time and therefore change would not be anticipated (Chapter two) and (2) this allows direct comparison with the existing literature identified which uses personality assessed at a single time point as a variable in a cross-sectional correlational design, or as in this study, a predictive variable in a longitudinal design of analysis of variance.

9.5 Statistical methodology

To minimise the risk of a type I error, only correlated personality and NI variables, from participants in the randomised sub-group, were used for further analyses (Table 42). A full tabulation of personality and NI variables that correlated at T1, T2 and/or T3 is presented in Appendix N). Each of these significant correlations at T1 were then examined across the three time points by means of repeated measures analysis of variance (ANOVA). In order to identify possible differences on NI response in above and below average scorers on a personality measure over time (interaction effects), median values were derived for each of the personality variables and these were used to create groups of above and below median scorers on each variable: these groupings were then used for the repeated measures ANOVAs. It was agreed by the present writer and his supervisor that if data were transformed at T1, the same transformations should be completed at the following time-points (T2 and T3) also.

In addition to reporting significant F-ratios, when a statistically significant result was obtained, graphs are also presented in this chapter. Where significant ANOVAs were obtained, the ANOVAs and graphs for NI related variables, as shown in Table 12 (see study one), were also presented to see if there was a consistent pattern.

Table 42:: Personality and neuroimmunological correlations at T1: study two sub-group

Personality variable	**NI variable**	**T1 R_{xy}**
EPQ-R Psychoticism		
	CD4 expressing IFNγ (Th1)	*.381**
EPQ-R Extraversion		
	CD4 expressing IL2 (Th1)	*.335**
	CD19	*-.305**
EPQ-R Lie		
	CD8 expressing IL10 (Th2)	*.370**
	NKCA (Killer Cells)	*-.392**
PANAS Positivity		
	CD3 expressing IL2 (Th1)	*-.377**
	CD3 expressing IFNγ (Th1)	*-.365**
	CD4 expressing IL2 (Th1)	*-.364**

Table 42:: Personality and neuroimmunological correlations at T1: study two sub-group

	CD4 expressing IFNγ (Th1)	-.*355**
	CD16 (Killer Cells)	-.*329**
	CD8 (T cell)	-.310*
PANAS Negativity		
	prolactin receptor (NH)	-.*333**
	growth hormone receptor (NH)	.*292**
MHLC Chance		
	NKCA (Killer Cells)	-.*350**
	growth hormone concentration (NH)	.*344***
MHLC Powerful other		
	NKCA (Killer Cells)	-.*569***
	prolactin receptor (NH)	.*313**
CECS Depressed mood		
	CD2 (T cell)	.*336**
	prolactin concentration (NH)	-.*325**
CECS Total		
	prolactin concentration (NH)	-.*298**

9.5.1 Power. As noted in the prefix and in the design of study one, this thesis in set in the context of a Randomised Controlled Trial (RCT). The RCT protocol stated "Power calculations have been carried out using nQuery. We consider that a 10% difference in the primary outcome measure (FACT-B) would be clinically meaningful. With 60 patients in each group, there will be 95% power to detect a 10% difference in scores (a difference between means of 120 and 132, assuming a common standard deviation of 18)" (unpublished). Therefore, the sample size for this study was limited by the RCT.

9.6 Results

9.6.1 Statistically significant interaction effects over time.

EPQ-R E and CD19 A significant effect was found for the interaction of time and EPQ-R E. Within subject contrasts showed a signifiant interaction effect for T1 and T2 (F=9.496, p=.004), and T1 and T3 (F=5.037, p=.030) in CD19.

Table 43:: Median-split ANOVA EPQ-R E and CD19

Source	SS	DF	MS	F	Sig
Time	.993	2	.497	5.654	.005*
Time x EPQ-R E	.842	2	.424	4.791	.011*
Between Group	.040	1	.040	.463	.500

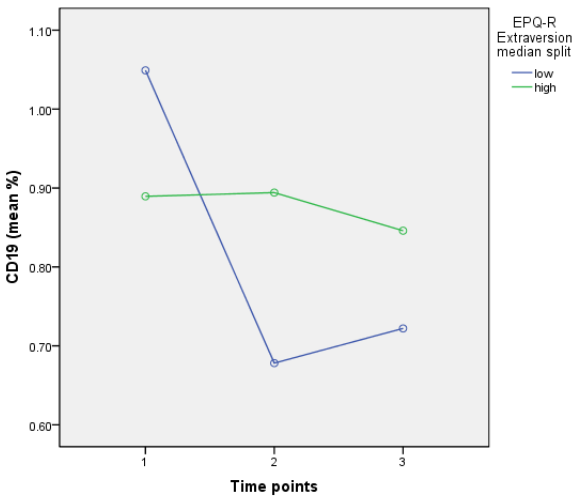

Figure 5. Median-split EPQ-R E and CD19 over time

As CD19 does not fit into the anti-cancer groupings (Table 12), no further exploration

of associated variables were identified.

9.6.2 Suggestions of interaction effects over time.

EPQ-R L and CD8/IL10 While not statistically significant (time x EPQ-R L F=1.936 df=2 p=.154) an interesting cross-over between T1 and T3 was observed for time x EPQR-L in CD8/IL10 (Figure 6).

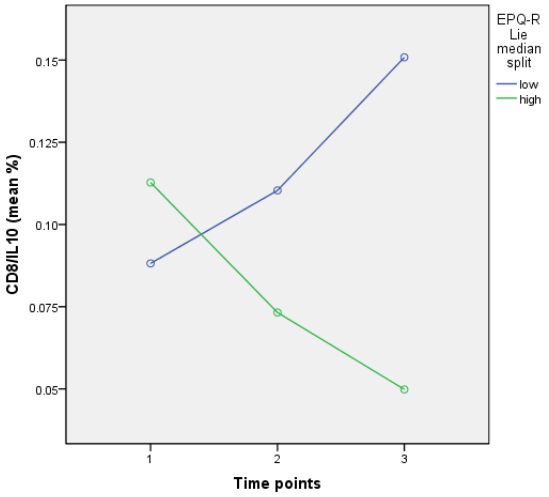

Figure 6. Median-split EPQ-R L and CD8/IL10 over time

A repeated measures analysis of variance for time x EPQ-R L was non-significant (F=2.401 df=2 p=.101). However, the graph shows convergence and a small interaction effect in LAK (Figure 7) .

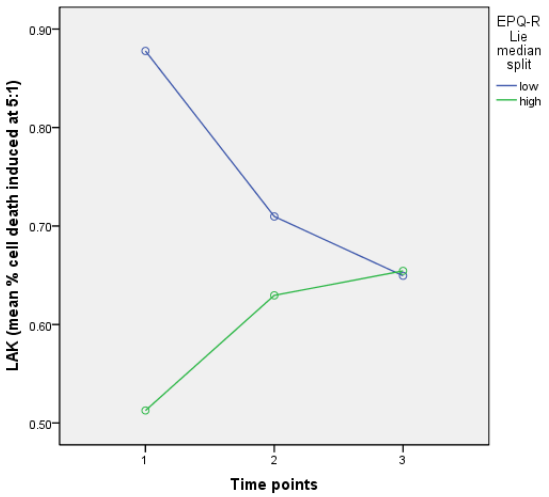

Figure 7. Median-split EPQ-R L and LAK over time

PANAS P and LAK While not statistically significant, repeated measures analysis of variance for time x PASAN P suggested divergence between T1 and T3 in LAK (Figure 8) (F=1.477 df=2 p=.238).

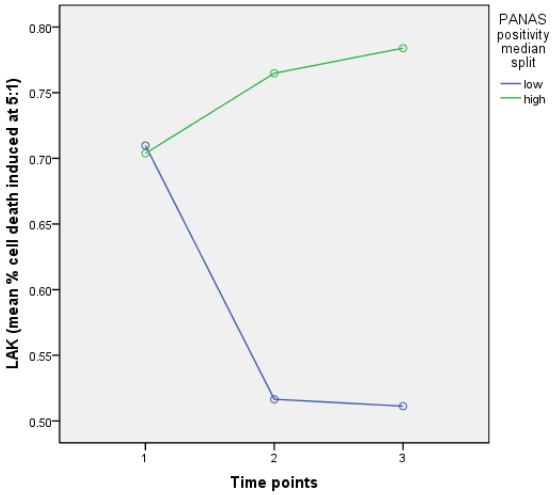

Figure 8. Median-split PANAS P and LAK over time

PANAS N and PRL-R A significant between group effect was found (F=4.117 df=1 p=.049), and the groups converged. (Time x PANAS N F=1.539 df=2 p=.221) in PRL-R (Figure 9).

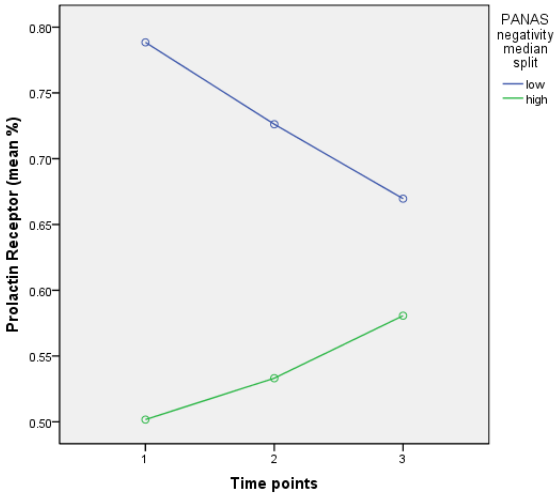

Figure 9. Median-split PANAS N and PRL-R over time

Repeated measures analysis of variance for cortisol showed non significant effects for time x PANAS N (F=.201 df=2 p=.818) a The groups appear to diverge in PRL-R over time (Figure 10).

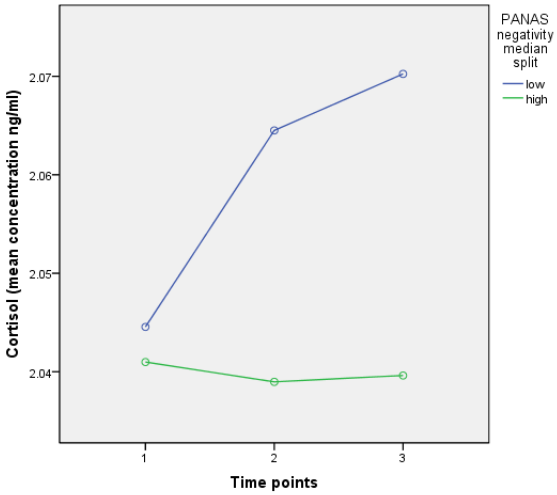

Figure 10. Median-split PANAS N and Cortisol over time

Repeated-measures analysis of variance for cortisol (Figure 11) and GH-R (Figure 12) showed non-significant but inconsistent effects for time x PANAS N (F=.706 df=1.043 p=.411). Mauchley's test indicated that the assumption of sphericity had been violated (p= <.005), and therefore a Greenhouse-Geisser correction was applied. Visually, however, the two graphs differ whereas as similar trend would have been expected.

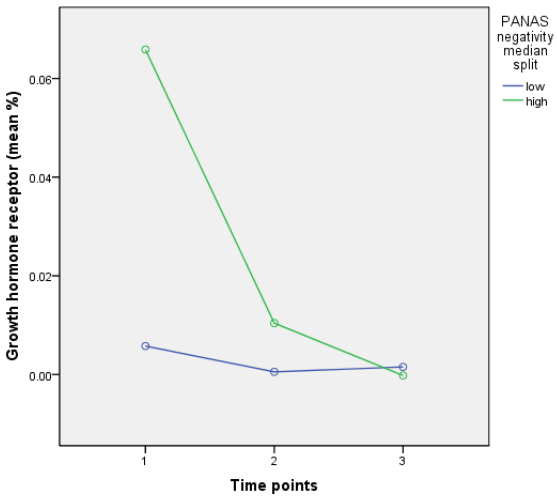

Figure 11. Median-split PANAS N and GHR-R over time

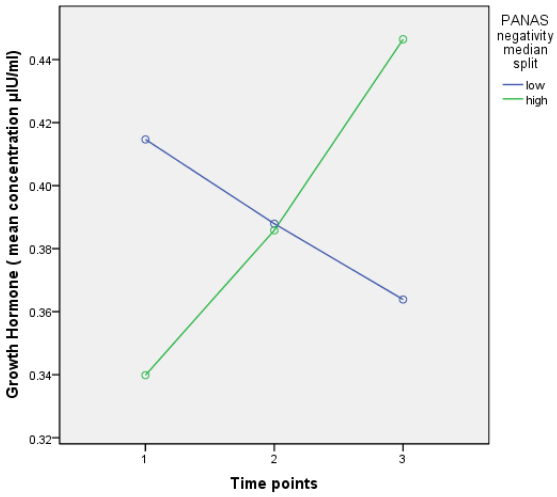

Figure 12. Median-split PANAS N and Growth Hormone over time

MHLC-C and GH Repeated measures analysis of variance for time x GH were non-significant (F=2.383 df=2 p=.097). The groups appear to interact in respect of GH concentration (Figure 13).

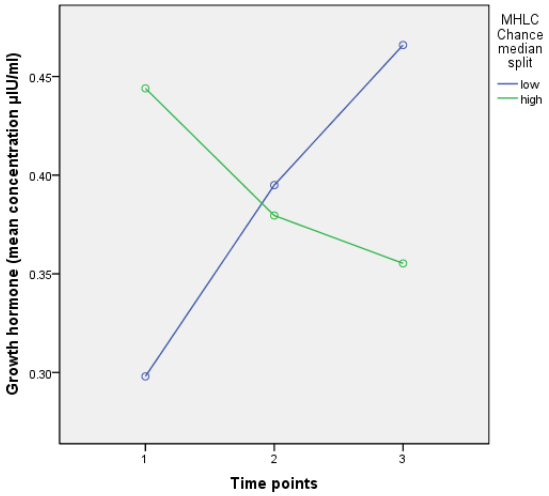

Figure 13. Median-split MHLC C and Growth Hormone over time

MHLC P and PRL-R Repeated measures analysis of variance for time x MHLC P were non-significant (F=1.792 df=2 p=.173). The groups appear to converge and interact in respect of PR-R (Figure 14).

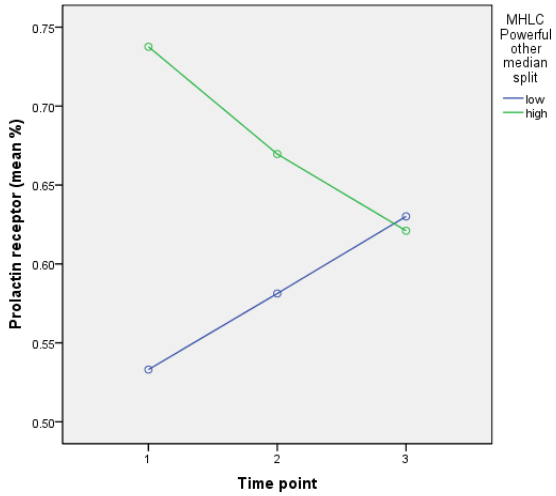

Figure 14. Median-split MHLC P and PRL-R over time

9.7 Discussion

In order to examine the possibility that high and low scorers on a personality dimension might respond differentially, median splits were computed for each of the personality and NI correlations significant at T1. One interaction effect was significant (significant F ratios are presented in the ANOVA tables but are not relevant to the discussion).

Extraversion and CD19 (Figure 5) showed a signifiant interaction effect for T1 and T2 (F=9.496, p=.004), and T1 and T3 (F=5.037, p=.030). In lower scorers, CD19 decreased significantly between T1 and T2 and remained decreased whereas CD19 was stable over all three time points in higher scorers. CD19 is a B cell marker, and discussed in Chapter 1 B cells are specific to certain antigens. When the paired antigen is recognised, the B cell multiplies and differentiates into plasma cells, producing its soluble mediator, a large glycoprotein antibody present in blood and tissue that is virtually identical to the originating B cell. As the connection between B cell (in its its antibody form) and antigen is maintained, the antibody can bind with the antigen.

One possible explanation for the interaction effect may be that introverts and extraverts respond differently to the stresses of breast cancer treatment. However in a study of 28 male undergraduates, no interaction was found between extraversion and the lymphocyte proliferative response to stress (S. Cohen et al., 2012). Extraverts were less susceptible

to Rhinovirus (RV23 or RV39), but no association was found between extraversion and CD19+ cells, or indeed circulating T-lymphocytes (CD3+), T helper cells (CD4+), cytotoxic T lymphocytes (CD8+) or NK Cells (CD3-CD16+CD56+) (S. Cohen et al., 2012). Commenting on the literature on extraversion and immunity, Cohen states that "many of the immune measures studied in this literature may have little or no implications for host resistance and hence we may not even expect them to be correlated with host resistance or for that matter with extraversion just because it predicts host resistance" (S. Cohen et al., 2012, page 150). The association between changes in CD19 and extraversion over time found in the present study is therefore of interest and has not been reported previously.

A number of non-significant but interesting interaction effects were identified.

The CD8/IL10 levels of higher and lower Lie scorers diverged progressively over the three time points (Figure 6). The Lie scale is believed to be a measure of social conformity (Eysenck, 1994) and CD8/IL2 is a measure of Th1-like response. Both groups started at an approximately similar level but low scorers on the Lie scale showed an increase in CD8/IL10 over time, and high scorers a decrease in CD8/IL10. This would suggest that lower scorers showed an increased Th2-like response over time and high scorers a decreased Th2-like response over time.

Conversely, LAK cell activity for higher and lower scorers on the Lie scale converged over the three time points, with lower scorers showing a progressive decline in LAK over time and higher scorers a progressive increase (Figure 7). Lymphokine activated killer (LAK) cells are IL-2 stimulated NK cells expressing CD57 and have been shown to mediate tumour cell cytotoxicity and to be suppressed in cancer patients. As with the CD8/IL10 findings above, this suggests an improving cancer response over time for the higher Lie scorers. One study found that high Lie Scores predicted poorer survival in patients with Hodgkin's disease and non Hodgkin's lymphoma (L. G. Walker, 2004; Ratcliffe et al., 1995) and it may be that the effect of Lie scores are different in solid tumours compared to haematological cancers.

There was an interesting relationship between LAK and PA. At T1, LAK cell activity was very similar for higher and lower PA. Higher scorers increased over time, whereas lower scores decreased steeply between T1 and T2 and plateaued (Figure 8). This would support the hypothesis thatPA is associated with a favourable anti-cancer response and is consistent with the Type C literature (Garssen, 2004, and Chapter 4).

Three interesting trends were found for NA. First, a significant between group effect

was noted between NA and PRL-R (F=4.117 df=1 p=.049). Lower scorers on NA started with a higher percentage of PRL-R and showed a steady decrease over time. In contrast, higher scorers had a relatively low percentage at T1 and this increased (Figure 9). In terms of a favourable cancer response, increased Prolactin is desirable, so the suggestion that lower NA is associated with higher Prolactin is consistent with the hypothesis outlined in study one. NA is considered to be conceptually similar to Neuroticism and, therefore, it would be anticipated that it would correlate negatively with an anti-cancer hormone response, consistent with the Type C literature (Garssen, 2004, and Chapter 2).

Second, higher NA scorers showed little change over time in Cortisol, whereas lower scorers showed increasing Cortisol concentrations (Figure 10). This suggests that low NA may be an indicator of a deteriorating anti-cancer response. The trend is consistent with that of PRL-R described above. It is also consistent with the survival studies which found that lower Neuroticism is related to poorer survival.

Third, the relationship between Growth Hormone and GH-R levels were inconsistent over time. High scorers on NA decreased progressively over time for GH-R, whereas for Growth Hormone they increased over time (Figures 11 and 12). This is inconsistent and, therefore, difficult to interpret, and it may simply be due to chance.

A non-significant interaction effect was obtained for Growth Hormone and CLOC. Lower scorers increased progressively over the three time points whereas lower scorers decreased progressively close to T2 (Figure 13). This suggests an improving anti-cancer hormonal response over time in lower scorers and a deteriorating response in higher scorers. This is particularly interesting because at T1, higher scorers on CLOC had higher levels of Growth Hormone. If this had been a single point study (T1), the conclusion would have been that higher chance scores were beneficial, whereas the reverse is true at T3, emphasising the potential value of a longitudinal perspective of anti-cancer hormonal responses.

A non-significant interaction effect was noted for PRL-R and PLOC. Lower scores on PLOC started with a low prolactin level which increased in a linear manner until it intersected with the higher scorers at T3: higher scorers decreased in a similar linear manner (Figure 14). As with Growth Hormone, lower scorers on CLOC show an improving anti-cancer hormonal response.

No *a priori* hypotheses were made for CLOC or PLOC because of the absence of relevant literature (Chapter 5).

It is interesting to note that, although all four EPQ-R scales correlated with one or more NI variable at one of the three time points, in no case did any correlate significantly at one or both of the other two time points. This points to the value of examining relationships over a period of time during treatment for early breast cancer. As noted above, a single point study would have led to different conclusions regarding the effect of personality on NI in a number of the measures included in this study.

In conclusion, it does appear that there is merit in adopting a longitudinal perspective in future studies.

Chapter 10: General Discussion.

10.1 Overview

Four structured reviews were carried out to identify previous work relating to personality constructs to cancer risk and prognosis. A further systematic review of personality and NI was carried out.

In terms of cancer risk and prognosis, the largest studies have tended to concentrate on Extraversion and Neuroticism. This is partly due to the influence of the early work of Kissen and Eysenck (1962) which suggested that low Extraversion and high Neuroticism acted as significant risk factors. Accordingly, a structured review of the use of Eysenckian personality traits to predict cancer risk or progression was undertaken. The results were inconclusive. Of the 11 papers studies reviewed, 6 reported significant results (Lemogne et al., 2013; Nakaya et al., 2010; Augustine et al., 2009; Nakaya et al., 2006, 2003; Aarstad et al., 2002) and five did not (Osthus et al., 2011; Shipley et al., 2007; Canada et al., 2005; Hansen et al., 2005; Schapiro et al., 2001). Of the significant findings, Neuroticism was the most common trait to feature and high Neuroticism was associated with lower age at surgery for lung cancer (a surrogate for age of cancer diagnosis) (Augustine et al., 2009), incidence of all cancer (Nakaya et al., 2003, 2006; Aarstad et al., 2002), risk of all cancer (Nakaya et al., 2003, 2006), death from lung cancer (Nakaya et al., 2006) and all cause death, particularly in females (Nakaya et al., 2006). However, trial designs, methods used, sample sizes, statistical analyses, and, most importantly, cancer type and stage varied, studies often combining cancer types when reporting results.

It was expected that the traits of positive and negative affectivity would also have been the subject of considerable interest in predicting risk of cancer and survival, especially as the most commonly used measures, PANAS PA and NA, are similar to Neuroticism and Extraversion respectively. The structured review did not return any studies to discuss. Nevertheless, it was evident that the literature all too easily drifts from personality traits into mood states which fall beyond the scope of this thesis.

Locus of Control has played a major part in health psychology research, particularly since the publication of Mischel's (1968) seminal work 45 years ago. Interestingly, however, only one relevant paper was identified.

Emotional control has been widely regarded as a key component of the Type C personality. The Courtauld Emotional Control Scale (CECS) was developed by M. Watson & Greer (1983) as a measure of emotional control, specifically the extent to which individuals

report controlling anger, anxiety and depressed mood. A single study was found through structured review. However, the related concept of anti-emotionality has been linked with immune change (Bleiker et al., 1996; van der Ploeg et al., 1989).

A wide-ranging structured review returned only one study reporting psychological measurement and NI outcomes in a cancer population. In a correlational study of 30 heterogenous cancer patients, Messina et al. (2010) found (1) $CD4^{+}CD25^{+}$ in a self-punishing group (assessed with the 10 card Rorschach test) was significantly higher than than those who did not self punish (11/18 vs. 3/12 (25%) $p<0.05$). (2) the percentage of patients with abnormally low $CD4^{+}/CD4CD25^{+}$ ratios were significantly higher in those with self punishment (16/18 vs. 4/12 $p<0.01$). (3) Mean regulatory T cell lymphocytes in the self punishment group were significantly higher than no self-punishment ($314\pm319/mm^{3}$ vs. $173\pm27mm^{3}$, $p<0.05$). (4) Mean $CD4^{+}/CD4^{+}CD25^{+}$ ratio in the self punishment group significantly lower than no self-punishment (2.6 ± 0.2 vs. 5.2 ± 0.8, $p<0.025$) and (5) No significant difference in mean number of $CD4^{+}$ lymphocytes. The authors concluded that regulatory T cell lymphocyte count is correlated with self-punishment. As between group differences in other lymphocyte sub-sets (NK, CD3 and CD8) were not significant, Messina et al. (2010) reported that while only 18 of 30 of all participants were self-punishers, interestingly nine of the 11 participants with breast cancer were self-punishers, indicative of the need for homogeneity of cancer type in studies. The study had a number of methodological weaknesses which could be improved upon: a mixed cohort of cancer types, single immunological and personality time points and, therefore, the temporal stability of the data is unknown.

In the light of these considerations, two studies were carried out.

Study one had a cross-sectional, correlational, within-group single time-point design. As with other correlational designs, as variables are measured simultaneously, causation cannot be inferred.

183 women were assessed 6 weeks post-surgery for early breast cancer using the revised Eysenck Personality Questionnaire (EPQ-R), the Positive and Negative and Affect Schedule (PANAS), the Multidimensional Locus of Control Scale (MHLCS) and the Courtauld Emotional Control Scale (CECS). Blood samples were collected for neuroendocrinological and immunological (NI) analyses. Based on structured literature reviews, hypotheses were generated regarding personality and NI relationships.

Following normalisation of distributions as required, the relationship between per-

sonality variables and NI variables were computed using Pearson's Product-Moment Correlation coefficients. As Psychoneuroimmunological (PNI) relationships may be affected by age, multiple linear regression was used to establish the extent to which significant relationships remained. At least one NI measure correlated significantly with at least one personality dimension.

Five immunological variables were predicted by two or more personality variables. (1) EPQ-R P and EPQ-R E both correlated significantly with the Th1-like response CD4/IL10. When entered simultaneously with age, Psychoticism and Extraversion accounted for 7.1% of the variance, better than either trait alone. (2) Neuroticism, Positive Affect (PA) and Anger correlated significantly with the Th1-like response CD4/IFNγ, together accounting for almost 10% of the variance, again greater than any single variable alone. (3) Neuroticism, Negative Affect (NA), Internal Locus of Control (ILOC) and Chance Locus of Control (CLOC) were all significantly correlated with the Th1-like response CD8/IL2 and collectively accounted for almost 10% of the variance, greater than any one variable alone. However, only CLOC was a significant independent predictor of percentage of CD8/IL2. (4) CLOC and PLOC correlated with NK cell activity, but were less predictive than each individual dimension alone, and (5) Anxiety combined with Depressed mood (emotional control) correlated with percentage cells expressing CD2, but was less predictive than each individual dimension alone.

The direction of the relationships are not always easy to reconcile with the existing literature on host defences and prognosis on the one hand, and personalty and survival on the other. This could be due to the particular characteristics of the participants, a very well adjusted group of women with early breast cancer six weeks post surgery, or it may reflect the subtlety of how the many components of the immune system interact to produce an effective anti-cancer response.

Study two was designed to investigate the stability of personality and NI correlations over 18 weeks, and to investigate any interaction between NI and higher and lower scorers on various measures of personality. 62 women with early breast cancer were studied. Personality was assessed 6 weeks post-surgery using the revised Eysenck Personality Questionnaire (EPQ-R), the Positive and Negative and Affect Schedule (PANAS), the Multidimensional Locus of Control Scale (MHLCS) and the Courtauld Emotional Control Scale (CECS). Blood samples were collected at 6, 18 and 24 weeks post surgery for NI analysis.

Pearson's product-moment correlations were computed for each personality variable and each NI measure to identify variables that produced statistically significant correlations at more than one time point, thereby indicating a significant degree of longitudinal stability. In order to identify possible differences between above and below average scorers on the personality variables (interaction effects), median values were derived for each of the personality variables and these were used to create groups of above and below median scorers.

Personality and NI relationships were examined across the three time points by ANOVA.

A statistically significant interaction between extraversion and CD19 was obtained for T1 and T2 ($F=9.496$, $p=.004$) and T1 and T3 ($F=5.037$, $p=.030$) indicating that in lower scorers CD19 decreased significantly over time whereas in higher scorers it was relatively stable. This is a novel finding which deserves further study.

A number of interesting statistically non-significant interesting effects were observed for EPQ-R Lie and CD8/IL10, EPQ-R Lie and LAK, Positive Affect (PA) and LAK, Negative Affect (NA) and PRL-R, NA and Cortisol, NA and Growth Hormone, NA and GH-R, CLOC and Growth Hormone, and PLOC and PRL-R.

Study two suggests that there is merit in evaluating personality-NI relationships within a longitudinal design.

A number of factors may have influenced the results, and are relevant to both studies. These are considered in this concluding discussion.

10.2 Strengths

Both studies have a number of strengths. First, all of the participants were females with early breast cancer, and they all received medical and surgical treatment in a single cancer service, thereby reducing patient, clinician and treatment variability. In addition, given that social support has been shown to affect NI responses, a strength of the studies is that all of the women received support from the same clinical team.

Psychometric tests were all administered in a standardised manner within a standard setting (the Oncology Health Service, Hull) by the same clinical team, and the questionnaires were administered in the same supportive and familiar environment. Care was taken to ensure that the member of staff who administered the psychometric measures to a particular patient was not involved in any formal ongoing psychosocial or medical support as it could be argued that that may have exerted a pressure on participants to respond in a

particular way and could be construed as a conflict of interests for the clinical team. The potential for bias was also reduced by ensuring that the questionnaires were scored by a member of the team who had not provided care or administered the questionnaires. All psychometric measures were administered in full.

Immunological measures were carried out using standardised laboratory protocols and the assays were all carried out by immunologists in the same laboratory (University of Hull, Hull) blindness to personality scores.

A considerable strength of study one is that this is the largest study to address the relationships between personality and NI responses. Study two is also of note for featuring a longitudinal design with three time-points. A further strength of study one is that the 183 participants were recruited from a consecutive series of 234 patients.

10.3 Medical considerations

NI responses need to interpreted in terms of the context of the time points in which they were studied.

At T1, the participants were six weeks post surgery. The effects of surgical trauma, wound healing, and anesthesia, *etc.* have been shown to affect NI parameters and these may have effected the results at T1 (Eremin & Sewell, 2011)

Also, in addition to coping with the psychosocial effects of a recent cancer diagnosis, and major surgery, the participants were about to start further anti-cancer hormone therapy (usually tamoxifen), radiotherapy and/or chemotherapy which are known to be stressful, for example hair loss.

These stressors are likely to have influenced the NI findings at T1 and the effects may have been influenced by personality traits. For example, Sharma and colleagues studied the effects of personality on length of stay and post-operative morbidity in patients with colorectal cancer. After adjusting for post-operative morbidity, Extroversion remained an independent predictor of length of stay. (Sharma et al., 2008) Also, patients who score higher on the EPQ extroversion scale have been found to show a higher tolerance to pain (Ramírez-Maestre et al., 2004). Finally, Neuroticism has been shown to amplify the extent to which individuals are distressed by a threatening situation (Alexander et al., 1993).

At T2, all the participants were receiving hormone therapy which can cause distressing and menopausal symptoms. Some were receiving chemotherapy and others radiotherapy, both of which are well known to have immunosuppressive effects (Eremin & Sewell, 2011). Unfortunately, the number of participants in each subgroup was too small

to analyse separately, or indeed to adjust for in a multivariate model.

At T3, all the participants were still receiving hormone therapy. In addition, others were still having the residual side effects of radiotherapy (especially fatigue), and the remainder were in the final stages of chemotherapy, with all of the associated side effects such as neutropenia. These different regimes are likely to have produced varying effects on the NI system further obfuscating any relationships between personality and NI responses. As at T2, it was not possible to analyse sub-groups separately.

10.4 Psychometric measurement considerations

The assumption has been made that the measures of personality used were reliable, stable over time, and measured what they purported to measure. Evidence for this has been reviewed in detail in Chapter eight. Nevertheless, there is evidence that questionnaire measurement of Type C characteristics may be effected by the context in which the questionnaires are administered and that measurement may be influenced by the ability of the tester to build rapport.

For example, Schmale & Iker (1971) used interviews and the Minnesota Multidimensional Personality Inventory (MMPI) to predict coronary heart disease. The interviews successfully predicted disease whereas the MMPI scores did not. In addition, Grossarth-Maticek et al. (1993) showed in an experimental study that different methods of administering a questionnaire greatly influenced the accuracy of the predictions of cancer and coronary heart disease risk. The best predictions were achieved for participants when their trust and understanding had been enhanced by the test administrator. In the present study, the psychometric measures were administered by oncology health service clinicians (clinical psychologists and specialist behavioural oncology nurses not involved in the participants' standard clinical care), and they went to some length to develop rapport with the women and to provide information about the nature and purposes of the psychometric assessments. It seems reasonable, therefore, to assume that the participants were well informed and trusting. Moreover, unlike what happened in many of the studies discussed in Chapter three, the questionnaires were not administered remotely by mail, as such a method of delivery provides the least control over completion and response bias.

L. R. Temoshok (2000) has argued that "type C cannot be assessed accurately by self-report questionnaires, which assume that people are fully aware of their emotions and how they handle them. This notion is contraindicated by my research that shows that the type C coping style involves a discrepancy between the conscious experience and self-report

of emotion, and physiological evidence of emotion or stress". (p.405). It may be, therefore, that the measurement of Type C by psychometric measurements, as in studies one and two are less than perfectly valid.

10.5 Immunological measurement considerations

As with personality, an assumption was made that the measures of immunological variables were reliable. Reasonable precautions were taken to control for known confounders at the point of measurement. For example, blood was taken at the same time of day at each time point for each participant to control for the influence of circadian rhythms, and patients were asked to rest before blood was taken to minimise any short term effects of physical exertion. However, it was not practically possible to standardise the timing of assessments between participants, and this may have influenced some of the hormones, such as Cortisol, and the subsequent findings. A further consideration is that known confounders such as diet, sleep and exercise were not recorded and have all been shown to influence various NI measures Vedhara & Irwin (2005).

10.6 Other factors

There has been good evidence for many years that depression suppresses functional measures of immunity, including NK cell activity and proliferative response to mitogens (Herbert & Cohen, 1993). The effects of mood disorders such as depression on inflammatory response (charecterised by increases in IL-1, IL-6, TNF alpha) are well documented, but it has also been shown that cell mediated immune activation may also be effected; some studies have shown, for example, an increase in serum levels of IL-2 receptor and evidence of a Th-2 like response (Maes, 2011).

Although the neuroendocrine effects of anxiety have been frequently described, the immunological effects are much less well understood (Hou & Baldwin, 2012). However, in ovarian cancer patients, anxiety has been found to be associated with a significantly enhanced Th1 like response (lower ratios of IFN-gamma (Th1 cells) versus IL-4 (Th2 cells)(Lutgendorf et al., 2008)

In a systematic review of psychological distress and its correlates in ovarian cancer Arden-Close et al. (2008) report three studies correlating distress and biomarkers. The studies found that (1) increased depressed mood was associated with increased levels of IL-6 in ascitic fluid (Costanzo et al., 2005), (2) higher levels of helplessness were associated with higher levels of vascular endothelial growth factor (Lutgendorf et al., 2002), and (3)

increased distress were associated with lower levels of NK cells in tumor-infiltrating lymphocytes (Lutgendorf et al., 2005). Thornton & Andersen (2006) suggest that longitudinal data may better clarify the role of subjective stress in immune function than cross-sectional studies, and that several studies (Shimamiya et al., 2005; Maes et al., 1999; Stone et al., 1987) have suggested that subjective stress may be more relevant than absolute levels.

It has been well known for many years that social support acts as a buffer against the psychological and the biological effects of stress (Herbert & Cohen, 1993). The relevance to ovarian cancer prognosis was demonstrated by (Lutgendorf et al., 2002) who found that social support was negatively associated with vascular endothelial growth factor (VEGF) which is a cytokine that plays a key role in tumour angiogenesis and ultimately survival. (Lutgendorf et al., 2002).

10.7 Future directions

There have been significant advances in immunology, but the relevance to breast cancer of changes in single immunological variables is unclear. Looking at the more global Th1-like:Th2-like balance was an attempt to see the 'bigger' and, perhaps, more clinically relevant picture. Further developments in tumour immunology may help to clarify the findings obtained in studies one and two. Rosenne et al. (2007) report on findings of synthetic ds-RNA, poly I–C, used in vivo in F344 rats. The trial suggested that Poly I-C increased the number of NK cells and protected the NK cells from suppression by surgery (immunosuppression). The implication is that as perioperative suppression of immunity is cited as a major risk factor in developing metastases, interventions that minimise this risk may improve long-term outcome. Although impressed with the findings, Schleifer (2007) cautions that further research is required. Sephton et al. (2006) however caution that research on NK cell function suffers from discrepancies in the methods of interpreting NK cytotoxicity data, and propose a model for interpreting these results.

Studying a group of women who not only have the same diagnosis, but also have the same medical and surgical treatments is in practice very difficult because treatments change relatively rapidly: when this study commenced, it was not envisaged that chemotherapy would be used as first line therapy, but the publication of trials showing a benefit for at least some of these women changed practice during the recruitment and follow up periods. However, even where treatment is standardised, for example to one type of chemotherapy, there will still be changes in the treatment individuals receive because of neutropenia, other side effects, and disease progression. This would have implications for multi-site studies.

An interesting group for future study would be men with low-risk localised prostate cancer. A study with such patients has the advantage of examining Personality and NI relationships in men, without the confounding effects on the immune system of chemotherapy, radiotherapy, hormone therapy and surgery.

10.8 Implications for clinical practice

Ranchor et al. (2010) suggested that one reason for continuing to explore the associations between personality and cancer is the potential for psychological programs to alter personality. However, given the results presented for study one and two, such an endeavour would seem premature. The predominantly negative findings of an association between personality traits and NI measures in studies one and two may provide some comfort to females who have a diagnosis of breast cancer.

10.9 Conclusion

The two studies reported in this thesis have generated a number of novel findings that could be explored further in future research taking into account the issues discussed above. However, in the comprehensive and relatively large studies presented above, there is little statistically significant suggestion that personality and psychological variables are related to immunological response in recently diagnosed breast cancer patients. Indeed, study two was designed to investigate the stability over time of any underlying personality and NI associations and to investigate the potential for an interaction between NI and higher and lower scorers on a measure of personality over time. It was predicted that conceptually related NI variables may show a consistent trend when assessed against higher or lower scorers on a measure of personality. The lack of any such trend fails to support such a hypothesis.

Clinically, therefore, there does not appear to be a strong case to justify the assessment of personality with the aim of attempting to predict immunological response post diagnosis of early breast cancer. Moreover, as evidence to support a particular personality or psychological variable (limited to those variables measured above) were conspicuous by their absence, the usefulness of attempting to modify personality (if personality is believed to be modifiable) is questionable as no particular personality or psychological variable (limited to those variables measured above) appears to predispose the holder to a favourable or unfavourable anti-cancer response.

Nevertheless, the results presented and conclusions drawn from this thesis are helpful

and contribute to the evidence against continuing the search for an association between personality and NI measures. Clinically, this thesis has contributed to the hypothesis that personality and psychological variables (limited to those variables measured above) are not a risk factor for a unfavourable NI response to early breast cancer. This may be reassuring to an early breast cancer who presents with the contrary belief and any associated psychological comorbidity such as guilt.

It was earlier suggested that that the human body is a complex Waldrop (1992) biological system, existing within a network of cultural, environmental and other systems Churchman (1971). This thesis was framed by a 'reductionistic complexity theory' stance following that of Cohen and Stewart (1994) in that complexity and reductionism are not incommensurable paradigms (Kuhn, 1970) but rather that complexity can be reduced to reveal rules which can in turn be used to create models. It is possible however, that the personality, psychological and NI variables statistically modelled within this thesis failed to show a relationship that may have been evident if other related variables were used.

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Appendix A

Publication 1: A randomised, controlled trial of the psychological effects of reflexology in early breast cancer

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A randomised, controlled trial of the psychological effects of reflexology in early breast cancer ☆

Donald M. Sharp [a,b,c,*], *Mary B. Walker* [a,c], *Amulya Chaturvedi* [d], *Sunil Upadhyay* [d], *Abdel Hamid* [d], *Andrew A. Walker* [a,c], *Julie S. Bateman* [c], *Fiona Braid* [c], *Karen Ellwood* [c], *Claire Hebblewhite* [c], *Teresa Hope* [c], *Michael Lines* [c], *Leslie G. Walker* [a,b,c]

[a] *The Institute of Rehabilitation, University of Hull, Kingston upon Hull, UK*
[b] *Hull York Medical School, The University of Hull, Kingston upon Hull, UK*
[c] *The Oncology Health Service, Queen's Centre for Oncology and Haematology, Hull and East Yorkshire Hospitals NHS Trust, Kingston upon Hull, UK*
[d] *Queen's Centre for Oncology and Haematology, Hull and East Yorkshire Hospitals NHS Trust, Kingston upon Hull, UK*

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ABSTRACT

Purpose: To conduct a pragmatic randomised controlled trial (RCT) to evaluate the effects of reflexology on quality of life (QofL) in women with early breast cancer.

Patients and methods: One hundred and eighty-three women were randomised 6 weeks post-breast surgery to self-initiated support (SIS) (comparator intervention), SIS plus reflexology, or SIS plus scalp massage (control for physical and social contact). Reflexology and massage comprised eight sessions at weekly intervals. The primary end-point was 18 weeks post surgery; the primary outcome measure was the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy (FACT-B) – breast cancer version. The secondary end-point was 24 weeks post surgery. Secondary outcome measures were the Hospital Anxiety and Depression Scale (HADS) and the Mood Rating Scale (MRS).

Results: At primary end-point, massage, but not reflexology, was significantly better than SIS on the TOI. Reflexology and massage were both better than SIS for MRS relaxation. Massage was better than reflexology and SIS for MRS easygoingness. At secondary end-point, reflexology, but not massage, was better than SIS on the TOI and MRS relaxation. There were no significant differences between reflexology or massage. There were no significant between group differences in HADS anxiety and depression.

Self-reported use of out of study complementary therapies indicated that this was unlikely to have a significant effect on findings.

Conclusions: When compared to SIS, reflexology and massage have statistically significant, and, for reflexology, clinically worthwhile, effects on QofL following surgery for early breast carcinoma.

☆ The study was registered with the International Standard Randomized Controlled Trial Registry (ISRCTN 87652313) (http://www.controlled-trials.com/).

* *Corresponding author:* Address: The Institute of Rehabilitation, University of Hull, 215 Anlaby Road, Kingston upon Hull, East Yorkshire, HU3 2PG, UK. Tel.: +44 1482 675046; fax: +44 1482 675636.
E-mail address: d.m.sharp@hull.ac.uk (D.M. Sharp).

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1. Introduction

1.1. Exposition

The diagnosis and treatment of breast cancer may cause clinically significant psychological and psychiatric morbidity.[1,2] In an attempt to minimise morbidity and enhance their quality of life (QofL), many women with breast cancer turn to complementary or alternative medicines (CAM)[3] and use of such interventions amongst cancer patients in general is widespread.[4–8]

Reflexology has its origins in Chinese medical thought and practice and consists of identifying and treating energy imbalances in the body through massage of reflexology points or 'terminals' in specific areas of the feet or hands.[9–12] A study in the United Kingdom, found reflexology was the most commonly used CAM (35.2%).[13]

Randomised controlled trials (RCTs) have reported positive effects of reflexology in premenstrual syndrome, Type II diabetes and low back pain.[14–16] A small RCT demonstrated a benefit for chemotherapy-related anxiety.[17] The effects of reflexology more generally on quality of life, mood and coping, in patients with cancer have not previously been evaluated in an adequately powered RCT.

Any beneficial effects of reflexology could be due to the purported effects on energy imbalances in the body or alternatively, they could be because reflexology enhances the relaxation response.[18] A randomised study of 96 women with locally advanced breast cancer demonstrated that relaxation training and guided imagery significantly enhanced mood and other aspects of quality of life during primary chemotherapy.[19] Approximately 50% of patients practised at least daily for 18 weeks and the intervention was of greatest benefit to them. Reflexology might be an alternative intervention for those patients unable to devote the time necessary to derive benefit from relaxation and guided imagery.

Alternatively, any effects of reflexology could be due to the additional social and physical contact the intervention entails.[20] A comparison of reflexology and an intervention which involves the same amount of physical and social contact but does not involve stimulation of reflexology points would clarify this. As reflexologists believe there are no reflexology points on the human scalp, scalp massage would be an appropriate choice of comparator intervention.

1.2. Aims of the study

The aims of the study, therefore, were to evaluate the effects of reflexology in comparison with two comparator interventions (self-initiated support (SIS) in the Oncology Health Centre and scalp massage) on cancer-related quality of life, relaxation, and mood, and adjustment, in women with newly diagnosed early breast cancer.

2. Methods

2.1. Recruitment procedures

Following local ethics approval (reference 01/01/010), patients were recruited at the Princess Royal Hospital, and Castle Hill Hospital, Kingston upon Hull, UK.

2.2. Study eligibility

Eligible patients met the following criteria: female; over 18 years of age; newly diagnosed histologically proven early breast cancer (T1, T2 [<3 cm], N0, N1a, M0); received breast surgery; WHO status 0 or 1; willing to give written, informed consent; and able to complete questionnaires. Exclusion criteria were history of cancer (excluding basal cell carcinoma), participating in another clinical trial and clinically significant cognitive impairment or dementia.

2.3. Enrolment and randomisation procedures

Patients were randomised 6 weeks (plus or minus 1 week) after breast surgery. The first patient was enrolled on 11th June 2002 and the final patient on 15th February 2005.

A permuted blocks randomisation sequence stratified for menopausal status, chemotherapy, and radiotherapy, was obtained online using Graph-Pad (http://graphpad.com): block size was 8 and was concealed. Sequences were stored in sealed, opaque, numbered envelopes. Randomisation was carried out remotely by telephone by the Clinical Trials Section within the Institute of Rehabilitation, Kingston upon Hull, UK. Staff involved in the randomisation procedure were independent of the clinical conduct of the study.

2.4. Setting

The study was carried out in the Oncology Health Centres, Kingston upon Hull. This service, staffed by clinical health psychologists and nurses, provides psychosocial support services for cancer patients and their relatives. Emphasis is placed on the prevention of psychological and psychiatric morbidity, and evidence-based interventions are offered to patients who develop clinically significant problems.[21–24]

2.5. Interventions

Women were randomised to one of three interventions:

- Intervention 1: reflexology plus self-initiated support (SIS) in the Oncology Health Centre.
- Intervention 2: scalp massage plus (SIS) (comparator intervention – identical amount of physical and social contact), or
- Intervention 3: SIS (comparator intervention – treatment as usual).

Patients randomised to reflexology or massage received 8 one-hour sessions at weekly intervals for 8 weeks commencing 7 weeks after surgery. Interventions were designed by our External Consultant, the Secretary of the Scottish Institute of Reflexology. Reflexology was administered by two therapists trained to the standards the Scottish Institute of Reflexology. Patients randomised to massage received gentle scalp massage according to a standardised protocol. Because reflexologists believe that the ears and neck have active reflexology points or 'terminals', care was taken to avoid these areas.

Reflexology and massage were administered according to standardised protocols. Protocols are detailed in Appendix

A. The External Consultant, monitored performance and adherence to the reflexology and massage protocols at regular intervals during the study. All three interventions included self-initiated support in the Oncology Health Centres. Women could access the Oncology Health Centres whenever they wished and received psychological support and treatment as usual in the Centres when they attended.

Each therapist saw a similar number of patients in each of the two physical contact arms of the study. As far as possible each patient had the same therapist throughout. Both treatments were given in the same rooms.

2.6. Conventional treatment

All patients underwent conventional oncological treatment according to current best practice.

2.7. Assessment schedule and outcome measures

Patients were assessed by a clinical and research specialist nurse, who was independent of treatment allocation and delivery, before randomisation (week 6 post surgery), 18 weeks after surgery (primary end-point 1) and 24 weeks after surgery (secondary end-point).

2.8. Baseline psychological assessment

Following recruitment to the study, before randomisation, patients completed the: Functional Assessment of Cancer Therapy (FACT-B). This is a widely used quality of life scale which has been used in previous research by ourselves and others to assess quality of life during both psychosocial and oncological interventions.[25–28] The FACT-B comprises two scales; the FACT-General Scale and the breast cancer concerns subscale.[28]

The Trial Outcome Index (TOI), composed of the sum of scores on the physical, functional and breast cancer concerns subscales, has been used in previous trials,[29] and its use in this investigation permits comparisons with this previous work.

Mood Rating Scale (MRS). This 6-item scale, based on the factor-analytically derived dimensions of the Profile of Mood States has shown acceptable reliability and sensitivity in UK populations.[30–33] The relaxation scale was of particular interest.

Hospital Anxiety and Depression Scale (HADS) used in the detection of clinically significant anxiety and depression.[34–38] Scores on the anxiety and depression scales were classified according to the recommended cut-off scores.[34] Mean scores were used to compare groups (square root transformation for anxiety and log transformation for depression).

Complementary Therapies Questionnaire (CMQ), an ad hoc questionnaire assessed concomitant use of complementary therapies in the three groups during the study.

Structured Clinical Interview for DSM IV^{TR} (SCID).[39] Clinical and research specialist nurses (behavioural oncology) or clinical health psychologists identified clinically significant psychiatric morbidity using the anxiety and mood disorders sections, of the SCID.

2.9. Outcome measures

2.9.1. Primary outcome

The primary outcome measure was the Trial Outcome Index (TOI) from the FACT-B at end-point 1 (week 18 post surgery).

2.9.2. Secondary outcomes

The secondary outcome measures (at weeks 18 and 24 post surgery) were the relaxation scale within the MRS, other MRS scales, the physical, functional, emotional, social and additional concerns scales of FACT-B, the HADS, the CMQ and the SCID, and the TOI at end-point 2 (week 24 post surgery).

2.10. Statistical methods

Power calculations were carried out using nQuery.[40] A10% difference in the primary outcome measure (FACT-B total) was considered clinically meaningful. With 60 patients in each group, there would be 95% power to detect a 10% difference in scores (a difference between means of 120 and 132, assuming a common standard deviation of 18).

Data were analysed using SPSS version 14. Alpha was set at 0.05 (two-tailed).

Pre-treatment equivalence of the three groups on clinical, psychological and sociodemographic data was assessed using one-way ANOVA for continuous variables and chi-square (exact test) for categorical variables.

An intention-to-treat analysis was carried out for the continuous outcome variables using univariate analysis of covariance, with age, T stage, and baseline values as covariates.[41] Where data were missing, the mean score for the cohort was imputed as analysis of the reasons for missing data suggested that it was not missing at random. To minimise the risk of a Type I error, paired comparisons were only considered when the three-group comparison was significant at $p < 0.05$ (two-tailed), and Bonferroni corrections used for paired comparisons.

A sensitivity analysis, without imputed data, with the same covariates and using the same analytical strategy was conducted.

For categorical outcomes, the three groups were compared using chi-square (exact test). Paired group comparisons were carried out using the same test. Paired comparisons were only considered appropriate when the three-group comparison achieved the critical p value. Where data were being compared at all three time points simultaneously, a Bonferroni correction was applied which adjusted the critical p value to $p < 0.015$. All data were included in the analyses of categorical variables, and missing data were not imputed as cohort averages would not have been appropriate.

3. Results

3.1. Recruitment

A consecutive series of 243 women were assessed for eligibility (Fig. 1). Of the 234 who were eligible, 183 (78.2%) agreed to be randomised. Four (1.7%) eligible patients refused randomisation because they did not wish reflexology.

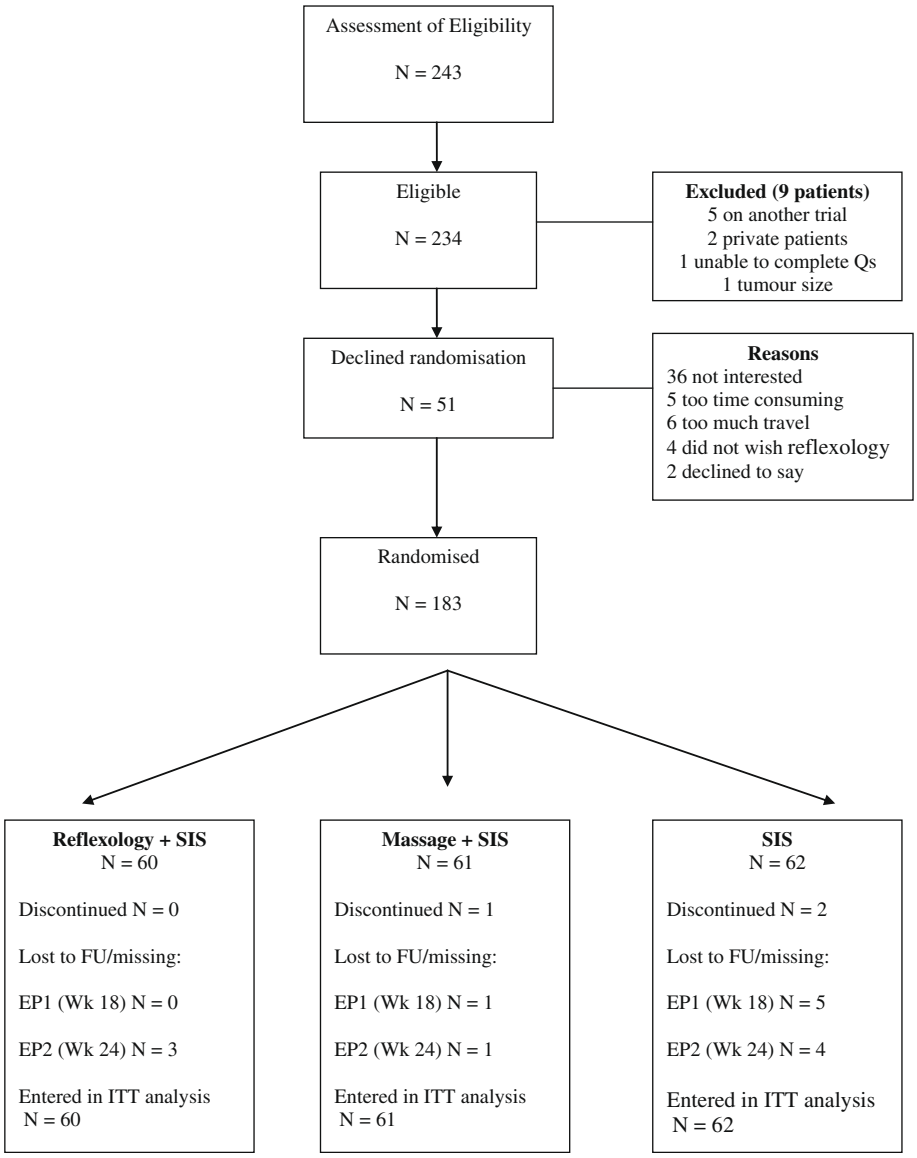

Fig. 1 – CONSORT flowchart of patient recruitment.

3.2. *Subjects*

Sixty patients were randomised to reflexology, 61 to massage, and 62 to self-initiated support.

The characteristics of the women by randomisation are shown in Table 1. The three groups did not differ significantly for any of the demographic, clinical or outcome variables.

3.3. *Missing data*

Complete data for all outcome measures were available for all 183 patients at baseline. At end-point 1, complete data were available for 177 patients. At end-point 2, complete data were available for 175 patients.

Complete data for all three time points were available for 57 (95%) patients randomised to reflexology, 60 (98%) randomised to massage and 56 (90%) randomised to SIS.

3.4. *Compliance with reflexology and massage*

Seventy-five percent of women received all eight sessions of reflexology and 75.4% received all eight sessions of massage. The mean number of sessions of reflexology was 7.65 (SD = 0.73, range 4–8)) and the mean number of massage sessions was 7.52 (SD = 1.06, range 2–8).

3.5. *Quality of life and mood*

3.5.1. *Primary end-point (week 18) (Table 2)*

At the primary end-point, TOI scores for the three groups differed significantly: massage patients had significantly higher scores on the TOI (indicating a better quality of life) than those receiving SIS. The differences between reflexology and SIS, and massage and reflexology, were not statistically significant.

Table 1 – Characteristics of patients.

	Total (*N* = 183)	Reflexology (*N* = 60)	Massage (*N* = 61)	SIS (*N* = 62)	*p* Value
Mean age (years)	58.78	59.37	57.70	59.36	.61
SD	10.31	10.47	10.12	10.23	
Age range	32–81	32–81	36–76	36–77	
Ethnicity					
Caucasian	183	60	61	62	1.00
Other	0	0	0	0	
ER status					
Positive	164	53	56	55	.78
Negative	18	6	5	7	
Unknown	1	1	0	0	
PR status					
Positive	150	47	52	51	.65
Negative	30	11	8	11	
Unknown	3	2	1	0	
T stage					
DCIS	3	2	0	1	.42
T1	124	40	43	41	
T2	52	15	18	19	
T3	4	3	0	1	
Breast surgery					
Wide local excision	144	47	46	51	.87
Quadrantectomy	1	1	0	0	
Mastectomy	26	8	11	7	
Mast + reconstruction	12	4	4	4	
Radiotherapy					
Yes	149	52	50	47	.31
No	34	8	11	15	
Chemotherapy					
Yes	30	10	11	9	.88
No	153	50	50	53	
Baseline TOI					
Mean	69.19	68.70	68.75	70.00	.80
SD	12.10	12.39	13.82	9.95	
Baseline HADS					
Depression					
<8	167 (91.3%)	54 (90.0%)	55 (90.2%)	58 (93.5%)	.84
8–10	9 (4.9%)	3 (5.0%)	3 (4.9%)	3 (4.8%)	
>11	7 (3.8%)	3 (5.0%)	3 (4.9%)	1 (1.6%)	
Anxiety					
<8	112 (61.2%)	37 (61.7%)	37 (60.7%)	38 (61.3%)	.63
8–10	45 (24.6%)	12 (20.0%)	15 (24.6%)	18 (29.0%)	
>11	26 (14.2%)	11 (18.3%)	9 (14.8%)	6 (9.7%)	
Baseline SCID					
Positive	19 (10.4%)	7 (11.7%)	7 (11.5%)	5 (8.1%)	.79
Negative	164 (89.6%)	53 (88.3%)	54 (88.5%)	57 (91.9%)	

The three groups did not differ on any of the five FACT scales, or FACT total score.

MRS scores at the primary end-point showed, massage and reflexology patients were significantly more relaxed than those randomised to SIS, and total MRS scores for reflexology and massage patients were significantly higher than SIS patients. At this end-point, massage patients were significantly more easy going than either reflexology or SIS patients.

Scores on HADS anxiety and depression did not differ significantly between the three groups. Also the proportion of patients obtaining one or more DSM IV diagnoses did not differ significantly.

3.5.2. *Secondary end-point (week 24) (Table 3)*

Reflexology patients scored significantly higher than those receiving SIS on the TOI. The differences between massage and SIS, and reflexology and massage, were not statistically significant.

The three groups differed on FACT functional wellbeing (one of three scales contributing to the TOI) and FACT total

Table 2 – Adjusted means (95% confidence intervals), overall comparisons and paired comparisons for the TOI, FACT scales, Mood Rating Scale (MRS) and HADS anxiety and depression, at end-point 1 (18 weeks) (statistically significant *p* values in bold.)

	A Reflexology + SIS N = 60	B Massage + SIS N = 63	C SIS N = 61	A versus B versus C F test p Value	A versus B F test p Value	A versus C F test p Value	B versus C F test P Value
TOI	72.25 (70.06–74.43)	73.06 (70.89–75.23)	69.05 (66.90–71.21)	**.02**	1.00	.13	.03
MRS – relaxation	100.94 (91.36–110.53)	100.23 (90.77–109.69)	74.02 (64.58–83.45)	**<.0005**	1.00	**<.0005**	**<.0005**
MRS – happiness	112.83 (105.51–120.14)	109.25 (101.97–116.53)	103.17 (95.98–110.36)	.17	1.00	.19	.73
MRS – energy	72.28 (61.89–82.67)	78.84 (68.52–89.17)	61.21 (50.96–71.47)	.06	1.00	.41	.06
MRS – clear headedness	114.64 (106.51–122.77)	117.02 (108.96–125.08)	108.97 (100.96–116.97)	.36	1.00	.98	.49
MRS – easy goingness	98.70 (90.12–107.27)	113.98 (105.49–122.46)	89.18 (80.73 to 97.63)	**<.0005**	**.04**	.37	**<.0005**
MRS – confidence	111.64 (105.06–118.22)	113.03 (106.49–119.56)	103.07 (96.6–109.54)	0.07	1.00	.21	.10
MRS – total	614.98 (581.90–648.05)	633.36 (600.61–666.11)	534.78 (502.20–567.36)	**<.0005**	1.00	**.003**	**<.0005**
FACT-B – physical wellbeing	23.30 (22.50–24,11)	24.24 (23.44–25.04)	22.90 (22.10–23.69)	.06	.32	1.00	.06
FACT-B – social/Family wellbeing	22.35 (21.42–23.28)	23.00 (22.08–23.93)	22.04 (21.13–22.95)	.34	1.00	1.00	.44
FACT-B – emotional wellbeing	20.36 (19.62–21.10)	20.36 (19.63–21.10)	19.97 (19.24–20.70)	.69	1.00	1.00	1.00
FACT-B – functional wellbeing	22.54 (21.60–23.5)	21.95 (21.02–22.9)	21.04 (20.11–21.97)	.08	1.00	.08	.52
FACT-B – additional concerns	26.34 (25.19–27.48)	26.85 (25.72–27.99)	25.20 (24.08–26.33)	.12	1.00	.49	.13
FACT-B – total Score	115.34 (112.29–118.32)	116.01 (113.02–119.90)	111.13 (108.16–114.09)	**.05**	1.00	.16	.07
HADS – anxiety (square root)	2.24 (2.11–2.38)	2.22 (2.09–2.35)	2.39 (2.25–2.52)	.17	1.00	.40	.25
HADS – depression (log_{10})	0.45 (0.39–0.51)	0.45 (0.40–0.51)	0.49 (0.43–0.54)	.67	1.00	1.00	1.00
HADS – total	**7.12 (6.11–8.11)**	**7.28 (6.28–8.28)**	**8.05 (7.01–9.09)**	.40	1.00	.60	.88

Table 3 – Adjusted means (95% confidence intervals), overall comparisons and paired comparisons for the TOI, FACT scales, Mood Rating Scale (MRS) and HADS anxiety and depression, at end-point 2 (24 weeks) (statistically significant *p* values in bold).

	A Reflexology + SIS N = 60	B Massage + SIS N = 63	C SIS N = 61	A versus B versus C F test p Value	A versus B F test p Value	A versus C F test p Value	B versus C F test p Value
TOI	74.82 (72.13–77.55)	72.39 (69.70–75.08)	69.42 (66.75–72.09)	**.02**	.62	**.02**	.37
MRS – relaxation	107.30 (97.91–116.69)	102.91 (93.65–112.18)	89.07 (79.82–98.32)	**.02**	1.00	**.02**	.12
MRS – happiness	110.34 (102.40–118.28)	103.98 (96.08–111.87)	103.08 (95.28–110.88)	.38	.79	.59	1.00
MRS – energy	68.62 (58.91–78.32)	76.92 (67.27–86.56)	61.45 (51.87–71.03)	.08	.69	.90	.07
MRS – clear headedness	115.62 (107.62–123.63)	118.53 (110.59–126.47)	113.91 (106.03–121.79)	.71	1.00	1.00	1.00
MRS – easy goingness	108.75 (99.26–118.25)	104.31 (94.92–113.71)	96.67 (87.31–106.02)	.20	1.00	.22	.77
MRS – confidence	114.32 (106.35–122.30)	105.14 (97.22–113.07)	104.42 (96.58–112.27)	.15	.32	.24	1.00
MRS – total	628.23 (589.91–666.55)	612.41 (574.47–650.36)	564.82 (527.07–602.56)	.06	1.00	.07	.24
FACT-B – physical wellbeing	24.57 (23.58–25.54)	23.82 (22.85–24.79)	23.10 (22.15–24.06)	.11	.85	.11	.90
FACT-B – social/family wellbeing	22.71 (21.76–23.67)	22.69 (21.74–23.64)	22.57 (21.64–23.51)	.98	1.00	1.00	1.00
FACT-B – emotional wellbeing	20.75 (19.98–21.52)	20.17 (19.40–20.93)	19.64 (18.88–20.40)	.13	.89	.13	.98
FACT-B – functional wellbeing	23.17 (22.01–24.33)	21.98 (20.83–21.13)	21.04 (19.90–22.17)	**.04**	.45	**.03**	.75
FACT-B – additional concerns	27.02 (25.88–28.16)	26.59 (25.46–27.72)	25.36 (24.24–26.48)	.11	1.00	.12	.38
FACT-B – total score	118.60 (114.93–112.26)	114.89 (111.26–118.52)	111.70 (108.10–115.30)	**.03**	.47	**.03**	.66
HADS – anxiety (square root)	2.14 (1.98–2.30)	2.2 (2.05–2.36)	2.36 (2.20–2.52)	.14	1.00	.17	.50
HADS – depression ($\log_{10}$)	0.39 (0.33–0.46)	0.44 (0.37–0.51)	0.50 (0.43–0.56)	.10	1.00	.09	.67
HADS – total	**6.38 (5.07–7.70)**	**7.46 (6.19–8.74)**	**8.25 (6.95–9.55)**	.14	.74	.14	1.00

Table 4 – Categorical outcomes for morbidity at the primary and secondary End-points.

		Total	A	B	C	*p* Value (A versus B versus C)
			Reflexology	Massage	Self-initiated support	
Primary end-point						
HADS Anxiety	<8	140 (79.5%)	48 (80.0%)	49 (81.7%)	43 (76.8%)	.70
	8–10	23 (13.1%)	6 (10.0%)	7 (11.7%)	10 (17.9%)	
	>11	13 (7.3%)	6 (10.0%)	4 (6.7%)	3 (5.4%)	
HADS depression	<8	165 (93.8%)	55 (91.7%)	55 (91.7%)	55 (98.2%)	.35
	8–10	10 (5.7%)	5 (8.3%)	4 (6.7%)	1 (1.8%)	
	>11	1 (0.6%)	0 (0.0%)	1 (1.7%)	0 (0.0%)	
SCID positive		9 (5.1%)	6 (10.2%)	3 (5.0%)	0 (0.0%)	.04[a]
SCID negative		166 (94.9%)	53 (89.8%)	57 (95.0%	56 100.0%)	
Secondary end-point						
HADS anxiety	<8	142 (81.1%)	47 (82.5%)	47 (78.3%)	48 (82.8%)	.94
	8–10	16 (9.1%)	5 (8.8%)	7 (11.7%)	4 (6.9%)	
	>11	17 (9.7%)	5 (8.8%)	6 (10.0%)	6 10.3%)	
HADS depression	<8	160 (91.4%)	52 (91.2%)	54 (90.0%)	54 (93.1%)	.81
	8–10	13 (17.4%)	5 (8.8%)	5 (8.3%)	3 (5.2%)	
	>11	2 (1.1%)	0 (0.0%)	1 (1.7%)	1 (1.7%)	
SCID positive		12 (6.9%)	6 (10.5%)	5 (8.3%)	1 (1.7%)	.17
SCID negative		163 (93.1%)	51 (89.5%)	55 (91.7%)	57 (98.3%)	

[a] When a Bonferroni correction for multiple comparisons is applied, $p < 0.015$ to achieve statistical significance.

score. In both cases, reflexology patients scored significantly higher than SIS. The differences between massage and SIS, and reflexology and massage, were not statistically significant.

The only significant difference for the MRS Scales was for relaxation: reflexology patients were significantly more relaxed than SIS patients.

Scores on HADS anxiety and depression did not differ significantly between the three groups. Also the proportion of patients obtaining one or more DSM IV diagnoses did not differ significantly (Table 4).

3.6. *Complementary medicine use*

None of the paired comparisons achieved statistical significance at baseline or either end-point.

3.7. *Sensitivity analysis*

A sensitivity analyses, using all available data, and without imputing missing data, was carried out for the TOI, FACT scales and MRS scales. All of the significant differences remained, and no new significant results emerged.

4. Discussion

This is the largest randomised controlled trial of reflexology reported in the cancer literature to date. The use of conventional outcome measures enables the magnitude of the effects obtained to be compared with those of other interventions (e.g. ATAC).[29] The study was carried out in a carefully defined population, namely women with early breast cancer who had received breast surgery six weeks prior to recruitment.

A consecutive series of 243 women were assessed for eligibility. Of the 234 who were eligible, 183 (78.2%) agreed to be randomised, this demonstrating a high level of acceptability in this population.

Compliance with reflexology and massage was very high and did not differ significantly between the groups.

Previously, we had shown using relaxation and guided imagery that the 48% of women with locally advanced breast cancer undergoing neoadjuvant chemotherapy who practised relaxation and guided imagery showed benefit. It appears that reflexology and massage are acceptable alternatives to such relaxation and guided imagery interventions.

The primary outcome measure was the Trial Outcome Index of FACT-B. At the primary end-point, massage, but not reflexology, was significantly better than self-initiated support. In a recent study in breast cancer conducted after the inception of the current trial Eton and colleagues[42] used a combination of distribution and anchor based approaches to the determination of minimally important differences (MID) in the TOI and concluded that the MID for FACT-B TOI is between 5 and 6 points. The adjusted mean difference between massage and self-initiated support was 4.01 points, which falls short of their suggested MID. At the secondary end-point, however, reflexology, but not massage, was significantly better than self-initiated support and the adjusted mean difference (5.4) does meet the MID criteria suggested by Eton and colleagues.[42] Week 18 was chosen as the primary end-point, because this was 4 weeks after the end of the final session of reflexology or massage. This suggests that the effects of reflexology may take longer to show on those quality of life variables assessed by the TOI.

The TOI appears an appropriate choice of outcome in that it proved more sensitive to intervention effects at the primary end-point than any of the five FACT-B subscales or indeed

FACT-B total scores. The three groups did differ on FACT-B total at the 0.05 level (with Bonferroni correction), but none of the paired comparisons was significant. At the secondary end-point, consistent with the TOI findings, FACT-B total scores also favoured reflexology over self-initiated support, as did scores on the functional wellbeing scale.

On MRS relaxation scale scores at the primary end-point, massage and reflexology patients were significantly more relaxed than those randomised to SIS. At the secondary end-point, however, only reflexology showed a statistically significant benefit over self-initiated support. These data suggest that the effect of reflexology and massage on TOI scores may be mediated by relaxation.

The only statistically significant difference to emerge between reflexology and massage was at the primary end-point when patients randomised to massage were more easy going than those receiving reflexology. These data are consistent with the TOI findings in that they also suggest that the beneficial effects of reflexology may have a slower onset than those of massage.

The three groups did not differ at any time point on the proportion of patients scoring in the normal, borderline, or clinically significant ranges of HADS anxiety or depression, or the proportion obtaining a positive DSM IV SCID diagnosis, or on transformed mean scores for HADS anxiety and depression.

The point prevalence of clinically significant psychiatric morbidity as assessed by the SCID and the proportion of patients scoring in the clinically significant range for anxiety and depression on the HADS did not differ significantly across the three arms of the trial at any time point. These rates were also very low in comparison with other studies of psychiatric morbidity in women with early breast cancer in the United Kingdom.[1,2] The low rates reported at recruitment and throughout the present study are consistent with our previous work on the benefits of fully integrated psychosocial support services.[19–24] Whatever the explanation, the low distress level in the main comparator intervention (self-initiated support) ensured a stringent test of the effectiveness of reflexology and scalp massage. Reported use of reflexology and massage out with the study protocol was very uncommon and unlikely to have materially affected the size of the between group differences in outcomes. Similarly, use of all other complementary therapies studied was similar across the three groups.

Scalp massage was chosen to control for the effects of extra physical and social contact, both of which could enhance relaxation and act as a buffer against stress and massage did enhance relaxation. Massage is often combined with aromatherapy, and beneficial effects of aromatherapy massage have been reported.[43–45] Further research to evaluate the relative contributions of the extra physical contact and the extra social contact would be of considerable interest.

The present study demonstrates that it is feasible to evaluate CAM using randomised controlled trial methodology employing conventional, well-validated outcome measures research funders should be encouraged, to support definitive trials of other complementary therapies using conventional, well-validated outcome measures in other cancer populations.

5. Conclusions

The findings reported here suggest that when compared to SIS, reflexology and massage have statistically significant, and, for reflexology, clinically worthwhile, effects on quality of life following surgery for women with early breast cancer accessing a UK NHS support centre.

Reflexology can therefore be considered an evidence-based complementary interventions for improving the quality of life of women with early breast cancer. Given that no statistically significant differences in efficacy were found between reflexology and the control intervention scalp massage, this latter intervention may also repay further investigation.

The present study further demonstrates that it is feasible to evaluate CAM using randomised controlled trial methodology employing conventional, well-validated outcome measures.

Conflict of Interest Statement

None declared.

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Trial Management Group (excluding authors): Professor M.J. Lind, Foundation Professor of Oncology, University of Hull, Mr. J. Wood, Divisional Manager (Cancer Services), Hull and East Yorkshire Hospitals NHS Trust, Mrs. J. Jenkinson, Breast Care Clinical Nurse Specialist, Hull and East Yorkshire Hospitals NHS Trust, Mr. W. Brown, Superintendent Radiographer, Hull and East Yorkshire Hospitals NHS Trust, Professor J.R.T. Monson, Professor of Surgery, University of Hull, Professor P.J. Drew, Professor in Tissue Engineering and Wound Healing, Hull York medical School, Mr. J. Fox, Consultant Breast Surgeon, Hull and East Yorkshire Hospitals NHS Trust, Mr. T. Mahapatra, Consultant Breast Surgeon, Hull and East Yorkshire Hospitals NHS Trust, Miss P. McManus, Consultant Breast Surgeon, Hull and East Yorkshire Hospitals NHS Trust.

Appendix A. Protocol for each reflexology session

A.1. *Preliminary techniques*

1. Cleanse both feet before treatment.
2. Massage both feet using warm up techniques with lotion.

A.2. *Treatment for right foot, work each area three times*

1. Hold Solar Plexus, breathing.
2. Work Diaphragm, area.
3. Work Lung and shoulder areas.
4. Work Eye, Eustachian Tube and Ear areas.
5. Work Parathyroids, Thyroid and Thyroid helpers areas.
6. Work Great Toe, Nail, Face, Head, Brain and Sinus areas.

6a. Work remaining Toes, Nail, Face, Head, Brain and Sinus areas.

7. Work Upper Lymphatic and Breast/Chest areas.
8. Work Arm, Knee and Hip areas.
9. Work Inguinal Lymphatic/Groin areas.
10. Work Stomach, Pancreas, Liver and Gall Bladder areas.
11. Work Adrenal, Kidney, Ureter and Bladder areas.
12. Work Spinal areas up and down foot [Coccyx, Sacral, Lumbar, Thoracic and Cervical].
13. Work Sacro-iliac, Ovary, Fallopian Tube and Uterus areas.
14. Work Sciatic area.
15. Work Small Intestines, Ileo-caecal valve, Ascending and Transverse colon areas.
16. Work Pituitary area
17. Warm down with massage techniques

A.3. *Treatment for left foot*

Repeat as for Right Foot with the following exceptions:

3 Work Lung, Heart and Shoulder areas.

10 Work Stomach, Pancreas and Spleen areas.

15 Work Small Intestines, Transverse Colon, Descending Colon, Sigmoid Colon and Rectum areas.

Appendix B. Protocol for each scalp massage session

B.1. *Preliminary techniques*

1. Patient seated, therapist behind, place hands slightly on top of head.
2. Support head and ask patient to breathe deeply 3 times.
3. Rock head gently to ease tension.
4. Breathe deeply three more times, rock head again.

B.2. *Scalp massage*

Confined to hairline, each move 3 times.

1. Circles around occiput, fingers, thumbs.
2. Friction around occiput.
3. Deep circles over scalp.
4. Windscreen wipers, fingers, heel of hands.
5. Sweep through hair.
6. Scalp movement, hands, fingers.
7. Deep circles and tension release upward movement.
8. Sweep through hair.
9. Finger tapping, hacking, ruffling, plucking.
10. Hair pulls.
11. Racking.
12. Hold head.
13. Hairline circles, full head circles.
14. Tension release upward movement.
15. Smooth hair, fingers gently through.
16. Repeat whole procedure again.
17. Hold head and breathe deeply three times.

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Appendix B

Publication 2: Alterations in the Th1/Th2 balance in breast cancer patients using reflexology and scalp massage

Alterations in the Th1/Th2 balance in breast cancer patients using reflexology and scalp massage

VICTORIA L. GREEN[1], AFRODITI ALEXANDROPOULOU[1], MARY B. WALKER[2], ANDREW A. WALKER[2], DONALD M. SHARP[2], LESLIE G. WALKER[2] and JOHN GREENMAN[1]

[1]Postgraduate Medical Institute, University of Hull in association with Hull-York Medical School; [2]Postgraduate Medical Institute, Oncology Health Centres, University of Hull and Hull and East Yorkshire Hospitals NHS Trust, in association with Hull-York Medical School, Kingston upon Hull, UK

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Abstract. The diagnosis and treatment of breast cancer can adversely affect quality of life. Here the aim was to determine the effects of reflexology on host defences and endocrine function in women with early breast cancer. Six weeks after surgery for early breast cancer, 183 women were randomly assigned to self-initiated support (SIS), SIS plus foot reflexology, or SIS plus scalp massage. Peripheral blood mononuclear cells and serum were isolated at T1 (6 weeks post surgery; baseline), T2 and T3 (4 and 10 weeks post completion of intervention, respectively). Lymphocyte phenotyping found that $CD25^+$ cells were significantly higher in the massage group compared with the SIS group at T3. The percentage of T cells, and more specifically the T helper subset expressing IL4, decreased significantly in the massage group compared with the SIS group at T3. This change was accompanied by an increase in the percentage of $CD8^+$ T cytotoxic cells expressing IFNγ in the massage group. Natural killer and lymphokine activated killer cell cytotoxicity measurements, serum levels of cortisol, prolactin and growth hormone, and flow cytometric assessment of their corresponding receptors all revealed no significant differences between the three groups of patients. This study provides evidence that the immunological balance of patients can be altered in a potentially beneficial manner by massage. The original trial was registered with the International Standard Randomised Controlled Trial Registry (ISRCTN87652313).

Introduction

Worldwide, over one million women are diagnosed annually with breast cancer, equating to a tenth of all new cancers and 23% of female cancers. Eighty percent of cases occur in women over 50 years of age, although it is also the most commonly diagnosed cancer in women under the age of 35 (1). The diagnosis and treatment of breast cancer is commonly associated with considerable psychiatric morbidity (2). For example, Hall *et al* (3) reported that of 269 women with early breast cancer, 49.6% were clinically anxious and 37.2% were clinically depressed in the first 3 months following surgery, whereas Burgess *et al* (4) found that of 222 women with early breast cancer, 48% were clinically anxious and/or depressed in the first year.

Complementary and alternative medicines (CAM) are widely used by patients with cancer to help them cope with the stress of the diagnosis and treatment of the disease (5,6); with an annual expenditure exceeding £1.6 billion in the UK (7). A recent study found that 69% of breast cancer survivors reported using some form of CAM, and of these, 73% changed or initiated use due to cancer diagnosis (8). Of the many forms of CAM available, reflexology has been reported to be the most popular amongst cancer patients in the UK (used by over 35% of those receiving CAM treatment) (9).

Stress-induced immunosuppression, including that associated with the diagnosis and treatment of cancer, is now a well established immunological phenomenon (10,11). A meta-analysis by Herbert and Cohen (12) revealed a relationship between stress and decreased functional immune measures, and a more recent meta-analysis of over 300 studies also showed that the immune outcomes were dependent on the types of stress involved, e.g., acute vs. chronic stress (13).

Various parameters of the immune system are adversely affected by stress. These include natural killer (NK) cell activity, the numbers and percentages of circulating white blood cells and immunoglobulin levels (12). NK cells, and their more active IL2-stimulated counterparts, lymphokine activated killer (LAK) cells, have anti-tumour properties, but are generally suppressed in cancer patients (14); the relationship of such effects to the development and/or progression of cancer has been widely discussed but remains unresolved (15-17).

T helper cells play a key role in controlling the immune response. These can be subdivided further into T-helper 1 (Th1)- and T-helper 2 (Th2)-like cells; defined by the cytokine repertoire they produce and the responses they

Correspondence to: Dr Victoria L. Green, Centre for Biomedical Research, University of Hull, Cottingham Road, Hull, HU6 7RX, UK
E-mail: v.l.green@hull.ac.uk

Key words: breast cancer, complementary and alternative therapies, stress, immune response, neuroendocrine

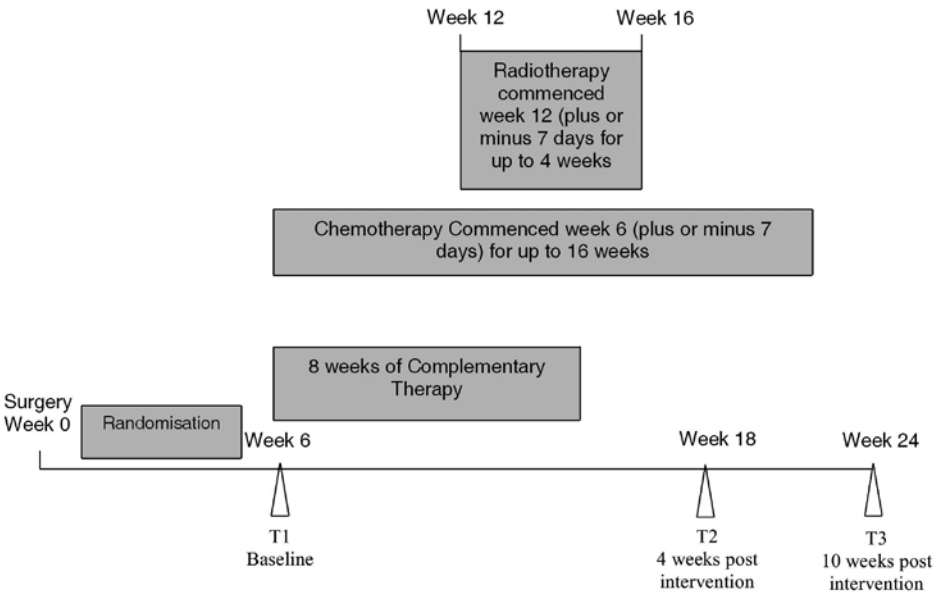

Figure 1. Timeline of complementary therapy (reflexology or scalp massage), chemotherapy and/or radiotherapy with respect to surgery and randomisation. T1 (week 6), T2 (week 18) and T3 (week 24) are the sample time points.

induce. Th1-like cells are principally involved in promoting cell-mediated immunity, initiating a cytotoxic response and generally are considered as the host's main anti-cancer mechanism (18), whereas Th2-like cells stimulate a humoral or antibody-mediated response, involved principally against extracellular pathogens. A stress response induces a shift in favour of Th2-like cells (10), which is observed in different types of cancer by changes in the concentrations of specific serum cytokines (19-21).

Stress can also alter the circulating levels of neuroendocrine hormones, in particular cortisol and to a lesser extent prolactin and growth hormone, whose effects on the immune system are widespread (22,23). These are caused, at least in part, through direct activation of specific cell surface receptors expressed by immune cells (24-26). The hypothalamic-pituitary-adrenal (HPA) axis is generally regarded as the most probable pathway by which the effects of psychosocial and complementary interventions on the immune system are mediated (27-29). The stress of diagnosis and treatment of cancer is also likely to act via the HPA axis and be involved in the progression of cancer (30).

Several studies suggest that psychosocial interventions aimed at promoting coping can alter the levels of HPA hormones (31-33). In patients with cancer, psychosocial interventions can normalize (34-36), or reduce (37) cortisol levels, as well as reduce prolactin levels (36). There is potential, therefore, for stress-reducing CAM interventions to influence the immune system via this neuroendocrine pathway.

A number of previous randomised trials evaluating the effects of various behavioural, psychosocial and complementary therapies in cancer patients have demonstrated both improvements in quality of life as well as changes in biological parameters (38-43). However, diagnostic and therapeutic heterogeneity, as well as the use of different tumour types and outcome measures, limit the conclusions that can be drawn.

Previous research on breast cancer patients has shown that patients do not always comply with relaxation and guided imagery (38,42); therefore, the present study was designed to evaluate an alternative well-received intervention to promote relaxation. Hence, the current randomised controlled trial evaluated the effects of reflexology and scalp massage on host defences and neuroendocrine function. Reflexology was compared with two comparator conditions, namely treatment as usual, which involves self-initiated support (SIS) in the Oncology Health Centres (44), and scalp massage, as a control for physical and social contact inherent in reflexology. Patients receiving reflexology or scalp massage had similar access to the Oncology Health Centres. It was hypothesised that, compared with SIS, women with breast cancer randomised to reflexology or to scalp massage would show reduced immunological and endocrine signs of stress. Immunologically this would include increases in the percentages of T helper cells expressing Th1 cytokines (i.e., IFNγ, IL2) and decreases in those expressing Th2 cytokines (i.e., IL4, IL10); increases in the percentage of overall T cells, NK cells, T cytotoxic cells and activated T lymphocytes with no change in B cell or monocyte number; and increases in NK/LAK activity. From a neuroendocrine perspective, it was hypothesised that decreases in cortisol, prolactin and growth hormone levels, along with decreases in the number of lymphocytes expressing their corresponding receptors would be observed.

Materials and methods

Design, approval and registration. This was a three-armed randomised, controlled trial. Data were collected at three time points: T1 (6±1 week post breast surgery), T2 and T3 (4 and 10 weeks post completion of CAM, respectively) (Fig. 1).

Ethical approval was obtained from Hull and East Yorkshire Local Research Ethics Committee (reference 01/01/010), and the study was registered with the International

Table I. Patient characteristics.

	Total (n=183)	Reflexology (n=60)	Massage (n=61)	SIS (n=62)	P-value
Mean age (years)	58.78	59.37	57.70	59.26	0.61
SD	10.31	10.47	10.12	10.23	
Age range	32-81	32-81	36-76	36-77	
Ethnicity					1.00
Caucasian	183	60	59	62	
Other	2	0	2	0	
ER status					0.78
Positive	164	53	56	55	
Negative	18	6	5	7	
Unknown	1	1	0	0	
PR status					0.65
Positive	150	47	52	51	
Negative	30	11	8	11	
Unknown	3	2	1	0	
T stage					0.42
DCIS	3	2	0	1	
T1	124	40	43	41	
T2	52	15	18	19	
T3	4	3	0	1	
Breast Surgery					0.87
Wide local excision	144	47	46	51	
Quadrantectomy	1	1	0	0	
Mastectomy	26	8	11	7	
Mast + reconstruction	12	4	4	4	
Radiotherapy planned					0.31
Yes	149	52	50	47	
No	34	8	11	15	
Chemotherapy planned					0.88
Yes	30	10	11	9	
No	153	50	50	53	

Standard Randomized Controlled Trial Registry (ISRCTN 87652313).

Patients. Women over 18 years of age with early breast cancer [T1, T2 (<3 cm), N0, N1a, M0], awaiting adjuvant therapy, were recruited consecutively after surgery. A diagnostically homogeneous group of patients was chosen to minimise the effects of disease and stage-related variables (Table I) (45). Patients with a previous cancer diagnosis or more advanced disease were not eligible for recruitment, as were those participating in other clinical trials and those suffering from clinically significant cognitive impairment or dementia.

Randomisation. Patients who gave written informed consent (n=183) were randomised to one of three interventions in the Oncology Health Centres at Castle Hill or Princess Royal Hospitals in Hull: self-initiated support (SIS) plus foot reflexology (n=60), SIS plus scalp massage (identical amount of comparator physical and social contact intervention from the same therapists who administered reflexology; n=61), or SIS alone (treatment as usual; n=62) (44).

A permuted block randomisation sequence for each stratum (menopausal status, chemotherapy and radiotherapy) was generated using Graph-Pad (http://www.graphpad.com); block size was 8 and was concealed. The sequences were stored in sealed, opaque, numbered envelopes. Randomisation was carried out remotely at the Clinical Trials Section of the Institute of Rehabilitation, University of Hull. Biological assessments were carried out in a completely blinded manner.

Interventions. Patients randomised to reflexology or massage received 8 sessions at weekly intervals for 8 weeks commencing 7 weeks after surgery. Eight sessions at weekly intervals was chosen on the recommendation of an external consultant who was formerly the Secretary of the Scottish Institute of Reflexology.

Reflexology was administered by two part-time staff who had been trained to the standards required for membership of the Scottish Institute of Reflexology. Their performance and adherence to the reflexology protocol was monitored at regular intervals during the study by an external consultant experienced in administering reflexology to patients with cancer.

Scalp massage was used as a control for attention, physical contact and non-specific therapist effects. Patients randomised to massage received gentle scalp massage from the same therapists according to a quality assured protocol. Since reflexologists believe that the ears and neck have 'terminals', care was taken to avoid these areas. Scalp massage was chosen, rather than foot or hand massage, because any manipulation or pressure to the feet and hands, according to reflexology theory, will stimulate pressure points and, therefore, will be a weak form of reflexology rather than an appropriate 'placebo'.

Women randomised to SIS were invited to attend, or telephone, one of the Oncology Health Centres whenever they wished. They received 'treatment as usual' in the Centres when they attended, as did those randomised to reflexology or massage. The Oncology Health Centres are staffed by clinical health psychologists and nurses, and provide psychosocial support services for more than 1,500 new patients per year and almost as many new relatives. Emphasis is placed on the prevention of psychological and psychiatric morbidity, and evidence-based psychopharmacological and psychotherapeutic interventions are offered to patients who develop clinically significant problems. Patients can access the service without referral, and appointments are not necessary.

In order to control for practitioner variables, each practitioner saw a similar number of patients in each of the two physical contact arms of the study. As far as possible, each patient had the same therapist throughout, and both treatments were given in the same rooms.

Conventional treatment. All patients underwent conventional treatment according to current best practice (surgery, radiotherapy, chemotherapy and hormone therapy) as clinically indicated.

Biological assays

Peripheral blood mononuclear cell (PBMC) isolation. Venous blood (50 ml) was collected into syringes containing 1,250 IU heparin from all patients at T1, T2 and T3 and transported to the Centre for Biomedical Research at the University of Hull. PBMCs were isolated using Ficoll-Hypaque (Sigma), density gradient centrifugation (46). The PBMCs were washed with phosphate-buffered saline (PBS; pH 7.4), enumerated using a haemocytometer and assessed for viability by trypan blue exclusion, before resuspension in foetal bovine serum (Invitrogen) containing 10% (v/v) dimethylsulphoxide (Sigma). Aliquots were then frozen at 1˚C/min and stored in liquid nitrogen until use.

Serum separation. Venous blood (8 ml) was collected into serum separator tubes at approximately the same time of day (to control for diurnal variation) for each patient at T1, T2 and T3. These were incubated at 4˚C for 30 min before centrifugation at 1,500 x g for 10 min. The top serum layer was aliquoted and stored at -80˚C until ELISA analysis.

Immunophenotyping of peripheral blood mononuclear cells. An aliquot of PBMCs from each of the three time points was resuspended in complete medium [RPMI-1640 medium supplemented with 10% (v/v) foetal bovine serum, penicillin (100 U/ml)/streptomycin (100 μg/ml) and L-glutamine (2 mM), all purchased from Invitrogen]. Approximately $2x10^5$ PBMCs were labelled with 5 μl (0.1 mg/ml) of one of a panel of fluorescein isothiocyanate (FITC)-conjugated monoclonal antibodies (AbD Serotec, Oxford, UK) for 30 min in the dark at room temperature. These antibodies were specific for the surface markers: CD2 and CD3 (T cells), CD4 (T helper cells), CD8 (T cytotoxic cells), CD16 and CD56 (NK cells), CD14 (monocytes), CD19 (B cells) and CD25 (activated lymphocytes/regulatory T cells). Purified mouse IgG1-FITC was used as an irrelevant control. Following labelling, the cells were washed with PBS, pH 7.4, containing 0.1% (w/v) bovine serum albumin and 10 mM NaN_3 (PBS/BSA/azide; Sigma) and recovered by centrifugation before immediate acquisition of 10,000 cells/sample using a FACS Calibur™ machine (Becton Dickinson, Biosciences, Oxford, UK). Analysis was performed using CellQuest Pro V software (Becton Dickinson) with gates being set around the lymphocytes and the monocytes based on forward scatter/side scatter distribution. Histograms were drawn for each antibody using the lymphocyte gate, except for CD14 which used the monocyte gate. The plots using the irrelevant control were used to set a marker whereby ≤3% of cells were positive with this reagent. To calculate the percentage of specific binding, the irrelevant value was subtracted from the percentage of cells staining with the test antibody.

Th1/Th2 cellular determination. The method used was a modification of that by Jung *et al* (47). Briefly, PBMCs were incubated for 4 h at 37˚C with 5% CO_2 in either activation medium [complete RPMI containing ionomycin (2 μg/ml), brefeldin A (20 μg/ml) and phorbol 12-myristate 13-acetate (20 ng/ml), all from Sigma] or control medium [complete RPMI containing solely brefeldin A (20 μg/ml)]. Approximately $2x10^5$ PBMCs, were then incubated for 30 min in the dark with 5 μl (0.1 mg/ml) of FITC labelled monoclonal antibody specific for the surface markers CD3 or CD8; purified mouse IgG1 provided the irrelevant control (AbD Serotec). After incubation, the cells were washed with PBS/BSA/azide, and fixed using Leucoperm A (AbD Serotec) for 15 min in the dark. Following further washes, the cells were permeabilised with Leucoperm B before being incubated with 5 μl r-phycoerythrin (RPE)-labelled anti-cytokine antibody [IL2, IFNγ (Becton Dickinson), IL4, IL10 (AbD Serotec), 0.1 mg/ml] for 30 min at room temperature in the dark. TNFα (Becton Dickinson) provided a positive activation control, and purified mouse IgG1 provided the negative control. Cells were acquired and analysed as described previously using a FACS Calibur™. The lymphocyte subset was gated on the basis of forward and side scatter characteristics (Fig. 2A). Stimulated lymphocytes produced Th1 (IL2/IFNγ) and Th2 (IL4/IL10) cytokines (Fig. 2B). CD3 was used as a total lymphocyte marker, and the CD4 fraction was determined by subtraction of the percentage of $CD8^+$ cells. Unstimulated controls (Fig. 2C) were used to set the quadrants so that <1% of these cells were positive for both the surface and the cytokine antibodies (upper right quadrant).

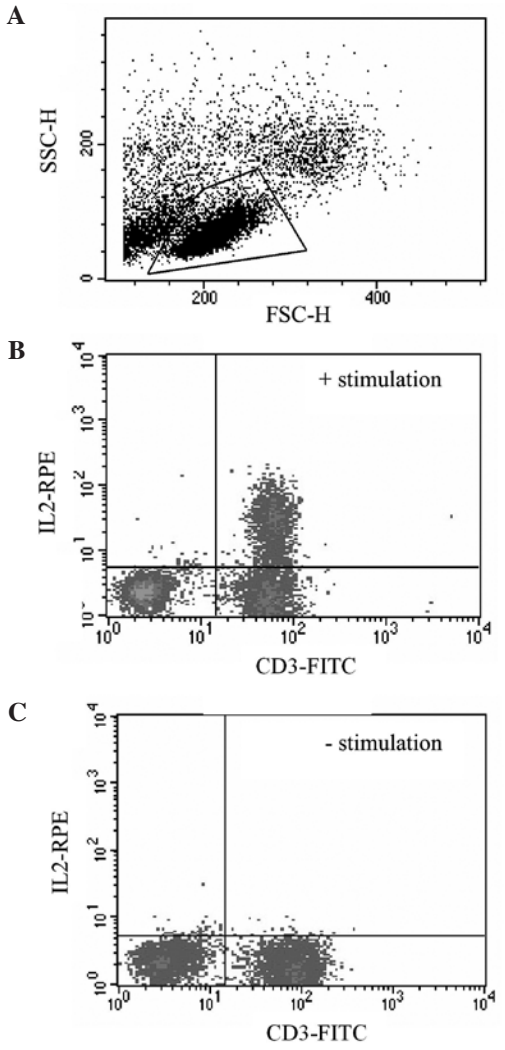

Figure 2. Flow cytometry analysis gating strategies. (A) Forward scatter (FSC-H) and side scatter (SSC-H) characteristics of a PBMC population with the lymphocytes isolated in the quadrilateral gate. Gated-PBMCs labelled with both CD3-FITC and IL2-RPE, with (B) and without (C) prior stimulation with PMA, ionomycin and brefeldin.

NK and LAK cell cytotoxicity. The cytotoxic activity of both NK and LAK cells within the PBMC population was determined using a modification of the Live/Dead Cell-mediated cytotoxicity kit (Molecular Probes/Invitrogen) (48). Briefly, $2x10^6$ log-phase growing target cells [erythroleukaemic cell line (K562)] for NK and Burkitt lymphoma cell line (Daudi) for LAK] were prelabelled with a green fluorescent membrane dye ($DiOC_{18}(3)$, 30 μM) for 1 h at 37˚C. Once thawed PBMCs were incubated for 48 h in complete RPMI medium with or without recombinant IL2 (500 U/ml; AbD Serotec) (49) to stimulate LAK formation and for NK determination respectively; this also allows for the adherence and removal of monocytes. Following washing, viable effector cells were enumerated using trypan blue exclusion, and 1.5 or $3x10^5$ cells were added to $3x10^4$ target cells to give a 5:1 and 10:1 ratio, respectively, in a total volume of 140 μl. An equal volume of the membrane impermeable dye, propidium iodide (PI; 150 μM; Sigma), was added to each tube before centrifuging briefly at 1,000 x g for 1 min and incubation at 37˚C for 3.5 h in a humidified atmosphere. Appropriate controls of target and effector cells alone were also prepared. Following incubation, the cytotoxic activity was analysed by flow cytometry; samples were acquired for 45 sec with no gating and data were obtained for both the green (FL-1, $DiOC_{18}(3)$) and red (FL-3, PI) fluorescence, as well as forward and side scatter characteristics. Data analysis was performed on dot plots of FL-1 vs. FL-3. Quadrants were set using the appropriate controls to exclude the effector cells from the analysis, and the lysis of target cells was determined from the percentage of cells present in the upper right (UR) quadrant (green and red positive, i.e., dead target cells) divided by the total number of green target cells (UR + LR).

Serum hormone measurements. The hormones prolactin, cortisol and growth hormone were all measured in duplicate, using Enzyme Linked Immunosorbant Assay (ELISA, DRG Instruments GmbH, Germany). All samples from the same patient were analysed on the same ELISA plate to minimise intra-patient variability. Prolactin levels were measured using a standard solid phase sandwich ELISA technique, with a lower detection limit of 2 ng/ml, according to the manufacturer's protocol. Cortisol levels were analysed using a competitive ELISA with a lower detection limit of 2.5 ng/ml, according to the manufacturer's protocol. Growth hormone levels were determined using a solid phase Enzyme Amplified Sensitivity Immunoassay, in which monoclonal antibodies against distinct epitopes of human growth hormone are used to create the sandwich; with a lower detection limit of 0.11 μIU/ml. Data for each sample were extracted from the standard curve.

Hormone receptor measurements. Following activation of PBMCs as described above, the cells which were to be used for the detection of the prolactin receptor (PRL-R) and the glucocorticoid receptor (Gluc-R) were permeabilised. PBMCs were then incubated for 30 min at 4˚C with 5 μl (1 mg/ml) mouse anti-human antibodies: GH-R unconjugated, Gluc-R-FITC conjugated (both AbD Serotec) and PRL-R Ab-1 (B6.2) unconjugated (Neomarkers, Fremont, CA). Purified mouse IgG1 was used as the negative control. Following washing with PBS/BSA/azide unconjugated antibodies were detected using a secondary rabbit anti-mouse F(ab'), IgG:FITC antibody (AbD Serotec) for 30 min at 4˚C. PBMCs were washed again before flow cytometric analysis.

Statistics. Data were analysed using SPSS v13 for MS Windows. α was set at 0.05 (two-tailed). The comparability of the three groups at baseline (T1; clinical, socio-demographic and psychosocial variables) was assessed using one-way analyses of variance (ANOVA) for continuous variables, and the Chi-square exact test for categorical variables. All data were included in the analyses of categorical variables, and missing data were not inputed, as cohort averages would not have been appropriate.

An intention to treat analysis was carried out (50), and continuous variables were analysed using univariate analyses of covariance (ANCOVA), with age, tumour stage and baseline (T1) values as covariates. To minimise the risk of a Type I error, paired comparisons were only considered when the f-value for the three-group comparison was significant, and Bonferroni corrections were applied for subsequent paired comparisons. Data were log transformed when the distributions differed significantly from the normal.

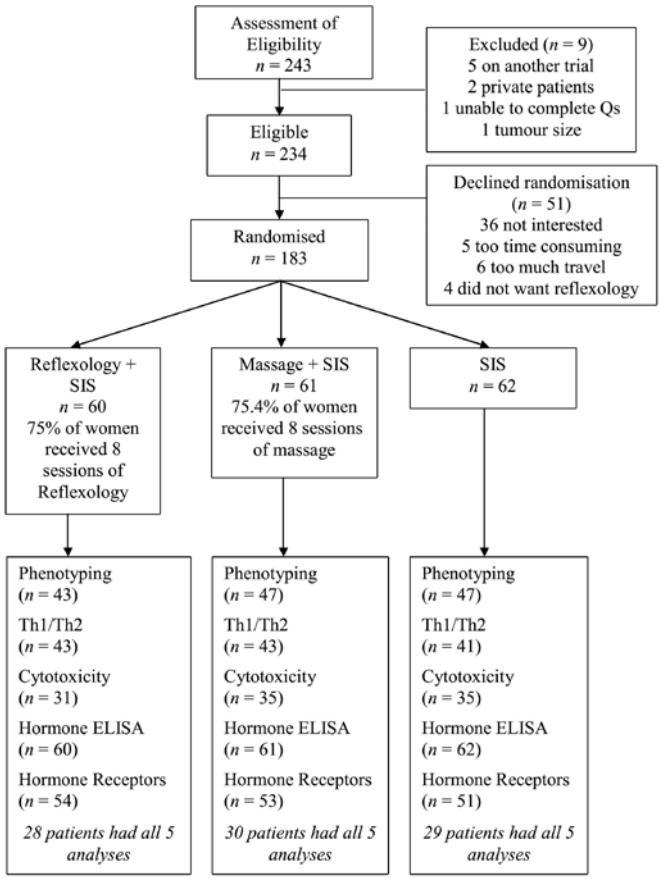

Figure 3. Consort flow chart depicting the recruitment of patients into the three treatment groups and the use of samples in each of the biological assays employed.

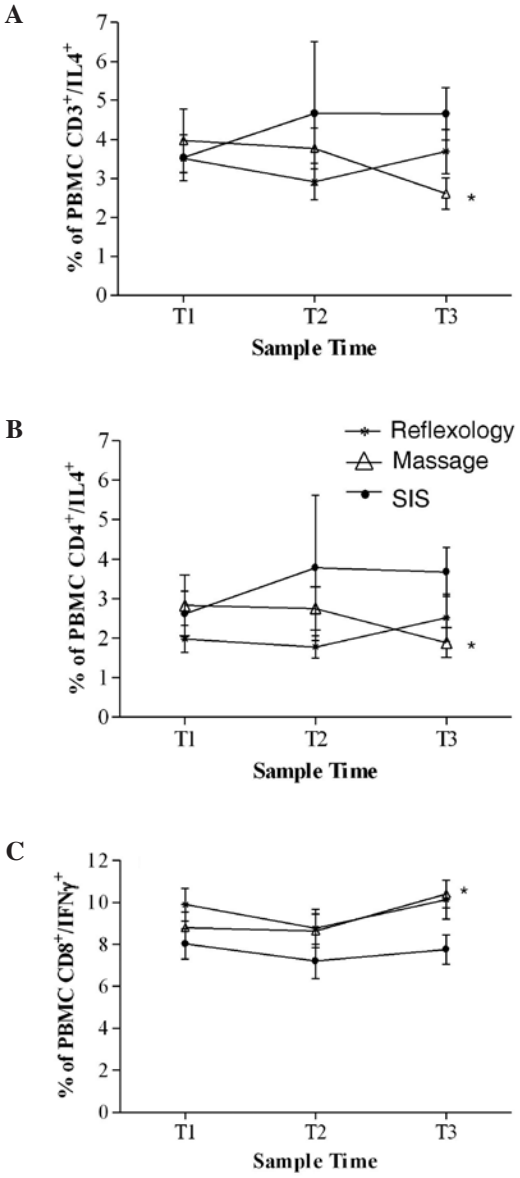

Figure 4. Percentage of PBMCs from patients with early breast cancer positive for (A) CD3/IL4 (B) CD4/IL4 and (C) CD8/IFNγ, at T1, T2 and T3. *Significant differences between groups ($p<0.05$).

Results

Recruitment and use of samples. A consecutive series of 243 women was assessed for eligibility (Fig. 3). Of the 234 who were eligible, 183 (78.2%) agreed to be randomised. The most common reason for not wishing to participate was lack of interest, often because women expressed a desire to 'get on with their lives'. Four (1.7%) eligible patients refused randomisation because they did not wish to partake in reflexology.

Sixty patients were randomised to reflexology, 61 to massage and 62 to SIS alone. The characteristics of the women by randomisation are shown in Table I. The three groups did not differ significantly for any of the demographic or clinical variables, including radiotherapy and/or chemotherapy.

The CONSORT diagram (Fig. 3) indicates the samples used for the different biological assays. The number of aliquots of PBMCs obtained from each patient varied, and there were insufficient aliquots from each patient to be used for all techniques. Samples were selected for each analysis on the basis that there were sufficient aliquots of PBMCs present for each of the three time points to enable a full dataset to be collected.

Effects of reflexology and massage on phenotypic distribution of PBMCs. Flow cytometry was used to determine the changes which occurred in the distribution of the mononuclear cell populations (Table II). At T3, ANCOVA showed that the percentage of $CD25^+$ lymphocytes in the patients receiving massage was significantly higher than for those in the SIS group ($p=0.05$). No significant between-group differences were found for the remainder of the phenotypic markers.

The percentages of NK, B cells, $CD3^+$ and $CD4^+$ T cells were very similar to those previously reported both pre- and post-psychosocial intervention by Carlson *et al* in a cohort of patients with either breast or prostate cancer (51).

Effects of reflexology and massage on Th1/Th2 cell balance in PBMCs. Table III shows the results from the flow cytometry method used to determine the percentage of lymphocytes producing Th1 (IL2/IFNγ) and Th2 (IL4/IL10) cytokines. ANCOVA showed a significantly lower percentage of $CD3^+$ cells expressing IL4 at T3 in the massage patients compared with the SIS patients ($p=0.02$, Fig. 4A). The same was true in the $CD4^+$ subset of T cells expressing IL4 which mirrored the results of the $CD3^+$ cells (Fig. 4B; $p=0.02$).

Table II. Mean percentage of PBMCs from early breast cancer patients expressing phenotypic markers at T2 and T3.

	A Reflexology + SIS	B Massage + SIS	C SIS	A vs. B vs. C f-test p-value	A vs. B f-test p-value	A vs. C f-test p-value	B vs. C f-test p-value
T2							
CD3	69.6±2.8	70.2±2.6	66.3±2.7	0.56	1.0	1.00	0.93
CD2	75.3±3.6	75.0±3.5	70.2±3.5	0.51	1.0	0.92	0.97
CD4	47.0±2.3	45.7±2.2	44.2±2.2	0.69	1.0	1.00	1.00
CD8	20.6±1.1	19.7±1.1	22.5±1.1	0.17	1.0	0.64	0.19
CD16	16.7±1.2	16.8±1.1	17.6±1.1	0.83	1.0	1.00	1.00
CD56	9.9±1.2	11.1±1.1	11.4±1.1	0.62	1.0	1.00	1.00
CD14	7.8±1.1	8.2±1.1	8.4±1.1	0.93	1.0	1.00	1.00
CD19	6.5±0.8	7.4±0.8	7.5±0.8	0.63	1.0	1.00	1.00
CD25	7.3±1.0	6.5±1.0	5.3±1.0	0.36	1.0	0.47	1.00
T3							
CD3	71.8±2.0	69.8±1.9	69.9±1.9	0.71	1.00	1.00	1.00
CD2	75.8±3.1	74.7±2.9	74.7±2.9	0.96	1.00	1.00	1.00
CD4	47.8±1.8	48.0±1.8	47.5±1.8	1.00	1.00	1.00	1.00
CD8	21.8±1.5	21.9±1.4	21.1±1.4	0.92	1.00	1.00	1.00
CD16	18.2±1.8	20.2±1.8	17.8±1.7	0.59	1.00	1.00	1.00
CD56	13.5±1.7	14.8±1.6	13.2±1.6	0.76	1.00	1.00	1.00
CD14	9.3±1.0	9.3±1.0	8.1±1.0	0.60	1.00	1.00	1.00
CD19	6.8±0.9	9.3±0.9	7.4±0.9	0.11	0.14	1.00	0.38
CD25	10.1±1.5	10.8±1.5	5.7±1.5	0.03[a]	1.00	0.12	0.05[a]

Values are estimated marginal mean ± SEM. [a]Denotes significant values. Also shown are the results from the univariate analysis of variance. All values are adjusted for baseline.

At T3, ANCOVA showed that a significantly higher percentage of $CD8^+$ cells were expressing IFNγ in the massage group compared with the SIS group (p=0.02, Fig. 4C). No significant between-group differences were found for any of the other T cell subsets expressing Th1- or Th2-like cytokines.

Effects of reflexology and massage on the cytotoxic activity of PBMCs. The NK and LAK cell activity was determined at effector:target ratios of 5:1 and 10:1 using a flow cytometry-based method. These ratios were chosen since they provided the most reproducible results in initial studies and spared sufficient PBMCs for use in other experiments. There were no significant between-group differences in the cytotoxic activity of either NK or LAK cells at any time point (Table IV).

Effects of reflexology and massage on serum hormone levels and receptor expression in PBMCs. Analysis of the serum hormones or hormone receptors (cortisol, prolactin and growth hormone) also found no significant between-group differences (Tables V and VI). All the values obtained for the serum hormone concentrations were within the normal range described in the manufacturer's protocols.

Discussion

This study of 183 women with early breast cancer is the largest randomised, controlled trial of reflexology reported to date. Over 78% of a consecutive series of eligible women consented to participate in the study, which suggests that the results are representative and generalisable.

Scalp massage was chosen to control for the effects of extra physical and social contact, both of which could enhance relaxation and act as a buffer against stress. Massage is often combined with aromatherapy, and beneficial effects have been reported previously (52). Research designed to evaluate the relative contributions of the extra physical and social contact would be of considerable interest, especially in light of this study's findings.

Imbalances in proportions of immune cells in patients with cancer have been previously documented (53,54), resulting in generalised and/or specific immunosuppression. Here the only change observed in lymphocyte subsets was the increase over time in the percentage of $CD25^+$ cells from patients receiving either massage or reflexology, and by T3 the difference was significantly greater in the massage patients compared with the SIS group. The current finding is

Table III. Mean percentage of Th1 (IL2, IFNγ) and Th2-like (IL4, IL10) T (CD3), cytotoxic (CD8) and helper (CD4) cell proportions in PBMCs from breast cancer patients at T2 and T3.

	A Reflexology + SIS	B Massage + SIS	C SIS	A vs. B vs. C f-test p-value	A vs. B f-test p-value	A vs. C f-test p-value	B vs. C f-test p-value
T2							
CD3/IL2	23.5±1.5	25.2±1.5	22.5±1.6	0.45	1.00	1.00	0.64
CD3/IFNγ	19.3±1.1	20.3±1.1	17.2±1.2	0.17	1.00	0.61	0.19
CD3/IL4	2.9±1.1	3.9±1.1	4.9±1.2	0.48	1.00	0.69	1.00
CD3/IL10	1.2±0.4	1.5±0.4	0.9±0.4	0.63	1.00	1.00	1.00
CD8/IL2	2.6±0.2	2.8±0.2	2.5±0.2	0.59	1.00	1.00	0.93
CD8/IFNγ	8.1±0.6	9.2±0.6	8.0±0.6	0.26	0.51	1.00	0.45
CD8/IL4	0.8±0.17	1.2±0.2	1.0±0.2	0.21	0.25	0.92	1.00
CD8/IL10	0.4±0.15	0.4±0.2	0.5±0.2	0.82	1.00	1.00	1.00
CD4/IL2	20.9±1.4	22.5±1.4	20.0±1.5	0.46	1.00	1.00	0.66
CD4/IFNγ	10.7±0.8	11.2±0.8	9.6±0.8	0.32	1.00	0.87	0.43
CD4/IL4	1.8±1.1	2.9±1.2	4.1±1.2	0.38	1.00	0.49	1.00
CD4/IL10	0.7±0.4	1.1±0.4	0.6±0.4	0.57	1.00	1.00	1.00
T3							
CD3/IL2	26.7±1.7	26.7±1.8	26.0±1.8	0.94	1.00	1.00	1.00
CD3/IFNγ	20.5±1.0	21.2±1.1	19.5±1.1	0.52	1.00	1.00	0.76
CD3/IL4	3.7±0.6	2.5±0.6	4.8±0.6	0.03[a]	0.44	0.56	0.02[a]
CD3/IL10	0.9±0.2	0.8±0.2	0.9±0.2	0.72	1.00	1.00	1.00
CD8/IL2	3.0±0.2	2.8±0.3	2.5±0.3	0.48	1.00	0.70	1.00
CD8/IFNγ	9.4±0.6	10.6±0.6	8.3±0.6	0.03[a]	0.45	0.59	0.02[a]
CD8/IL4	1.7±0.3	1.0±0.3	1.0±0.3	0.07	0.12	0.17	1.00
CD8/IL10	0.3±0.1	0.2±0.1	0.3±0.1	0.86	1.00	1.00	1.00
CD4/IL2	24.9±1.6	24.1±1.7	23.5±1.7	0.82	1.00	1.00	1.00
CD4/IFNγ	11.6±0.7	11.1±0.7	11.2±0.7	0.89	1.00	1.00	1.00
CD4/IL4	2.7±0.6	1.7±0.6	3.7±0.6	0.02[a]	0.9	0.20	0.02[a]
CD4/IL10	0.8±0.2	0.6±0.2	0.7±0.2	0.85	1.00	1.00	1.00

Values are estimated marginal mean ± SEM. [a]Denotes significant values. Also shown are the results from the univariate analysis of variance. All values are adjusted for baseline.

consistent with previous results from the present group who reported that the percentage of $CD25^+$ cells was significantly greater in breast cancer patients receiving relaxation training and guided imagery compared with SIS (38). Research in the 1990s showed that activated $CD25^+$ T lymphocytes could induce tumour cell death and play a role in inhibiting tumour growth in animal models (55,56), suggesting that the enhanced percentage of $CD25^+$ cells in the present study could be beneficial to breast cancer patients. However, more recent work has focused intensely on a subpopulation of $CD25^+$ cells, namely $CD4^+CD25^+$ cells, now commonly known as T regulatory cells. These cells are frequently increased in patients with several types of malignancies and are correlated positively with disease stage and poor prognosis (57). They also play a role in immune evasion mechanisms employed by cancer cells (58), and can decrease the activity of $CD8^+$ T cells and NK cells (59). Further characterisation of the $CD25^+$ subpopulations was not possible due to the lack of cells for the analysis of T regulatory cell markers such as FoxP3, GITR and CD127.

Previously, a small scale study of breast cancer patients found increases in lymphocyte and NK cell numbers over time following massage therapy and progressive muscle relaxation (60). Hypnotic guided imagery in breast cancer patients has also been reported to increase absolute NK cell numbers (61), but this increase was not maintained after a 3-month follow-up. In the current study, no between-group differences were observed in NK cell numbers, and changes in $CD25^+$ lymphocytes were only apparent at 6 months.

In support of a delayed NK cell response, a randomised controlled study by Fawzy *et al* (43) evaluating the effect of a 6-week structured psychiatric group intervention in melanoma patients who had undergone surgery, demonstrated an increase in absolute NK and large granular lymphocyte numbers which

Table IV. Mean percentage K562 and Daudi cell death induced by NK and LAK cells respectively, in PBMCs from breast cancer patients at 5:1 and 10:1 (effector:target) ratios at T2 and T3.

Ratio	A Reflexology + SIS	B Massage + SIS	C SIS	A vs. B vs. C f-test p-value	A vs. B f-test p-value	A vs. C f-test p-value	B vs. C f-test p-value
T2							
NK 5:1	5.2±1.1	6.1±1.0	5.5±1.1	0.83	1.00	1.00	1.00
NK 10:1	5.4±1.4	7.8±1.3	7.6±1.8	0.42	0.65	1.00	1.00
LAK 5:1	5.8±0.9	4.6±0.9	6.2±1.0	0.44	1.00	1.00	0.69
LAK 10:1	5.8±1.6	4.5±1.4	5.2±1.8	0.82	1.00	1.00	1.00
T3							
NK 5:1	5.5±1.1	5.5±1.1	8.2±1.1	0.12	1.0	0.22	0.23
NK 10:1	5.5±1.4	5.3±1.3	9.8±1.6	0.09	1.0	0.16	0.12
LAK 5:1	5.3±1.0	4.9±1.0	6.2±1.0	0.62	1.0	1.00	1.00
LAK 10:1	5.3±1.6	6.2±1.6	7.1±1.8	0.78	1.0	1.00	1.00

Values are estimated marginal mean ± SEM. Also shown are the results from the univariate analysis of variance. All values are adjusted for baseline.

Table V. Mean concentration of cortisol (ng/ml), prolactin (ng/ml) and growth hormone (μIU/ml) in serum from breast cancer patients at T2 and T3.

Serum hormones	A Reflexology + SIS	B Massage + SIS	C SIS	A vs. B vs. C f-test p-value	A vs. B f-test p-value	A vs. C f-test p-value	B vs. C f-test p-value
T2							
Cortisol	123.2±5.6	110.4±5.6	117.9±5.8	0.28	0.33	1.00	1.00
Prolactin	6.4±1.1	5.3±1.1	4.3±1.1	0.39	1.00	0.51	1.00
Growth hormone	2.6±0.5	1.5±0.5	2.5±0.5	0.25	0.40	1.00	0.50
T3							
Cortisol	131.7±6.3	117.8±6.1	122.5±6.3	0.29	0.36	0.91	1.00
Prolactin	6.3±0.9	4.4±0.9	4.7±0.9	0.27	0.39	0.61	1.00
Growth hormone	3.0±1.1	3.2±1.0	3.6±1.1	0.92	1.00	1.00	1.00

Values are estimated marginal mean ± SEM. Also shown are the results from the univariate analysis of variance. All values are adjusted for baseline.

only became evident at the 6-month follow-up. Other studies, which have demonstrated no changes in overall lymphocyte cell numbers and subsets, have usually had relatively brief follow-up periods (51). In contrast, van der Pompe *et al* (36) demonstrated lower percentages of NK, CD8 and CD4 cells following 13 weeks of experiential-existential group psychotherapy in breast cancer patients who had undergone surgery at least 4 months prior to the study. Thus, changes in lymphocyte subsets may well occur following a CAM intervention, but effects could be delayed most probably due to the suppressive effects associated with the proximity to surgery and adjuvant chemotherapy and/or radiotherapy treatments.

Natural cytotoxicity can be reduced in certain types of cancer patients, and conventional treatments can suppress this further (62); however, the ability of NK and LAK cells to kill human cancer cells efficiently *ex vivo* has led to much work

Table VI. Mean percentages of PBMCs from breast cancer patients expressing the receptors for cortisol (Gluc-R), prolactin (PRL-R) and growth hormone (GH-R) at T2 and T3.

T2							
Hormone receptors	A Reflexology + SIS	B Massage + SIS	C SIS	A vs. B vs. C f-test p-value	A vs. B f-test p-value	A vs. C f-test p-value	B vs. C f-test p-value
Gluc-R	72.6±2.8	77.3±2.8	68.2±3.1	0.09	0.70	0.89	0.09
PRL-R	70.8±2.8	63.7±2.8	67.5±3.1	0.21	0.23	1.00	1.00
GH-R	1.8±0.7	1.4±0.7	1.8±0.8	0.91	1.00	1.00	1.00
T3							
Gluc-R	73.9±3.2	73.9±3.0	74.4±3.2	1.00	1.00	1.00	1.00
PRL-R	74.0±3.1	66.5±2.9	67.4±3.0	0.16	0.22	0.37	1.00
GH-R	1.1±1.0	3.4±0.9	1.7±1.0	0.23	0.30	1.00	0.71

Values are estimated marginal mean ± SEM. Also shown are the results from the univariate analysis of variance. All values are adjusted for baseline.

assessing their potential as a form of immunotherapy (63,64). Using effector:target ratios of 5:1 and 10:1 we found no significant differences between groups for the interventions, which is in agreement with other studies (61,43). This suggests that the mechanism by which reflexology and massage enhance quality of life does not directly involve the increased activation of the cytotoxic NK and LAK cells, but could however be mediated by increased cell number. Numerous effector:target ratios have been used ranging from 1:1 to 50:1 (61,65), however if ratios above 10:1 were used in the current study there would have been insufficient cells to study the breadth of immune parameters.

The most notable findings with respect to the Th1/Th2 balance were that, in the massage patients at T3, there was a significantly lower percentage of both $CD3^+$ and $CD4^+$ cells expressing the Th2 cytokine IL4 compared with SIS, and this was accompanied by a significant increase in the percentage of $CD8^+$ cells expressing the Th1 cytokine IFNγ. The fact that different cell populations are both changing in a manner that produces a Th1-like response is highly intriguing. It also suggests that the commonly observed increase in circulating IL-10 in cancer patients, produced by Th2-like cells, is a later phenomenon caused as a consequence of changes in other T cell subsets. Overall the results strongly suggest that there has been some form of rebalancing of the Th1/Th2 system in the patients receiving scalp massage.

In the present study, IL4 proved to be a good marker for Th2-like cells; however, IL10 was detected at very low levels, in accordance with previous studies, which found percentages of approximately 0.2-0.6% in caregivers and controls (66). A further practical limitation of the study, in addition to the lack of PBMCs, was that the neuroendocrine factors were only measured at a single time-point, and it is well known that some of these have pronounced circadian rhythms. This was a practical constraint due to the inability to take multiple blood or other biological samples in a day. However, variations were minimized by taking blood at similar time-points. Other studies have commonly used saliva, an easier fluid to sample; however, this was not available in the current trial.

The practical limitations described above are possibly responsible for the fact that no effect of massage or reflexology was observed on hormone concentrations or receptor levels. These results contrast with previous studies in cancer patients which demonstrated that psychotherapeutic treatment and greater social support can normalise or reduce cortisol levels, as well as lowering prolactin levels. In breast and colorectal cancer patients, mindfulness-based stress reduction has not only been shown to improve quality of life, but was also associated with decreased afternoon cortisol levels (67).

A quality of life study conducted on the same patients showed a high level of satisfaction and compliance with both reflexology and massage, and demonstrated that at T2, massage improved quality of life, but reflexology did not have an effect until T3 (68). This is partly in accordance with the immune factors as many did not become significant until the final endpoint (T3). The primary end point for the quality of life study, T2, was chosen as 4 weeks after the end of the final session of reflexology or massage. The effectiveness of the support provided during SIS could provide one explanation for the lack of differences found between the groups, as we have previously shown that the provision of a fully integrated oncology health service with drop-in facilities and trained staff to identify and resolve concerns immediately, is associated with very low levels of psychosocial morbidity in women with locally advanced breast cancer (42).

This study has demonstrated that in women with early breast cancer, scalp massage, the active control condition, but not reflexology, the treatment of interest, administered according to standardised protocols induced a range of immunological changes including an increase in the percentage of $CD25^+$ cells and a shift towards a Th1-like response. Further studies in other cancer populations should now be undertaken, and

attempts made to evaluate the underlying biopsychosocial mechanisms, as well as the possible clinical consequences of these changes.

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Appendix C

PubMed search terms for a literature review of Eysenckian personality

1. ((((("personality"[MeSH Terms] OR "personality"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) AND English[Language]) AND eysenck[All Fields]

2. ((((("personality"[MeSH Terms] OR "personality"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) AND English[Language]) AND psychoticism[All Fields]

3. ((((("personality"[MeSH Terms] OR "personality"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) AND English[Language]) AND ("extraversion (psychology)"[MeSH Terms] OR ("extraversion"[All Fields] AND "(psychology)"[All Fields]) OR "extraversion (psychology)"[All Fields] OR "extraversion"[All Fields])

4. ((((("personality"[MeSH Terms] OR "personality"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) AND English[Language]) AND ("Neuroticism"[Supplementary Concept] OR "Neuroticism"[All Fields] OR "neuroticism"[All Fields])

5. ((((("personality"[MeSH Terms] OR "personality"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) AND English[Language]) AND lie[All Fields]

Appendix D

PubMed search terms for a literature review of positive or negative affect

(((((positive[All Fields] OR negative[All Fields]) AND ("affect"[MeSH Terms] OR "affect"[All Fields])) AND ("personality"[MeSH Terms] OR "personality"[All Fields])) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND english[Language]) AND ("risk"[MeSH Terms] OR "risk"[All Fields])

Appendix E

PubMed search terms for a literature review of locus of control

((((("personality"[MeSH Terms] OR "personality"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) AND English[All Fields]) AND "locus of control"[All Fields]

Appendix F

PubMed search terms for a literature review of emotional control

((((("personality"[MeSH Terms] OR "personality"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])) AND ("risk"[MeSH Terms] OR "risk"[All Fields])) AND English[All Fields]) AND "emotional control"[All Fields]

Appendix G

OVID search terms for literature review of cancer personality and immunology

1. personality.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui, tc, id, tm]

2. individual differences.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui, tc, id, tm]

3. 1 or 2

4. immunology.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui, tc, id, tm]

5. cancer.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui, tc, id, tm]

6. 3 and 4 and 5

7. Limit 6 to English Language

Appendix H

PUBMED Search terms for literature review of cancer personality and immunology

((("personality"[MeSH Terms] OR "personality"[All Fields]) OR ("individuality"[MeSH Terms] OR "individuality"[All Fields] OR ("individual"[All Fields] AND "differences"[All Fields]) OR "individual differences"[All Fields])) AND ("immunology"[Subheading] OR "immunology"[All Fields] OR "allergy and immunology"[MeSH Terms] OR ("allergy"[All Fields] AND "immunology"[All Fields]) OR "allergy and immunology"[All Fields])) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND English[lang]

Table H1:: Age norms, means and standard deviations of P, E, N and L: Females

age group (year)		**P**			**E**		**N**		**L**	
	n	**mean**	**SD**	**n**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
16-20	203	7.06	4.11	161	15.47	4.99	14.03	4.85	5.45	3.25
21-30	256	6.20	3.86	159	14.17	4.68	12.53	4.78	6.33	3.82
31-40	135	5.87	3.72	38	13.55	4.93	11.71	4.94	6.79	3.74
41-50	109	4.62	3.05	50	12.36	4.95	10.94	5.92	8.02	3.88
51-60	102	4.05	3.21	45	13.62	5.47	11.31	5.36	8.82	3.97
61-70	73	4.19	3.26	41	12.15	5.08	9.98	5.51	11.20	3.09
Total	878	5.73	3.85	494	14.14	5.06	12.47	5.22	6.88	3.97

Adapted from the (Eysenck & Eysenck, 1991, page 17)

Appendix I

CD markers selected for measurements

Table I1:: CD markers selected for investigation

CD	**identity/function**	**T cell**	**B cell**	**NK cell**	**monocyte / macrophage**	**granulocyte**	**other**
CD2	LFA-3 receptor (adhesion)	*					
CD3	TCR signalling complex	*					
CD4	MHC Class II receptor	^					
CD8	MHC Class II receptor	^					
CD14	LPS-binding protein receptor				*	*	
CD16	FcγRIIIA/FcγRIIIB			*	*		
CD19	B cell co-receptor subunit		*				
CD25	IL2-R	~	~				
CD56	NCAM (neural cell adhesion molecule)	^		*			*

* = molecule expressed; ^ = sub-population only; ~ sub-population of activated cells only

Adapted from Roitt et al. (2001, pages 437-438)

Appendix J

Cytokines selected for measurement

Table J1:: cytokines selected for investigation

cytokine	**immune system source**	**principal target**	**principal effects**
IL2	T cells	T cells	T cell proliferation and differentiation, activation of cytotoxic lymphocytes and macrophages.
IL4	T cells	B cells, T cells	B-cell growth factor, isotype selection, IgE, IgG1
IL10	T cells	Th1 cells	inhibition of cytokine synthesis
IFNγ	T cells, NK cells	leucocytes, tissue cells, Th2 cells	MHC class I and class II induction, macrophage activation, increased endothelial cell/lymphocyte adhesion, M0 cytokine synthesis, antiviral state, anti-proliferative (Th1 cells)

Adapted from Roitt et al. (2001, page 441)

Appendix K

Personality Transformations

Table K1:: Transformations of Psychological data

measure (scale)	**none**	**(re)reflected**	**log**
EPQ-R P	✓		
EPQ-R E		✓	✓
EPQ-R N	✓		
EPQ-R L	✓		
PANAS P		✓	✓
PANAS N			✓
MHLCS I	✓		
MHLC C	✓		
MHLC P	✓		
CECS Ag	✓		
CECS D	✓		
CECS Ax	✓		
CECS T	✓		

Appendix L

NI transformations

Table L1:: Transformations of NI data

group	measure	none	(re)reflected	log
Th1-like response				
	CD3/IL2	✓		
	CD3/IFNγ			✓
	CD4/IL2	✓		
	CD4/IFNγ			✓
	CD8/IL2			✓
	CD8/IFNγ			✓
Th2-like response				
	CD3/IL4			✓
	CD3/IL10			✓
	CD4/IL4			✓
	CD4/IL10			✓
	CD8/IL4			✓
	CD8/IL10			✓
Killer cell structure and function				
	NK			✓
	LAK			✓
	CD16	✓		
	CD56			✓
T cell phenotypes				
	CD2	✓		
	CD3		✓	✓
	CD4		✓	✓
	CD8	✓		
	CD25			✓
Neurohormones				
	Cortisol	✓		

Table L1:: Transformations of NI data

	Gluc-R		✓	✓
	Prolactin	✓		✓
	PRL-R		✓	✓
	Growth hormone	✓		
	GH-R		✓	✓
Others				
	CD14			✓
	CD19			✓

Appendix M

Personality and NI correlations in 183 females at T1 (6-weeks post surgery)

Correlations

		EPQ-R Psychoticism	EPQ-R Extraversion	EPQ-R Neuroticism	EPQ-R Lie	PANAS Positivity	PANAS Negativity	MHLC Internal	MHLC Chance	MHLC Powerful others	CECS Anger	CECS Depressed mood	CECS Anxiety	CECS Total
T1 CD3 expressing IL2	Pearson Correlation	.003	.129	.006	-.020	-.180*	-.023	-.150	-.113	-.026	.010	.055	.027	.036
	Sig. (2-tailed)	.976	.168	.950	.835	.050	.802	.104	.222	.781	.913	.558	.768	.699
	N	116	116	116	116	119	119	119	119	119	118	118	118	118
T1 CD3 expressing IFNγ	Pearson Correlation	.153	.027	.180	-.043	-.131	.137	-.063	-.030	.015	.118	.059	.052	.091
	Sig. (2-tailed)	.101	.770	.054	.645	.155	.137	.495	.748	.870	.202	.524	.580	.326
	N	116	116	116	116	119	119	119	119	119	118	118	118	118
T1 CD4 expressing IL2	Pearson Correlation	-.023	.122	-.031	-.021	-.183*	-.066	-.144	-.101	-.012	-.012	.040	.012	.016
	Sig. (2-tailed)	.806	.194	.741	.826	.047	.478	.120	.277	.897	.899	.668	.898	.866
	N	115	115	115	115	118	118	118	118	118	117	117	117	117
T1 CD4 expressing IFNγ	Pearson Correlation	.140	-.035	.218*	.053	-.200*	.155	-.111	.028	-.003	.186*	.135	.125	.174
	Sig. (2-tailed)	.135	.708	.019	.577	.030	.094	.233	.767	.978	.044	.147	.178	.061
	N	115	115	115	115	118	118	118	118	118	117	117	117	117
T1 CD8 expressing IL2	Pearson Correlation	.117	.057	.212*	.048	-.172	.216*	-.190*	-.203*	-.136	.121	.150	.011	.111
	Sig. (2-tailed)	.212	.545	.023	.607	.063	.019	.040	.028	.141	.193	.106	.904	.234
	N	115	115	115	115	118	118	118	118	118	117	117	117	117
T1 CD8 expressing IFNγ	Pearson Correlation	.105	.043	.080	-.104	-.149	.038	-.017	-.146	.002	.079	.034	-.057	.025
	Sig. (2-tailed)	.266	.649	.395	.270	.108	.679	.857	.114	.979	.395	.715	.540	.788
	N	115	115	115	115	118	118	118	118	118	117	117	117	117
T1 CD3 expressing IL4	Pearson Correlation	.069	.181	-.095	.103	-.131	-.106	-.047	-.029	-.066	.139	.001	.072	.084
	Sig. (2-tailed)	.461	.052	.309	.271	.155	.252	.615	.755	.478	.133	.990	.439	.363
	N	116	116	116	116	119	119	119	119	119	118	118	118	118
T1 CD3 expressing IL10	Pearson Correlation	.227*	.162	-.006	-.029	.047	.083	.044	.014	-.092	-.154	-.001	-.045	-.079
	Sig. (2-tailed)	.014	.083	.950	.754	.612	.371	.632	.882	.320	.096	.991	.625	.397
	N	116	116	116	116	119	119	119	119	119	118	118	118	118
T1 CD4 expressing IL4	Pearson Correlation	.030	.163	-.239*	.090	-.017	-.172	.064	-.026	-.025	.121	.083	.048	.097
	Sig. (2-tailed)	.749	.084	.010	.341	.857	.063	.494	.782	.788	.194	.378	.609	.299
	N	114	114	114	114	117	117	117	117	117	116	116	116	116
T1 CD4 expressing IL10	Pearson Correlation	.221*	.185*	-.025	-.046	.052	.067	.038	.010	-.126	-.134	.011	-.038	-.064
	Sig. (2-tailed)	.019	.050	.795	.625	.580	.475	.688	.914	.179	.154	.909	.690	.500
	N	113	113	113	113	116	116	116	116	116	115	115	115	115
T1 CD8 expressing IL4	Pearson Correlation	.095	-.058	.210*	.086	-.158	.110	-.129	-.059	-.119	.009	-.158	.001	-.052
	Sig. (2-tailed)	.313	.539	.024	.358	.087	.238	.164	.527	.199	.924	.088	.991	.575
	N	115	115	115	115	118	118	118	118	118	117	117	117	117
T1 CD8 expressing IL10	Pearson Correlation	-.013	-.118	.060	.176	-.021	.028	-.040	-.029	-.073	.038	.069	.079	.067
	Sig. (2-tailed)	.890	.219	.532	.065	.823	.770	.672	.758	.439	.691	.471	.409	.482
	N	111	111	111	111	113	113	113	113	113	112	112	112	112
T1 NK	Pearson Correlation	.000	-.157	-.030	-.183	.150	.004	-.120	-.200*	-.448**	-.139	-.150	-.008	-.115
	Sig. (2-tailed)	1.000	.128	.775	.074	.141	.966	.238	.047	.000	.174	.140	.941	.259
	N	96	96	96	96	98	98	99	99	99	98	98	98	98
T1 LAK	Pearson Correlation	.008	-.134	.041	-.112	.087	.075	-.069	.077	.043	.104	.109	.176	.144
	Sig. (2-tailed)	.938	.197	.692	.284	.399	.465	.500	.454	.673	.312	.293	.086	.161
	N	94	94	94	94	96	96	97	97	97	96	96	96	96
T1 CD16	Pearson Correlation	.097	.054	.004	-.027	-.067	-.085	-.047	-.077	.024	-.045	.089	.014	.020
	Sig. (2-tailed)	.271	.537	.961	.757	.442	.327	.585	.375	.781	.603	.309	.871	.819
	N	132	132	132	132	135	135	135	135	135	134	134	134	134

Correlations

		EPQ-R Psychoticism	EPQ-R Extraversion	EPQ-R Neuroticism	EPQ-R Lie	PANAS Positivity	PANAS Negativity	MHLC Internal	MHLC Chance	MHLC Powerful others	CECS Anger	CECS Depressed mood	CECS Anxiety	CECS Total
T1 CD56	Pearson Correlation	.017	.000	.003	.072	-.133	.014	-.096	-.068	-.001	.022	.064	-.010	.032
	Sig. (2-tailed)	.842	.998	.973	.413	.124	.876	.266	.431	.992	.800	.460	.911	.713
	N	132	132	132	132	135	135	135	135	135	134	134	134	134
T1 CD2	Pearson Correlation	-.058	-.155	.064	-.038	-.167	-.084	.026	-.035	.032	.125	.192*	.228**	.206*
	Sig. (2-tailed)	.506	.076	.469	.665	.053	.330	.767	.684	.712	.150	.026	.008	.017
	N	132	132	132	132	135	135	135	135	135	134	134	134	134
T1 CD3	Pearson Correlation	.004	.001	.116	-.021	-.061	-.034	-.003	.012	.033	.062	.146	.163	.138
	Sig. (2-tailed)	.960	.988	.185	.807	.483	.692	.969	.890	.707	.476	.091	.060	.112
	N	132	132	132	132	135	135	135	135	135	134	134	134	134
T1 CD4	Pearson Correlation	-.051	-.088	.036	-.109	-.119	-.193*	-.045	-.022	.064	.072	.072	.117	.100
	Sig. (2-tailed)	.565	.318	.680	.212	.168	.025	.602	.802	.458	.408	.409	.178	.249
	N	132	132	132	132	135	135	135	135	135	134	134	134	134
T1 CD8	Pearson Correlation	.041	-.102	.106	-.111	-.103	.115	-.115	-.031	-.126	.049	.104	.071	.082
	Sig. (2-tailed)	.643	.244	.227	.205	.233	.185	.183	.720	.145	.571	.233	.415	.346
	N	132	132	132	132	135	135	135	135	135	134	134	134	134
T1 CD25	Pearson Correlation	-.026	-.071	.011	.098	-.057	-.010	-.071	-.133	-.063	-.006	-.018	-.072	-.033
	Sig. (2-tailed)	.768	.418	.903	.264	.511	.905	.414	.123	.467	.946	.840	.412	.701
	N	132	132	132	132	135	135	135	135	135	134	134	134	134
T1 cortisol concentration	Pearson Correlation	-.026	-.135	.136	.068	-.038	.090	.107	.096	.048	.116	.045	.133	.116
	Sig. (2-tailed)	.731	.073	.071	.369	.616	.228	.150	.198	.522	.121	.545	.075	.123
	N	176	176	176	176	180	180	181	181	181	180	180	180	180
T1 glucocorticoid receptor	Pearson Correlation	-.075	.013	.126	-.118	-.098	.053	-.040	.054	.040	-.014	-.016	.022	.006
	Sig. (2-tailed)	.357	.872	.122	.145	.221	.507	.615	.501	.620	.863	.846	.784	.941
	N	153	153	153	153	157	157	158	158	158	157	157	157	157
T1 prolactin concentration	Pearson Correlation	-.070	-.028	.065	-.085	.010	.090	-.134	.033	-.099	-.029	-.155*	-.102	-.108
	Sig. (2-tailed)	.355	.716	.391	.259	.899	.230	.073	.655	.187	.703	.037	.174	.151
	N	176	176	176	176	180	180	181	181	181	180	180	180	180
T1 prolactin receptor	Pearson Correlation	-.132	-.065	.042	.044	-.075	-.099	-.024	.007	.121	.100	.075	.066	.100
	Sig. (2-tailed)	.106	.428	.605	.587	.354	.220	.766	.930	.131	.215	.352	.414	.213
	N	152	152	152	152	156	156	157	157	157	156	156	156	156
T1 growth hormone concentration	Pearson Correlation	-.019	-.073	.012	.049	-.132	-.045	.072	.094	.010	.057	.010	-.007	.026
	Sig. (2-tailed)	.804	.339	.877	.519	.079	.551	.337	.213	.893	.453	.894	.926	.732
	N	173	173	173	173	177	177	178	178	178	177	177	177	177
T1 growth hormone receptor	Pearson Correlation	-.033	-.037	.087	-.050	-.091	.148	-.132	-.056	-.045	-.044	-.042	-.068	-.056
	Sig. (2-tailed)	.689	.653	.289	.540	.259	.067	.101	.491	.574	.589	.606	.403	.489
	N	151	151	151	151	155	155	156	156	156	155	155	155	155
T1 CD14	Pearson Correlation	-.047	-.138	.027	.189*	-.138	-.101	-.037	-.063	-.053	.007	-.019	-.067	-.029
	Sig. (2-tailed)	.591	.115	.757	.030	.111	.245	.673	.468	.538	.933	.832	.440	.741
	N	132	132	132	132	135	135	135	135	135	134	134	134	134
T1 CD19	Pearson Correlation	-.116	-.052	-.094	-.037	.060	-.016	-.077	-.114	-.044	-.031	.069	.017	.018
	Sig. (2-tailed)	.187	.555	.286	.676	.486	.850	.373	.187	.613	.722	.427	.848	.838
	N	132	132	132	132	135	135	135	135	135	134	134	134	134

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Appendix N

T1 Personality and NI correlations at T1, T2 and T3 for 63 females

Table N1:: T1 Personality and neuroimmunological correlations at T1, T2 and T3

Personality variable	NI variable	T1 R_{XY}	T2 R_{XY}	T3 R_{XY}
EPQ-R Psychoticism				
	CD4 expressing IFNγ (Th1)	*.381**	.015	.131
EPQ-R Extraversion				
	CD4 expressing IL2 (Th1)	*.335**	.202	.081
	LAKCA (Killer Cells)	.139	*.394**	.348
	CD19	*-.305**	.024	-.112
EPQ-R Neuroticism				
	CD8 expressing IL4 (Th2)	.296	.099	*.412**
EPQ-R Lie				
	CD4 expressing IFNγ (Th1)	-.148	*-.380**	.027
	CD8 expressing IL10 (Th2)	*.370**	.020	-.207

Table N1:: T1 Personality and neuroimmunological correlations at T1, T2 and T3

	NKCA (Killer Cells)	-.*392**	-.224	-.117
	glucocorticoid receptor (NH)	-.172	-.*333**	-.014
	CD19	-.043	.020	.*338**
PANAS Positivity				
	CD3 expressing IL2 (Th1)	-.*377**	-.*337**	-.318
	CD3 expressing IFNγ (Th1)	-.*365**	-.261	-.284
	CD4 expressing IL2 (Th1)	-.*364**	-.307	-.307
	CD4 expressing IFNγ (Th1)	-.*355**	-.144	-.274
	CD8 expressing IFNγ (Th1)	-.316	-.*349**	-.256
	CD16 (Killer Cells)	-.*329**	-.*348**	-.107
	CD8 (T cell)	-.310*	-.*295**	-.089
	CD14 (NH)	-.243	-.*321**	-.120
PANAS Negativity				
	cortisol concentration (NH)	-.169	-.215	-.*292**
	prolactin concentration (NH)	-.108	-.*285**	-.059
	prolactin receptor (NH)	-.*333**	-.165	-.084

Table N1:: T1 Personality and neuroimmunological correlations at T1, T2 and T3

	growth hormone receptor (NH)	*.292**	.115	-.014
MHLC Internal				
	-	-	-	-
MHLC Chance				
	NKCA (Killer Cells)	*-.350**	-.025	-.072
	CD56 (Killer Cells)	-.180	*-.392***	-.235
	CD2 (T cell)	-.130	*-.353**	-.096
	CD3 (T cell)	-.142	*-.333**	.022
	CD4 (T cell)	-.171	*-.327**	.064
	CD25 (T cell)	-.263	*-.349**	-.245
	growth hormone concentration (NH)	*.344***	.084	-.060
	CD14	-.097	*-.376**	-.107
MHLC Powerful other				
	NKCA (Killer Cells)	*-.569***	-.272	-.275
	CD56 (Killer Cells)	-.150	*-.388***	-.155
	CD2 (T cell)	-.051	*-.346**	-.017

Table N1:: T1 Personality and neuroimmunological correlations at T1, T2 and T3

	CD4 (T cell)	-.100	*-.308**	.067
	CD25 (T cell)	-.134	*-.396***	-.238
	glucocorticoid receptor (NH)	.130	-.053	*.364**
	prolactin receptor (NH)	*.313**	.251	.218
CECS Anger				
	CD4 expressing IL4 (Th2)	.053	.094	*.341**
	growth hormone receptor (NH)	-.082	-.016	*-.287**
	CD19	.154	.038	*.399***
CECS Depressed mood				
	CD4 expressing IL10 (Th2)	-.021	*-.366**	-.017
	CD8 expressing IL4 (Th2)	-.106	.106	*.327**
	CD56 (Killer Cells)	.142	*.313**	.035
	CD2 (T cell)	*.336**	.120	.309*
	prolactin concentration (NH)	*-.325**	.011	.154
	CD14	.106	*.339**	.169
CECS Anxiety				

Table N1:: T1 Personality and neuroimmunological correlations at T1, T2 and T3

	CD3 expressing IL10 (Th2)	.092	-.*353**	.077
	CD4 expressing IL10 (Th2)	.036	-.*349**	-.032
CECS Total				
	CD3 expressing IL10 (Th2)	.039	-.*364**	.062
	CD4 expressing IL4 (Th2)	.048	-.*363**	.212
	prolactin concentration (NH)	-.*298**	-.057	.127
	growth hormone receptor (NH)	-.113	.088	-.*286**

Appendix O

Clustering of immunological variables by personality construct

(comprehensive data set from study two)

EPQ-R Psychoticism and CD4/IFNγ Mauchley's test indicated that the assumption of sphericity had been violated (p= .024), and therefore a Greenhouse-Geisser correction was applied. No significant effects were found.

Table O1:: Median-split ANOVA EPQ-R P and CD4/IFNy

Source	SS	DF	MS	F	Sig
Time	.195	1.590	.122	2.493	.106
Time x EPQ-R Psychoticism	.048	1.590	.030	.613	.511
Between Group	.007	1	.007	.225	.639

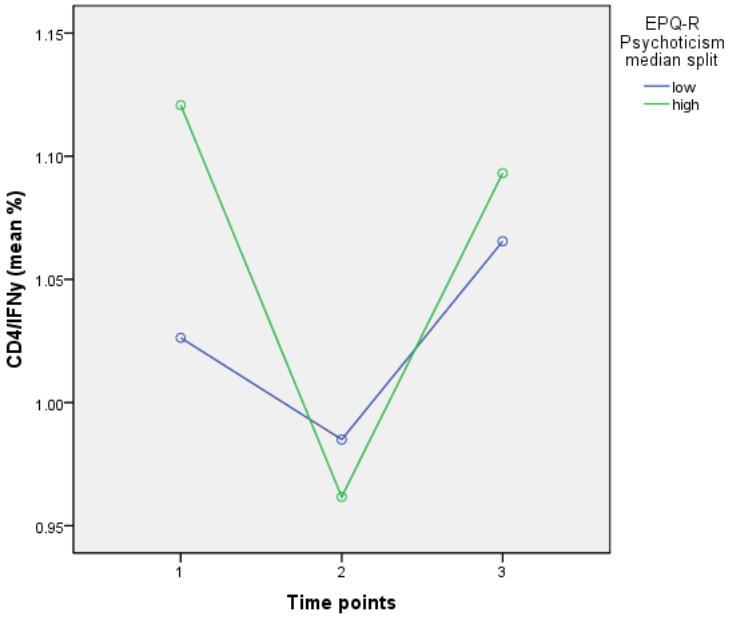

Figure O1. Median-split EPQ-R P and CD4/IFNγ over time

EPQ-R E and *CD4/IL2* Mauchley's test indicated that the assumption of sphericity had been violated (p= .010), and therefore a Greenhouse-Geisser correction was applied. Only a significant time effect was found.

Table O2:: Median-split ANOVA EPQ-R E and CD4/IL2

Source	SS	DF	MS	F	Sig

Table O2:: Median-split ANOVA EPQ-R E and CD4/IL2

Time	378.453	1.539	245.933	5.213	.015*
Time x EPQ-R E	162.881	1.539	105.846	2.244	.130
Between Group	29.026	1	29.026	.313	.581

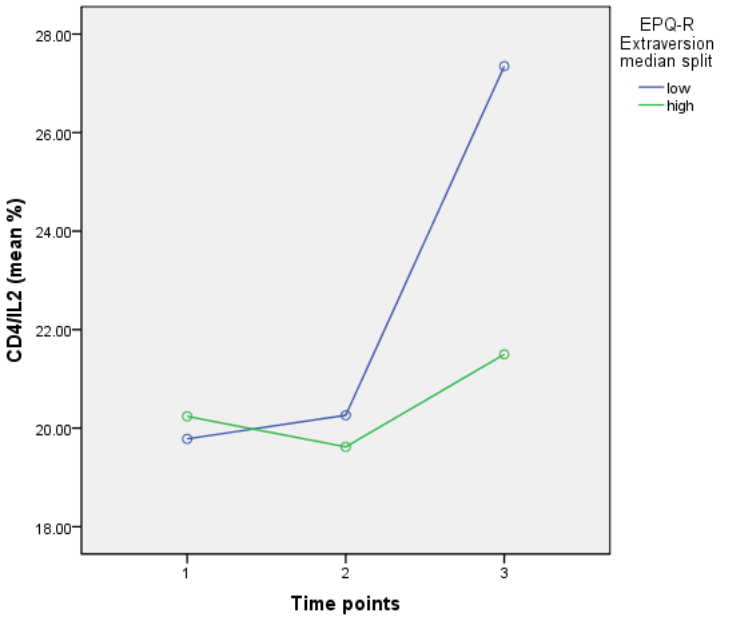

Figure O2. Median-split EPQ-R E and CD4/IL2 over time

EPQ-R E and CD19 A significant effect was found for time and the interaction of time and EPQ-R E. Within subject contrasts showed a significant interaction effect for T1 and T2 (F=9.496, p=.004), and T1 and T3 (F=5.037, p=.030).

Table O3:: Median-split ANOVA EPQ-R E and CD19

Source	SS	DF	MS	F	Sig
Time	.993	2	.497	5.654	.005*
Time x EPQ-R E	.842	2	.424	4.791	.011*
Between Group	.040	1	.040	.463	.500

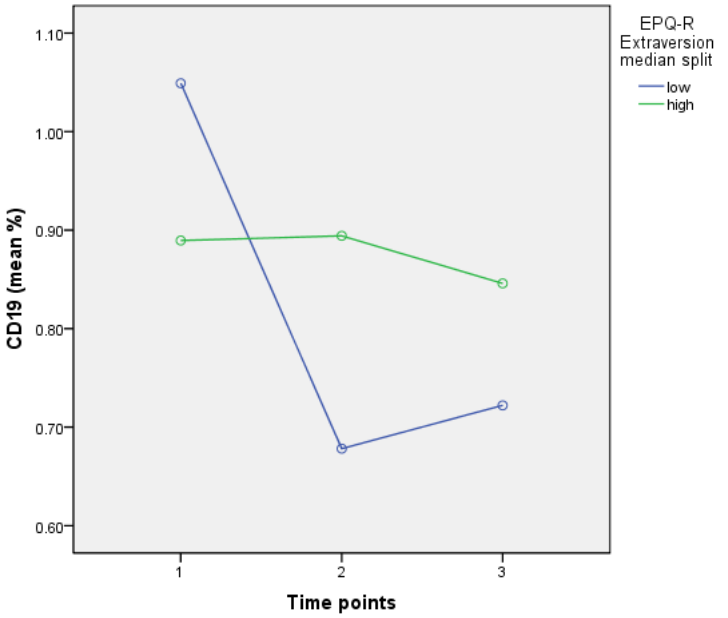

Figure O3. Median-split EPQ-R E and CD19 over time

EPQ-R L and CD8/IL10 No significant effects were found.

Table O4:: Median-split ANOVA EPQ-R L and CD8/IL10

Source	SS	DF	MS	F	Sig
Time	.001	2	.001	.048	.953
Time x EPQ-R L	0.57	2	.029	1.936	.154
Between Group	.010	1	.010	.986	.330

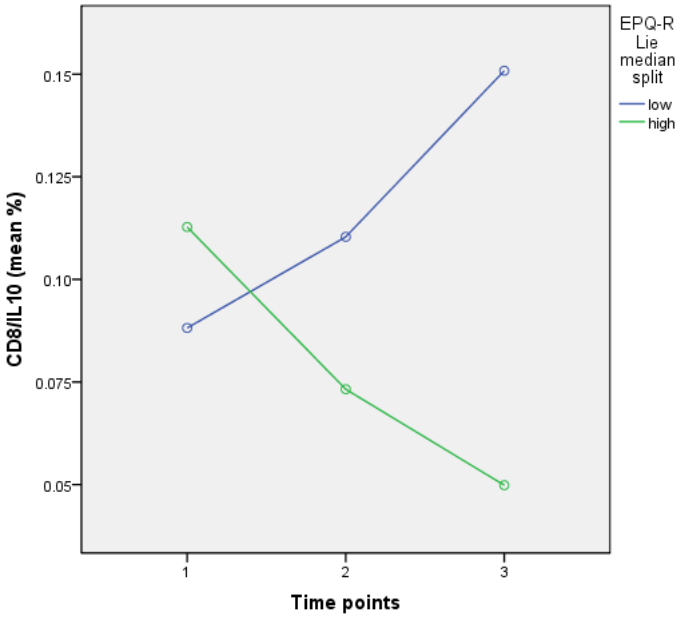

Figure O4. Median-split EPQ-R L and CD8/IL10 over time

EPQ-R L and NK A significant between group effect was found.

Table O5:: Median-split ANOVA EPQ-R L and NK

Source	SS	DF	MS	F	Sig
Time	.664	2	.332	3.774	.030
Time x EPQ-R L	.179	2	.090	1.018	.369
Between Group	.632	1	.632	6.045	.022*

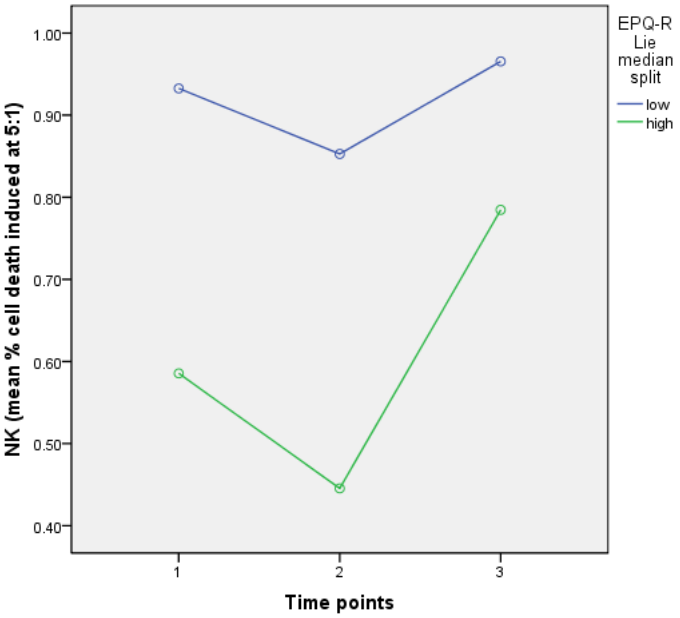

Figure O5. Median-split EPQ-R L and NK over time

The other three members of the killer cell grouping are presented below for comparison.

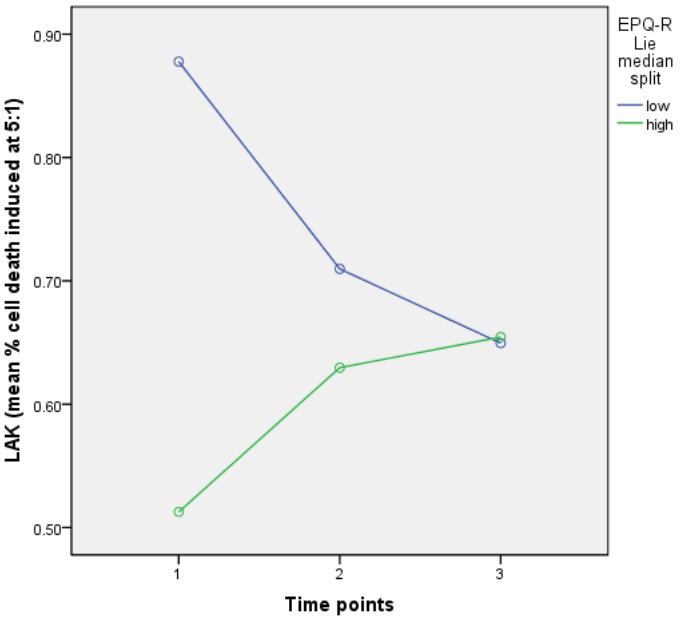

Figure O6. Median Split EPQ-R L and LAK over time

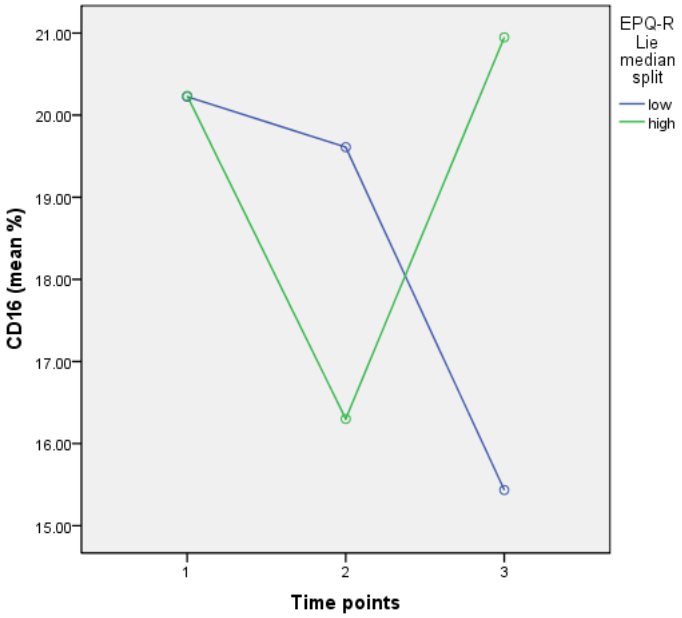

Figure O7. Median-split EPQ-R Lie and CD16 over time

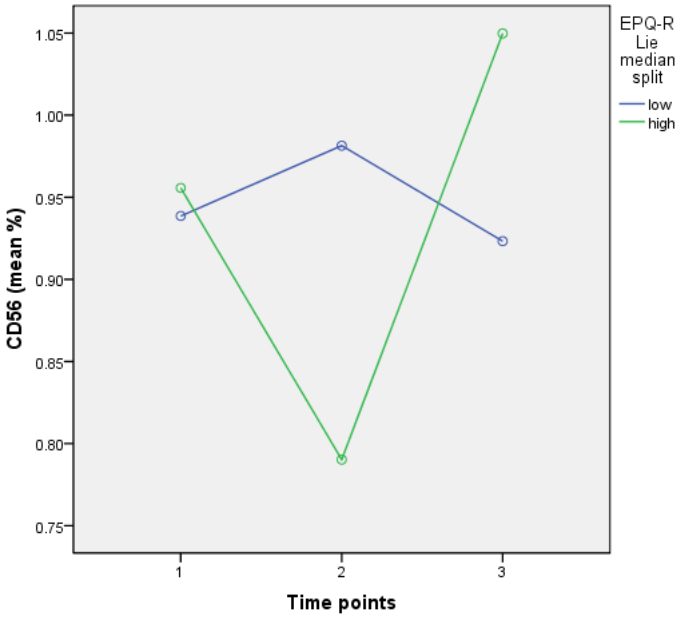

Figure O8. Median-split EPQ-R Lie and CD56 over time

PANAS P and CD3/IL2 Mauchley's test indicated that the assumption of sphericity had been violated (p= .013), and therefore a Greenhouse-Geisser correction was applied. Only a significant time effect was found.

Table O6:: Median-split ANOVA PANAS P and CD3/IL2

Source	SS	DF	MS	F	Sig
Time	331.091	1.566	211.392	3.786	.040*
Time x PANAS Positivity	1.888	1.566	1.205	.022	.956
Between Group	53.011	1	53.011	.479	.495

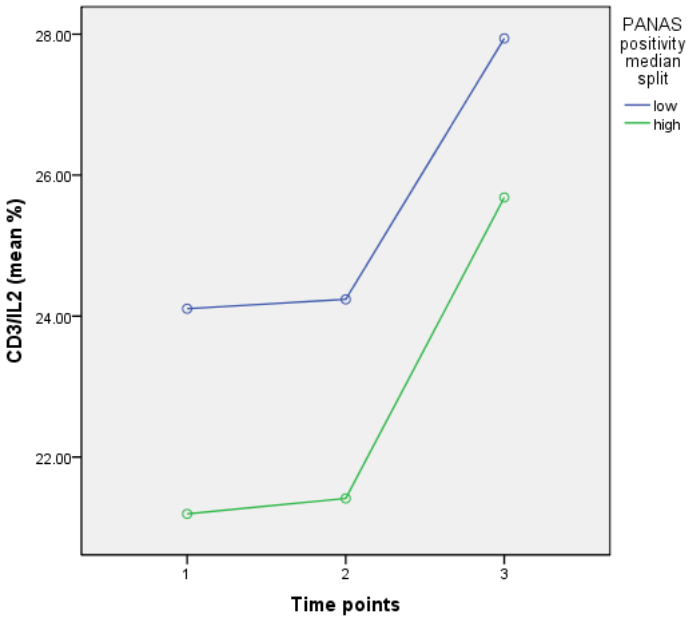

Figure O9. Median-split PANAS P and CD3/IL2 over time

PANAS P and CD3/IFNγ No significant effects were found.

Table O7:: Median-split ANOVA PANAS P and CD3/IFNy

Source	SS	DF	MS	F	Sig
Time	.110	2	.055	2.774	.071
Time x PANAS P	.005	2	.003	.136	.873
Between Group	2.713E-5	1	2.713E-5	.001	.977

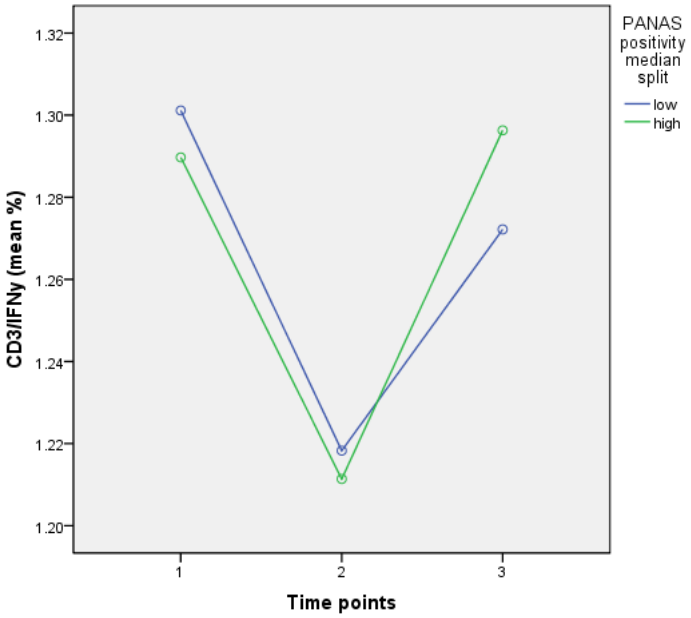

Figure O10. Median-split PANAS P and CD3/IFNγ over time

PANAS P and CD4/ IL2 Mauchley's test indicated that the assumption of sphericity had been violated (p= .019), and therefore a Greenhouse-Geisser correction wad applied. Only a significant time effect was found.

Table O8:: Median-split ANOVA PANAS P and CD4/IL2

Source	SS	DF	MS	F	Sig
Time	307.117	1.594	192.629	3.991	.034*
Time x PANAS P	.684	1.594	.429	.009	.979
Between Group	35.413	1	35.413	.381	.542

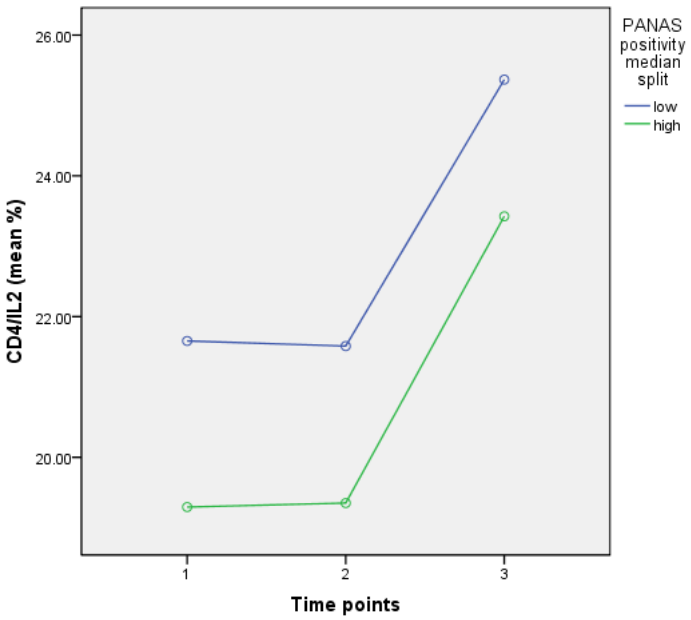

Figure O11. Median-split PANAS P and CD4/IL2 over time

PANAS P and CD4/IFNγ Mauchley's test indicated that the assumption of sphericity had been violated (p= .019), and therefore a Greenhouse-Geisser correction was applied. No significant effects were found.

Table O9:: Median-split ANOVA PANAS P and CD4/IFNy

Source	SS	DF	MS	F	Sig
Time	.181	1.582	.114	2.358	.118
Time x PANAS P	.006	1.582	.004	.077	.886
Between Group	.003	1	.003	.092	.764

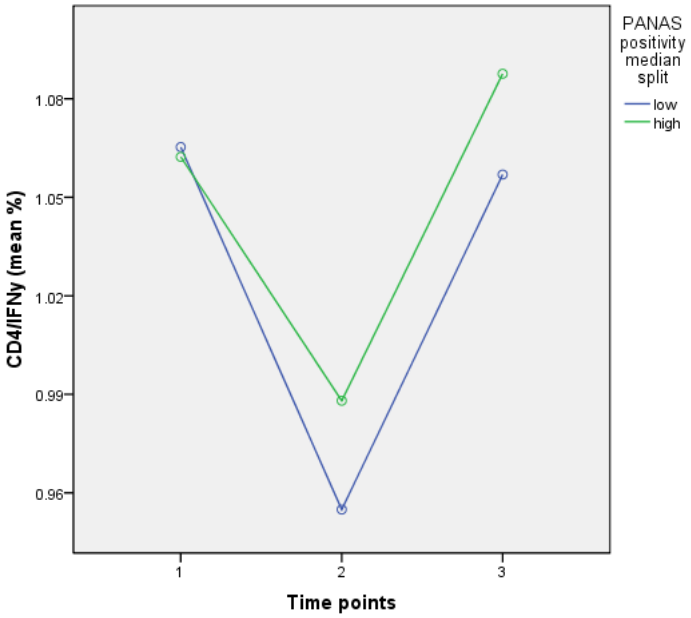

Figure O12. Median-split PANAS P and CD4/IFNγ over time

PANAS P and CD16 Mauchley's test indicated that the assumption of sphericity had been violated (p= <.005), and therefore a Greenhouse-Geisser correction was applied. A significant between group effect was found.

Table O10:: Median-split ANOVA PANAS P and CD16

Source	SS	DF	MS	F	Sig
Time	131.669	1.336	98.585	.582	.496
Time x PANAS P	102.329	1.336	76.617	.452	.560
Between Group	382.653	1	382.653	5.298	.026*

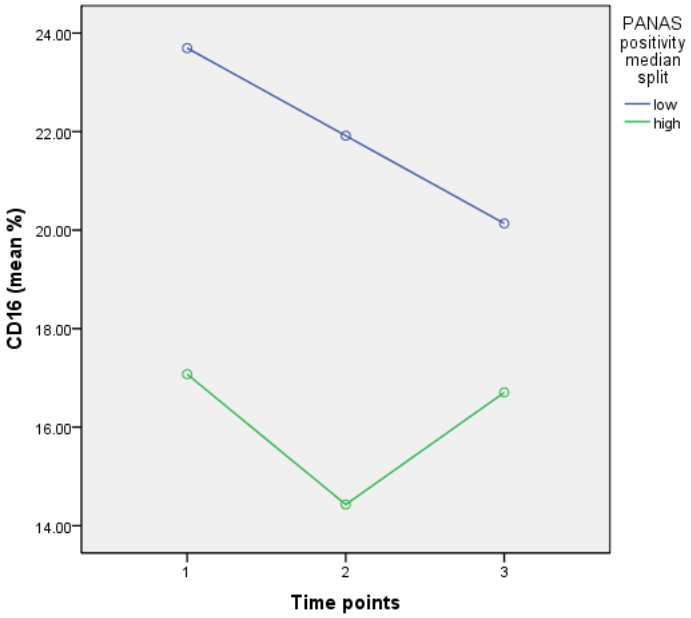

Figure O13. Median-split PANAS P and CD16 over time

The other three members of the T cell phenotype grouping are presented below for comparison.

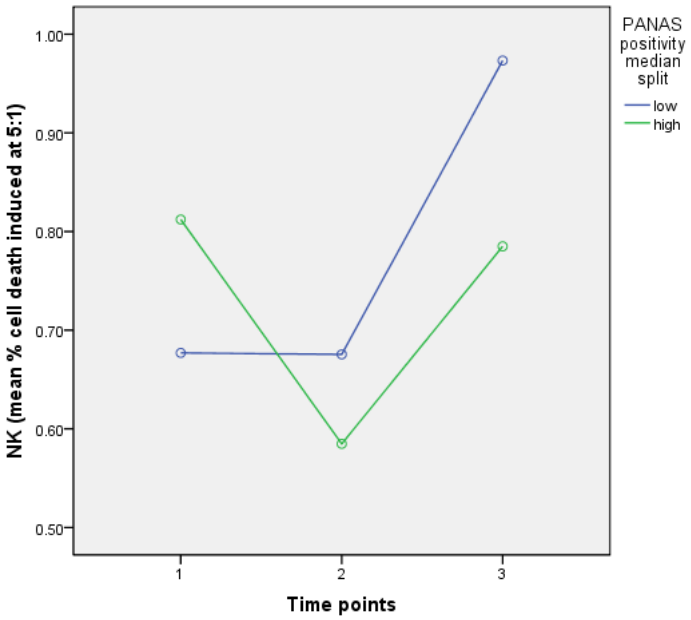

Figure O14. Median-split PANAS P and NK over time

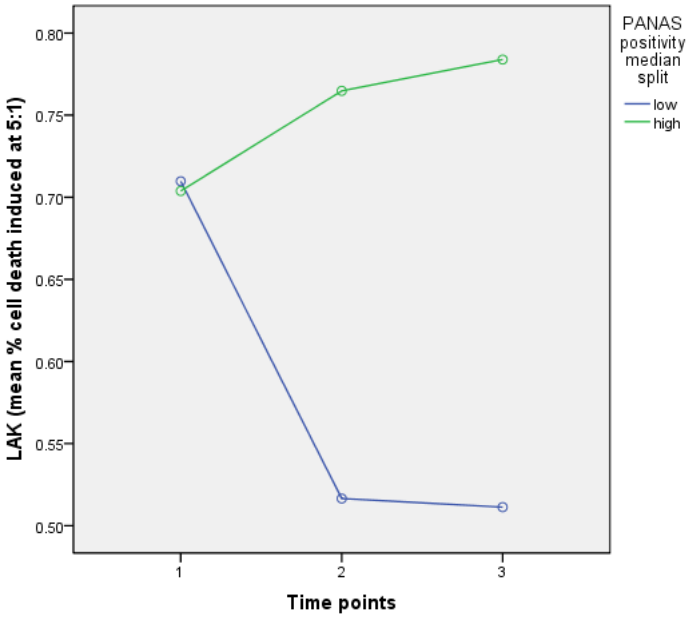

Figure O15. Median-split PANAS P and LAK over time

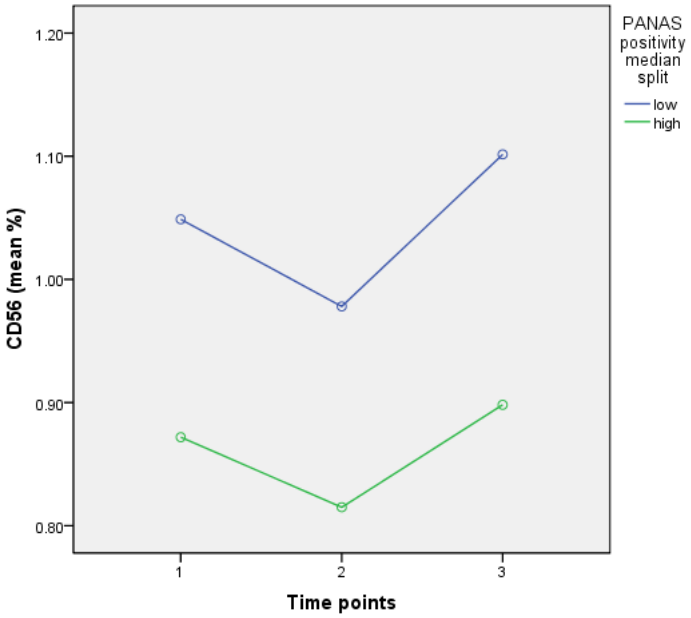

Figure O16. Median-split PANAS P and CD56 over time

PANAS P and CD8 Mauchley's test indicated that the assumption of sphericity had been violated (p= <.005), and therefore a Greenhouse-Geisser correction was applied. A significant between group effect was found.

Table O11:: Median-split ANOVA PANAS P and CD8

Source	SS	DF	MS	F	Sig
Time	22.430	1.387	16.173	.124	.807
Time x PANAS P	81.674	1.387	58.891	.451	.568
Between Group	478.975	1	478.975	5.609	.022*

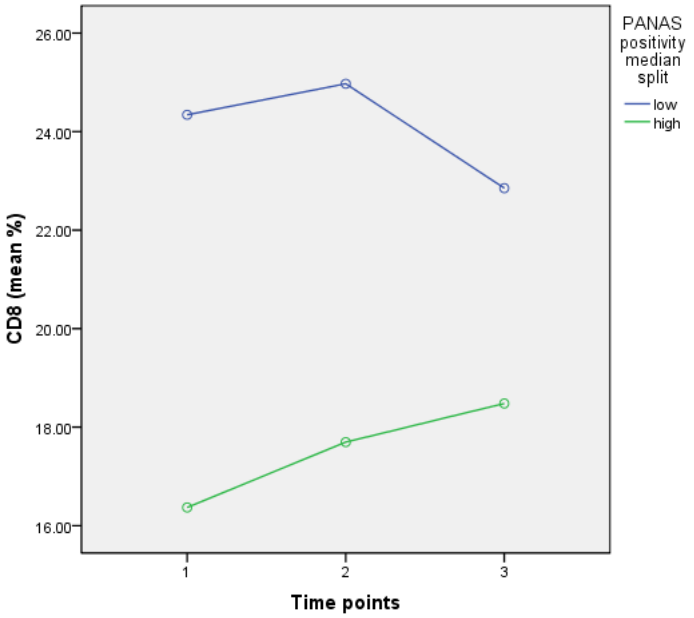

Figure O17. Median-split PANAS P and CD8 over time

The other four members of the T cell phenotype grouping are presented below for comparison.

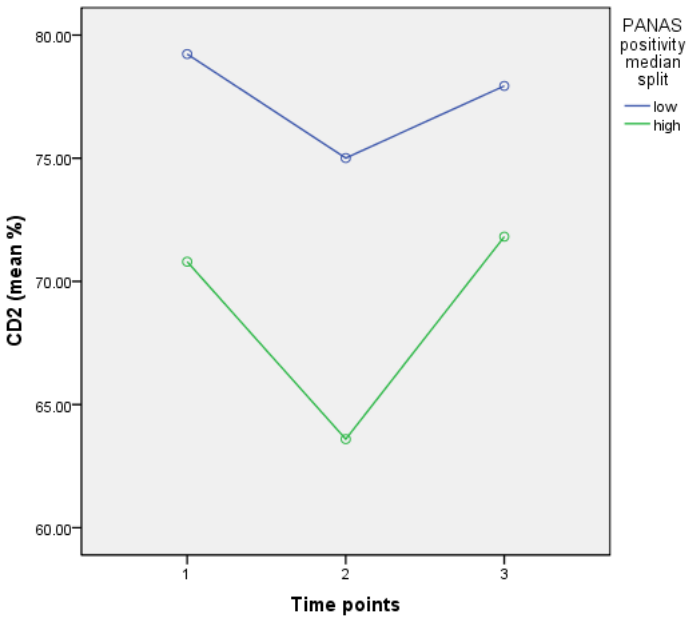

Figure O18. Median-split PANAS P and CD2 over time

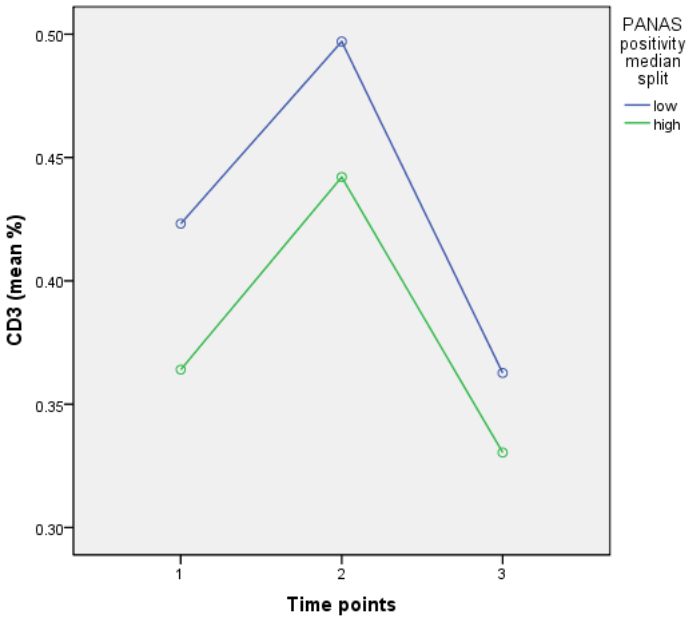

Figure O19. Median-split PANAS P and CD3 over time

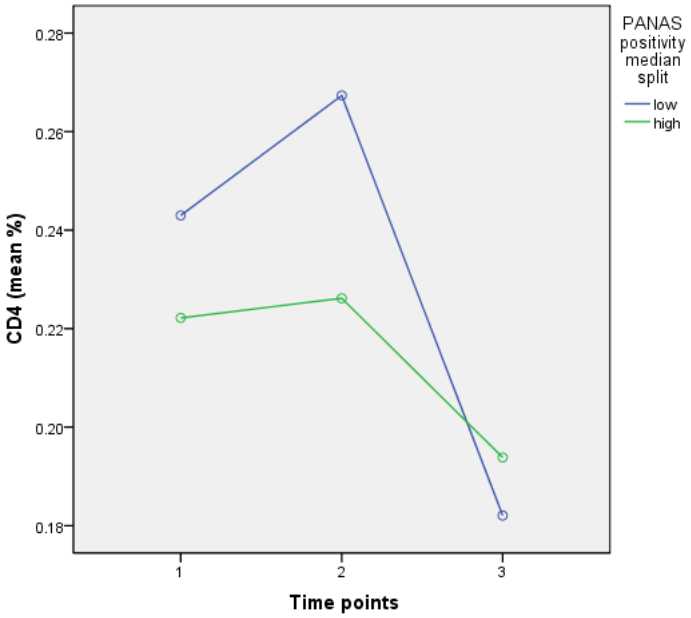

Figure O20. Median-split PANAS P and CD4 over time

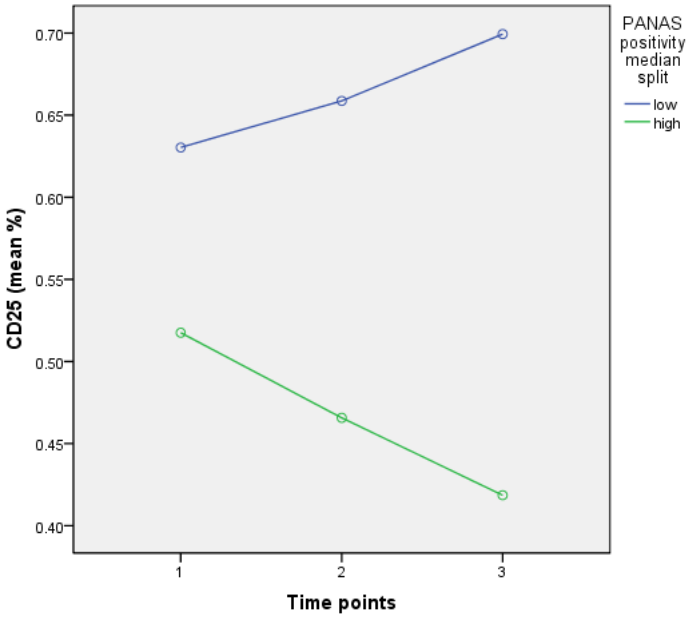

Figure O21. median split PANAS P and CD25 over time

PANAS N and PRL-R A significant between group effect was found.

Table O12:: Median-split ANOVA PANAS N and PRL-R

Source	SS	DF	MS	F	Sig
Time	.009	2	.005	.069	.934
Time x PANAS N	.206	2	.103	1.539	.221
Between Group	.377	1	.377	4.117	.049*

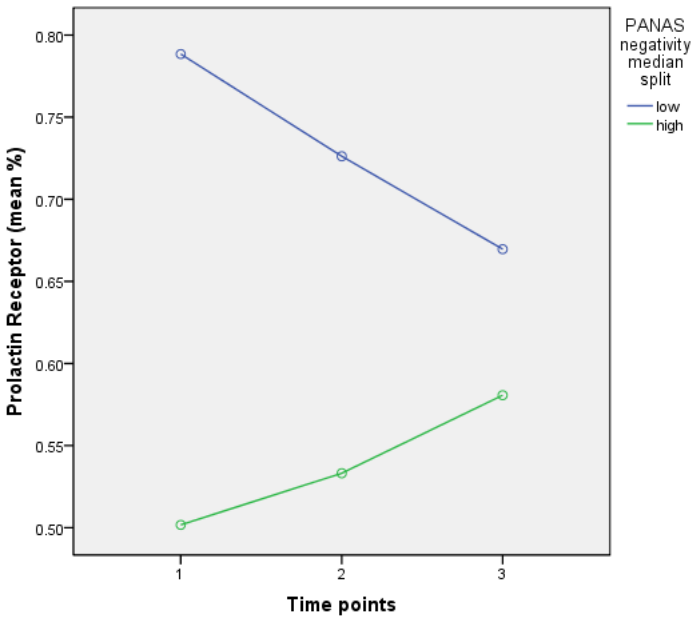

Figure O22. Median-split PANAS N and Prolactin over time

The other 5 members of the neuroendocrine grouping are presented below for comparison.

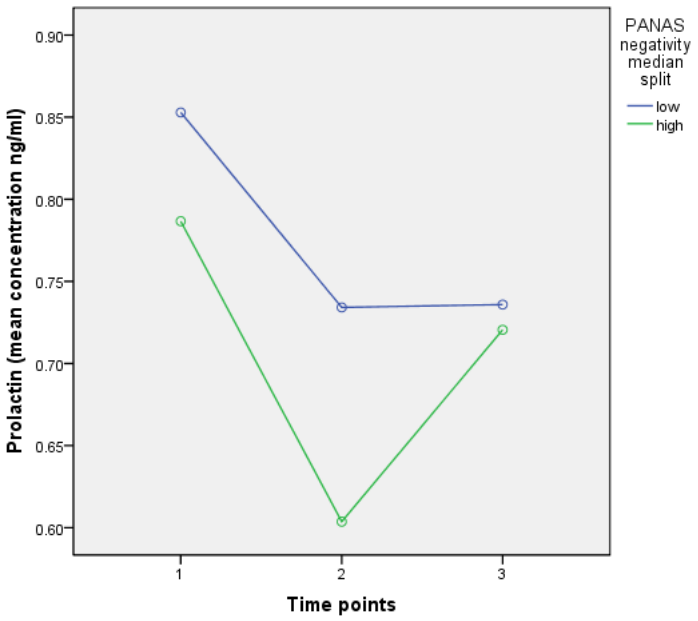

Figure O23. Median-split PANAS N and Prolactin over time

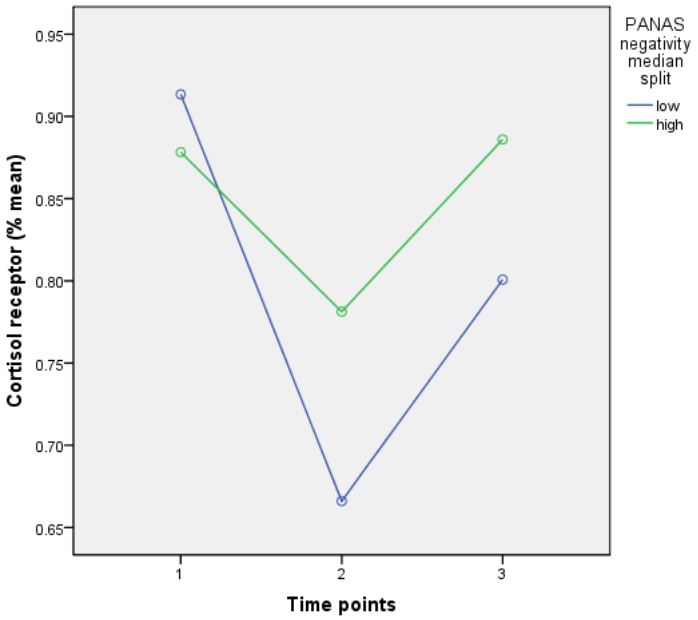

Figure O24. Median-split PANAS N and GLUC-R over time

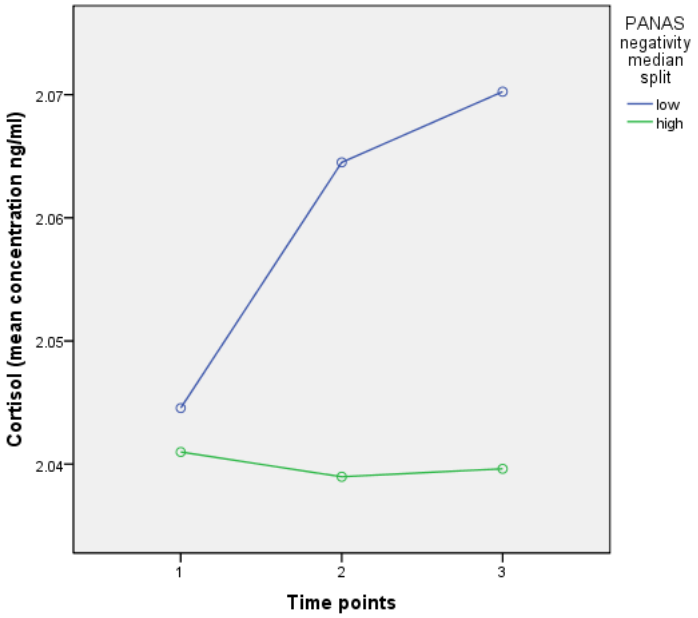

Figure O25. Median-split PANAS N and Cortisol over time

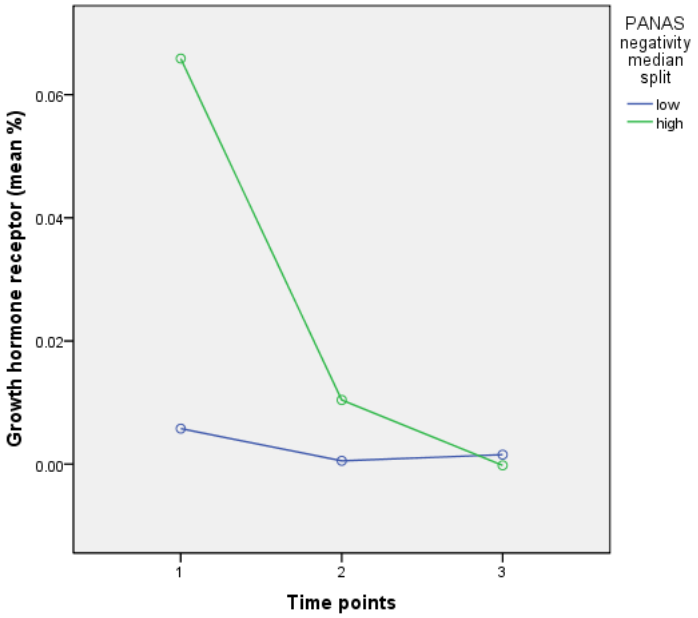

Figure O26. Median-split PANAS N and GH-R over time

As growth hormone receptor was also significantly correlated with PANAS N, a general linear model was explored. Mauchley's test indicated that the assumption of sphericity had been violated (p= <.005), and therefore a Greenhouse-Geisser correction was applied. No significant effects were found.

Table O13:: Median-split ANOVA PANAS N and Growth Hormone

Source	SS	DF	MS	F	Sig
Time	.031	1.043	.029	.950	.339
Time x PANAS N	.023	1.043	.022	.706	.411
Between Group	.005	1	.005	.906	.347

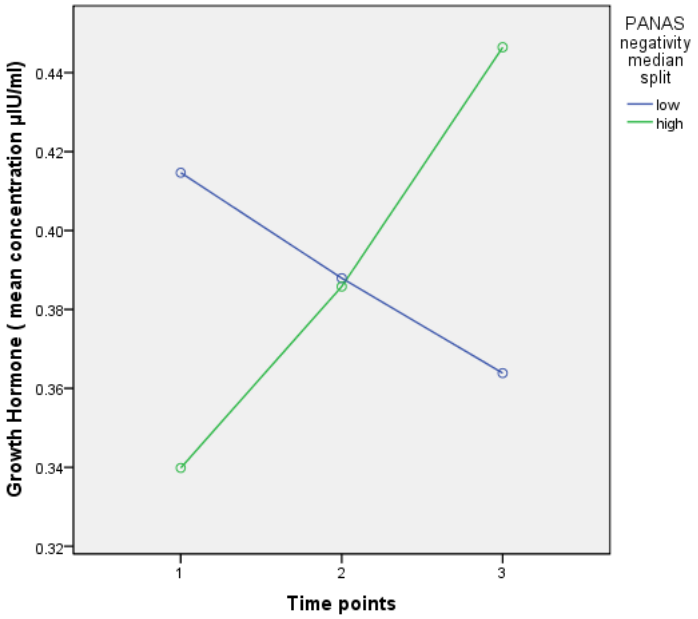

Figure O27. Median-split PANAS N and Growth Hormone over time

MHLC C and NK Only a significant time effect was found.

Table O14:: Median-split ANOVA MHLC-C and NK

Source	SS	DF	MS	F	Sig
Time	.811	2	.406	4.936	.011*
Time x MHLC C	.434	2	.217	2.638	.086
Between Group	.458	1	.458	4.107	.054

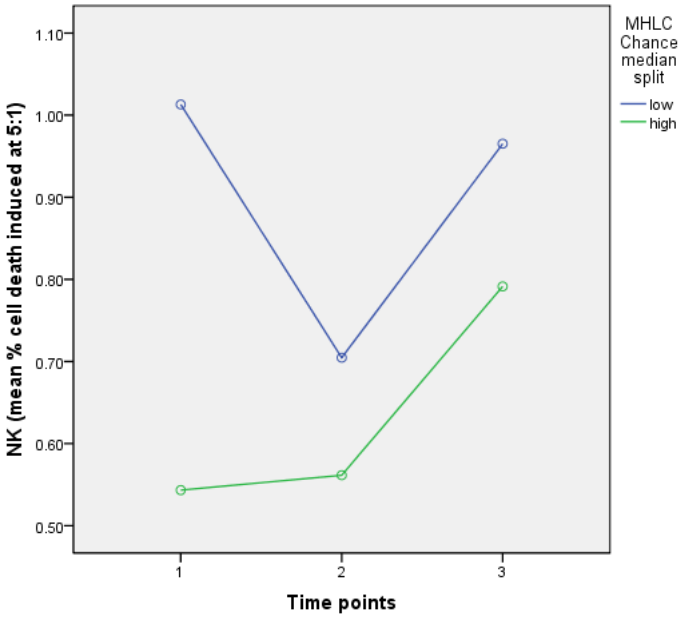

Figure O28. Median-split MHLC C and NK over time

MHLC C and Growth Hormone No significant effects were found.

Table O15:: Median-split ANOVA MHLC C and Growth Hormone

Source	SS	DF	MS	F	Sig
Time	.042	2	.021	.225	.799
Time x MHLC C	.445	2	.222	2.382	.097
Between Group	.001	1	.001	.008	.928

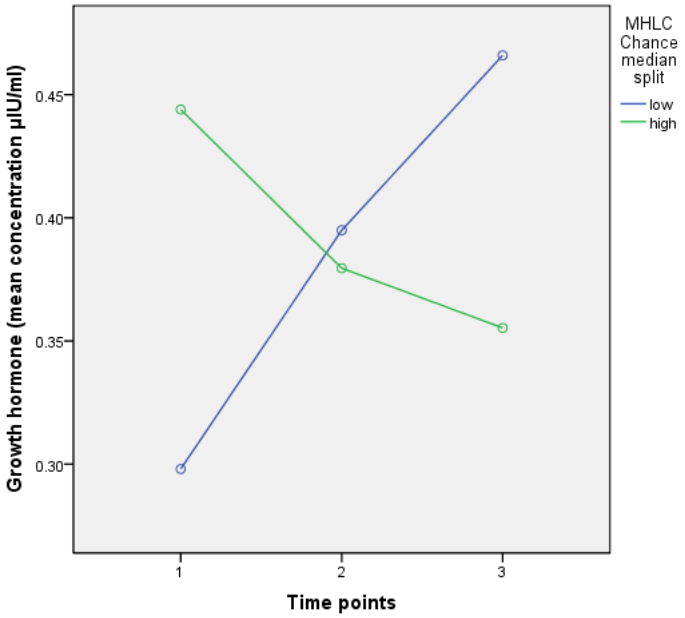

Figure O29. Median split MHLC C and Growth Hormone over time

MHLC P and NK A significant between group effect was found.

Table O16:: Median-split ANOVA MHLC P and NK

Source	SS	DF	MS	F	Sig
Time	.781	2	.390	4.544	.015
Time x MHLC P	.247	2	.123	1.437	.247
Between Group	.968	1	.968	10.614	.003*

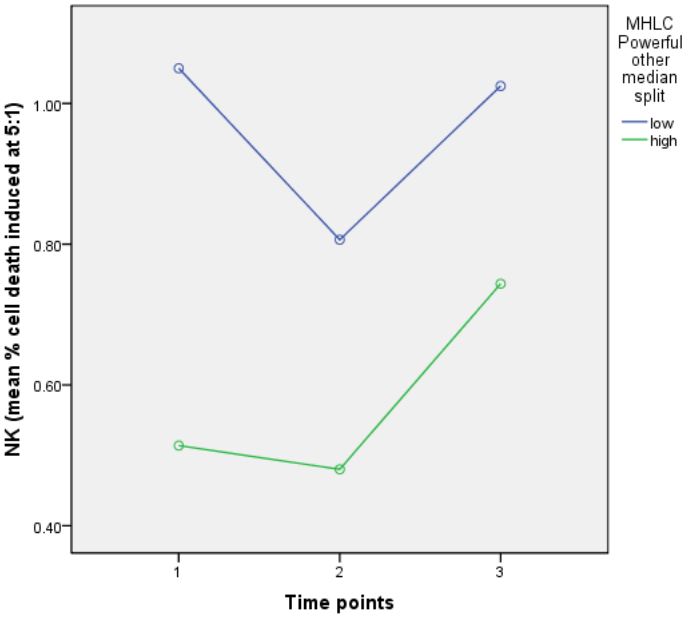

Figure O30. Median-split MHLC C and NK over time

The other three members of the killer cell grouping are presented below for comparison.

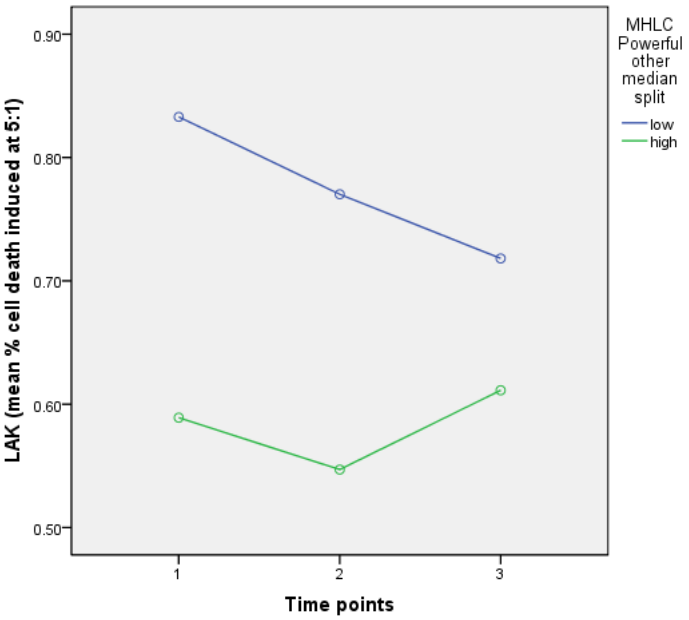

Figure O31. Median-split MHLC P and LAK over time

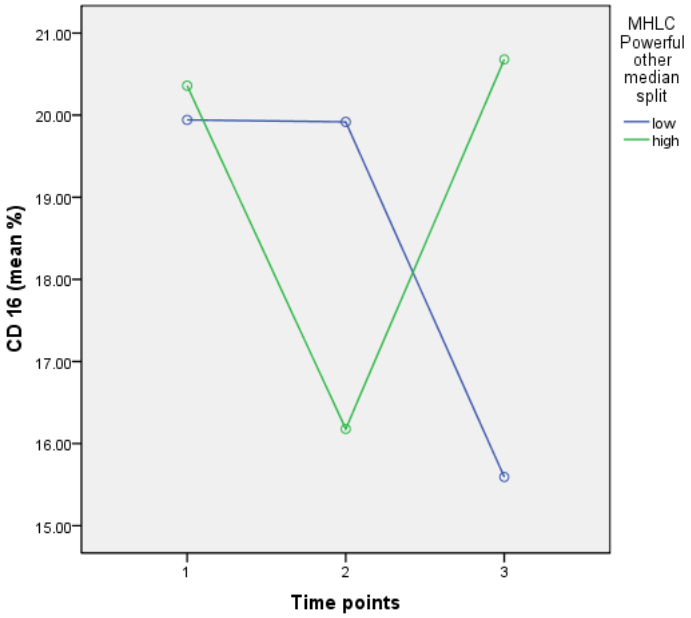

Figure O32. Median-split MHLC P and CD16 over time

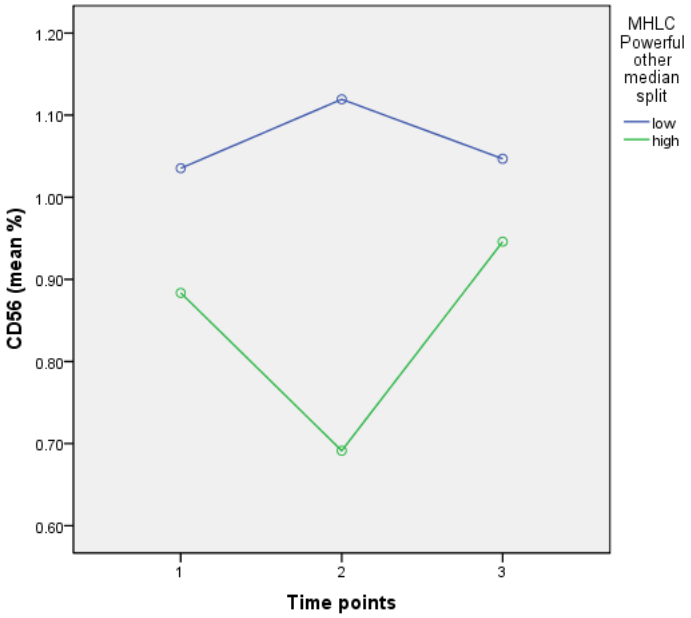

Figure O33. Median-split MHLC P and CD56 over time

MHLC P and PRL-R No significant effects were found.

Table O17:: Median-split ANOVA MHLC P and PRL-R

Source	SS	DF	MS	F	Sig
Time	.003	2	.001	.020	.980
Time x MHLC P	.238	2	.119	1.792	.173
Between Group	.093	1	.093	.942	.337

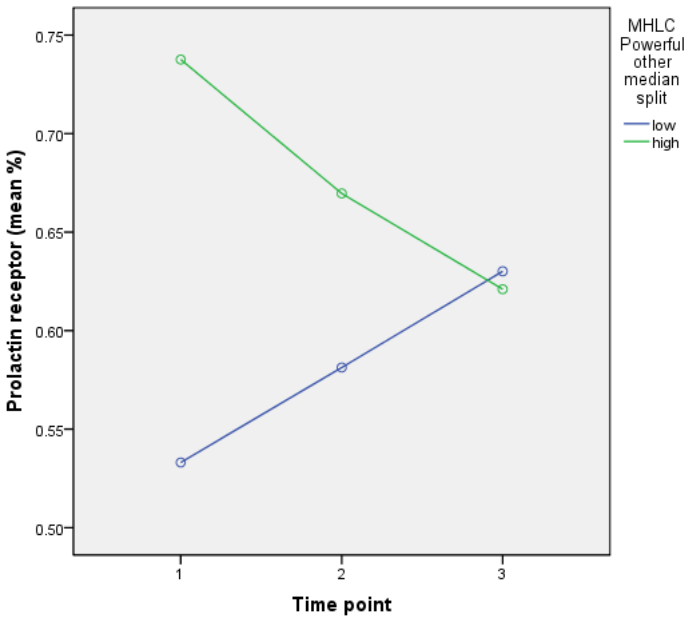

Figure O34. Median-split MHLC P and PRL-R over time

CECS D and CD2 Mauchley's test indicated that the assumption of sphericity had been violated (p= <.005), and therefore a Greenhouse-Geisser correction was applied. No significant effects were found.

Table O18:: Median-split ANOVA CECS D and CD2

Source	SS	DF	MS	F	Sig
Time	1134.338	1.486	763.399	1.971	.159
Time x CECS D	1324.669	1.486	891.491	2.302	.122
Between Group	357.247	1	357.247	1.852	.181

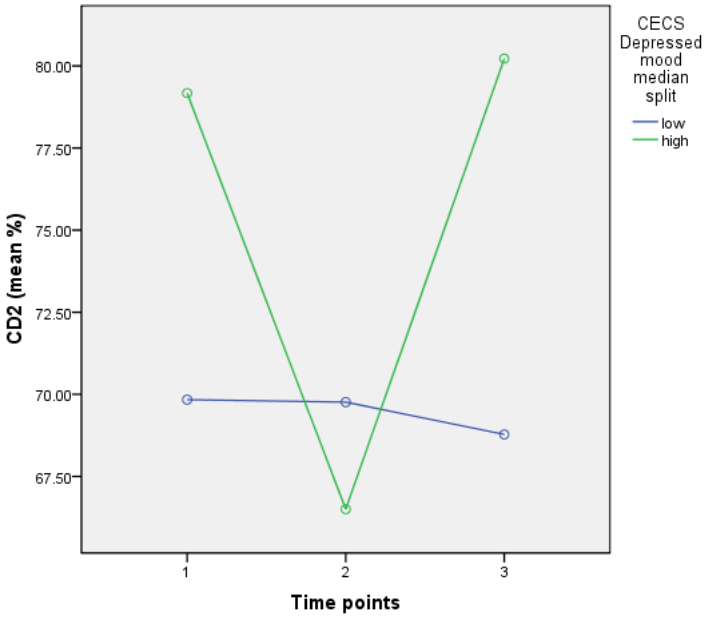

Figure O35. Median-split CECS D and CD2 over time

CECS D and Prolactin Only a significant time effect was found.

Table O19:: Median-split ANOVA CECS D and PRL

Source	SS	DF	MS	F	Sig
Time	.570	2	.285	7.499	.001*
Time x CECS D	.016	2	.008	.216	.806
Between Group	.006	1	.006	.256	.615

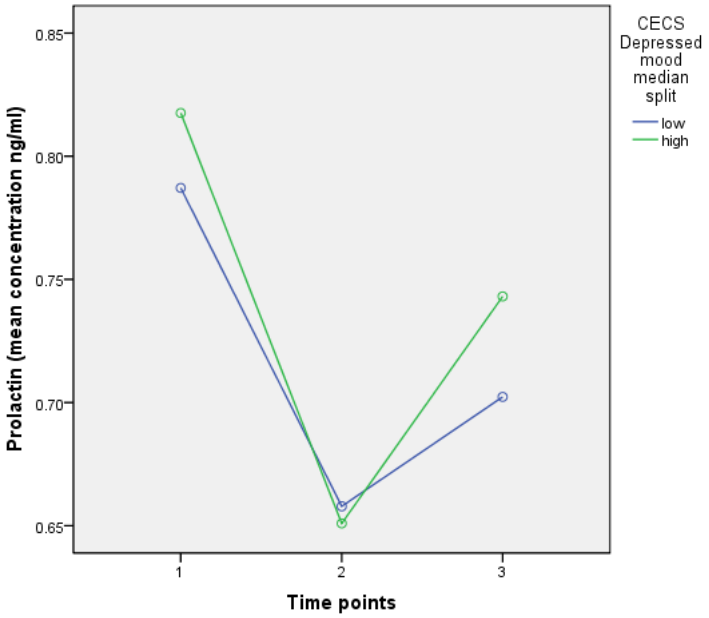

Figure O36. Median-split CECS D and Prolactin over time

CECS Total and Prolactin Only a significant time effect was found.

Table O20:: Median-split ANOVA CECS Total and Prolactin

Source	SS	DF	MS	F	Sig
Time	.655	2	.328	9.055	<.005*
Time x CECS T	.043	2	.022	.600	.550
Between Group	.016	1	.016	.688	.410

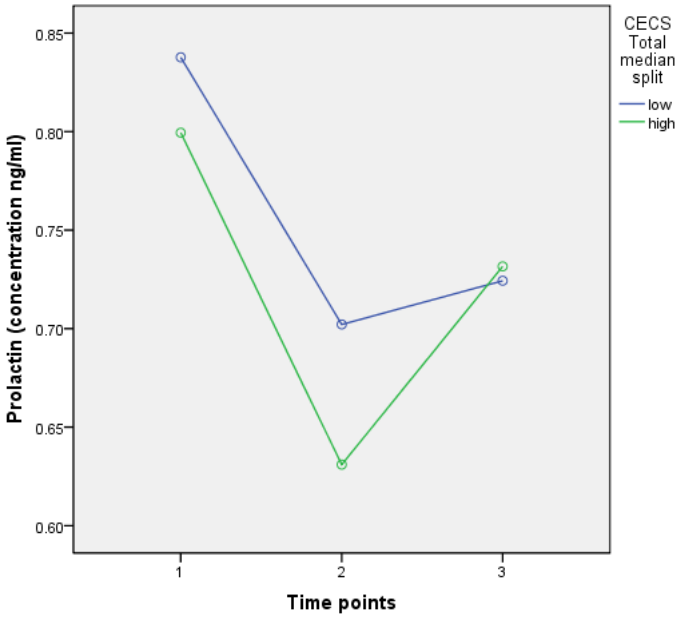

Figure O37. Median-split CECS Total and Prolactin over time