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School of Psychology

Social Support, Loneliness and Disease Markers in Colorectal Cancer

by

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ABSTRACT

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Inconclusive previous research has hinted at the significance of social support in cancer-related outcomes. Some recent studies have also attempted to show the role of proangiogenic cytokines as the possible underlying mechanisms in this relationship between social support and cancer progression. This thesis aimed to further investigate these pathways by investigating the association between social support, loneliness and disease markers in colorectal cancer.

This thesis systematically reviewed the longitudinal prospective findings ($N = 27$) on the relationship between social support and cancer progression, and found that the evidence from methodologically sound studies ($n = 16$) was strong for breast cancer (67%) but not for other types of cancer (0%) and mixed cancers (50%). It also suggested that disease-related variables should be considered when assessing the role of psychosocial factors in cancer-related outcomes.

Due to the issues associated with the self-reported assessment of social support and loneliness, this thesis aimed to use an implicit measure of loneliness, in addition to the conventional explicit measures of social support and loneliness. Therefore, Study 1 adapted and validated an Implicit Association Test of loneliness (IAT-L). This IAT-L showed low internal consistency, and weak construct and criterion-related validity in this study on 50 healthy volunteers (mean age = 24.1 years). In order to overcome these weaknesses, Study 2 used a modified IAT-L and investigated the relationship between implicit loneliness, social support, and cardiovascular reactivity to stress, to establish its predictive validity in another sample of 23 healthy female volunteers (mean age = 22.1 years). Results yielded satisfactory internal consistency of the modified tool (IAT-L (M)), and implicit loneliness was found to be more strongly correlated with cardiovascular reactivity to stress than the explicit measures of social support and loneliness. Finally, Study 3 used the IAT-L (M) to investigate whether implicit loneliness was related with the in situ levels of four important biological markers (three cytokines and oxytocin) along with explicit measures of social support and loneliness in 51 colorectal cancer patients (mean age = 68.3 years). Results showed that implicit loneliness explained significant variance in vascular endothelial growth factor (VEGF), extending previous findings with an implicit test. No significant relations were found for other biological markers. Social support and loneliness indices did not show any significant relationship with disease severity markers including stage and tumour size. Overall, this research attempted to make a unique contribution to the fields of health psychology and psychoneuroimmunology. Implications are discussed in terms of implicit testing of loneliness with reference to physiological outcomes, and devising targeted psychosocial and immunotherapeutic interventions for cancer patients with low social support.

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Abbreviations

ACTH	Adrenocorticotropic hormone
ANS	Autonomic nervous system
β	Beta
BMI	Body mass index
BP	Blood pressure
CAD	Coronary artery disease
CHD	Coronary heart disease
CNS	Central nervous system
CRF	Corticotropin releasing factor
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
IFN-γ	Interferon-gamma
IHD	Ischemic heart disease
IL	Interleukin
LVM	Left ventricular mass
MI	Myocardial infarction
mRNA	Messenger ribonucleic acid
NK	Natural killer
NKCC	Natural killer cell cytotoxicity
PNI	Psychoneuroimmunology
QoL	Quality of life
SAM	Sympatho-adrenomedullary
SBP	Systolic blood pressure
SNS	Sympathetic nervous system
SPSS	Statistical Package for Social Sciences
TNF-α	Tumour necrosis factor-alpha
VEGF	Vascular endothelial growth factor

Chapter One: Thesis Outline

The role of social support in physical health has been a focus of attention in health psychology for the past four decades. The new emerging field of psychoneuroimmunology (PNI) attempts to understand the possible biological pathways underlying this association, and progresses hand in hand with the biomedical sciences.

Chapter 2 discusses the issues related to the conceptualisation and categorisation of the construct of social support. It also sheds light on the limitations associated with the measurement of this construct and proposes techniques which can be borrowed from other fields of psychology, in order to improve the assessment and prediction of physical health outcomes. This chapter provides a necessary background for the selection and use of social support measures in the empirical studies included in this thesis.

It has been argued in the literature that social support plays an important role in cancer progression. Chapter 3 evaluates the evidence regarding the role of different indices of social support in cancer-related outcomes including cancer onset, severity and progression. Due to inconsistent findings for the precise role of social support in cancer progression, I systematically review the evidence, in order to reach a conclusive stance on the role of two most important and most frequently used indices of social support in the progression of cancer.

After discussing the role of social support in cancer outcomes in Chapter 3, in Chapter 4 I present the possible pathways which may be responsible for this link between social support and cancer outcomes. I also present a thorough summary of the evidence regarding the association of three important proangiogenic cytokines with psychosocial factors. I also discuss oxytocin as another potential mediator in the link between social support and cancer progression.

If we speculate that certain psychological states such as stress influence the course of cancer then perhaps emotional support would be the most appropriate and effective kind of support which is needed by a patient suffering from this disease.

Also, if we take into account the physical handicap due to the disease, instrumental support seems equally important, particularly after diagnosis. On the other hand, the perception of the availability of any or all kind(s) of social support is also beneficial as it is a buffer in ameliorating the effects of stressful situation. Since social support has also been suggested to be a stable variable having trait-like properties, it may be speculated that it is the overall perception of the adequacy of social support that determines its impact on physical health, influencing the course of cancer in this instance.

For the studies included in this thesis, social support and loneliness are assessed by standardised measures. Due to inconsistent findings regarding the role of social support in different aspects of physical illness, the choice of tools for the assessment of social support and loneliness is of utmost importance. These measures have been selected with due consideration for the present studies, in order to cover all the important evidence-based dimensions of these constructs.

Finally but more importantly, all of the research in the area of psychosocial oncology has been based on explicit or self-report measures of social support and loneliness. In contrast to these conventional measures, implicit measures provide indirect assessment of such constructs, which are less affected by presentational biases. Implicit measures of different constructs have been found to be more strongly correlated with physiological parameters than the explicit self-report measures of similar constructs. Since different aspects of social support may predict different disease features such as incidence/onset, severity, progression, recurrence, etc., future research in health psychology may also wish to use both explicit and implicit measures of psychosocial factors in order to maximise the chances to predict objective aspects of physical diseases.

Therefore, the aim of Study 1 is to adapt and preliminarily validate an implicit measure of loneliness. Study 2 has two purposes: to replicate and expand the findings of study 1 after modifying the implicit association test of loneliness, and to establish the predictive validity of this test, in terms of determining its efficacy to predict the physiological outcomes above than conventional explicit or self-report measures. Specifically, Study 2 aims to investigate the relationship of social support

and loneliness with cardiovascular reactivity to stress, using both implicit and explicit measures of loneliness and social support.

Study 3 uniquely measures the in situ levels of the four biological markers, discussed in Chapter 4, in colorectal cancer in order to investigate their association with social support and cancer severity markers (e.g., cancer stage). In conclusion, Study 3 aims to: (1) validate the immunohistochemical procedure to measure these biological markers in situ, (2) test if the in situ levels are associated with social support and loneliness, and (3) establish the predictive validity of the implicit test of loneliness i.e., to test whether implicit loneliness correlates with the levels of these biological markers and disease severity markers, as compared to the explicit measure of loneliness.

In the final chapter, the results of the three empirical studies are discussed with reference to their strengths and limitations. This chapter also discusses how this research has made a unique and substantial contribution to the fields of health psychology and psycho-oncology.

Chapter Two: Social Support

2.1 Aims of the Chapter

This chapter gives an overview of the history of the social support construct, and elaborates on how several definitions and conceptualisations of this construct evolved and underwent modifications over the past decades. It also addresses critical issues associated with the measurement of social support. The chapter includes an account of the literature on the role of social support in physical health. The possible pathways of this link are also covered, placing an emphasis on the physiological pathways.

2.2 History of the Concept of Social Support

Although there has been agreement in the literature on the significance of social interactions and the usefulness of the support derived from them, the definition and operationalisation of *social support* have undergone several alterations since its inception. In the process of defining it, different perspectives on the construct of social support have taken into account its meaning, source and function.

In the beginning, social support was defined as a broader concept than it currently is, merging all the associated properties and functions. The terms which fell under this umbrella were *intimacy*, *social integration*, *nurturance*, *worth*, *alliance* and *guidance*, and were used interchangeably by the researchers (Weiss, 1974). At this time, the specific sources and functions of social support remained undetermined and ambiguous. Sarason, Levine, Basham, and Sarason (1983) specified this wide array of definitions by placing emphasis on the missing information, and redefined it as the existence or availability of significant others to provide support, care, value and love. This concept was construed as resources provided by other persons in interpersonal transactions (Cohen & Syme, 1985) and highlighted the function of social support. The function of social support also emerged with reference to self-esteem i.e., an unconditional reassurance that support would be available whenever needed and that this was beneficial for the physical and psychological integrity of the individual (Caplan, 1974).

Cobb (1976) further asserted the importance of social support as a moderator of stress during different stages of the life cycle starting in *utero*. She defined social support as a belief that one is loved (emotional support), valued (esteem support) and connected or attached (network support). Barrera and Ainlay (1983) identified and labelled five major categories of social support as material aid, behavioural assistance, intimate interaction, feedback and positive social interaction. These categories were also summarised as the provision of three important functions of aid, affect and affirmation (Kahn & Antonucci, 1980). Some major and frequently used classifications of social support categories will be discussed in the later section of this chapter.

2.3 Theories Supporting the Significance of Social Support

The significance of the presence of social forces has been highlighted by several theorists since early times. In his book *Suicide*, Emile Durkheim (1966) describes how social forces are capable of modulating the behaviour of individuals in a society. The insufficient social integration caused by the lack of social or moral framework could lead to disorientation and alienation from the society resulting in a state of *anomie* or social instability. John Bowlby (1969), a British developmental psychologist who was inspired by the psychoanalytic and learning theorists, postulated that a child's first human relationship with the mother is the foundation stone of his or her personality. He related attachment behaviour with survival and described it as "a means of protection from danger and a source to learn the basic activities which are central to survival" (p. 223). He also classified attachment behaviour as a class of social behaviour which is "held to have a biological function but can establish the basis of future social experiences" (Bowlby 1969, p. 260). Abraham Maslow (1954) in his popular *theory of hierarchy of needs* discussed the need for affiliation and belongingness as one of the basic needs, and suggested that receiving and giving love, affection, trust and acceptance, affiliating and being part of a group are not only essential for survival but also for reaching the authentic elevation as a human being called the self-actualisation.

2.4 Lack of Social support: Social Isolation and Loneliness

Loneliness is a psychological state which results from the discrepancies between one's desired and actual relationships (Peplau & Perlman, 1982). Therefore, loneliness can be seen as a subjective feeling (Lynch, 1977) and a product of social isolation which is an unpleasant or inadmissible lack of (the quality of) certain social relationships (de Jong-Gierveld, 1987). Others have called social isolation and loneliness subjective feelings and put them on a continuum (Killeen, 1998). Either way, social isolation can be considered as a precursor of loneliness. Rokach (1988) also listed interpersonal isolation as a source for the subjective experience of loneliness.

An important determinant of loneliness in social isolation is choice (Killeen, 1998) which determines whether social isolation leads to aloneness, more positive states like solitude, or a negative subjective state of loneliness. An individual who embraces solitude and is alone by choice is less likely to experience loneliness than someone who has no control over his social isolation. Figure 1 depicts the alienation-connectedness continuum where the importance of choice and society's perception of the concepts influence the way in which social isolation is perceived.

It is important to note that loneliness may well be a result of inadequate social skills when people are unable to form relationships or maintain them (Wittenberg & Reis, 1986), or associated with problems in social relationships (de Jong-Gierveld, 1987) in which case it is more likely to produce the negative impact. Hence, loneliness as a subjective experience relies on the perception and personal interpretation of the situation, emphasising the role of cognitive appraisal (Perlman & Peplau, 1981).

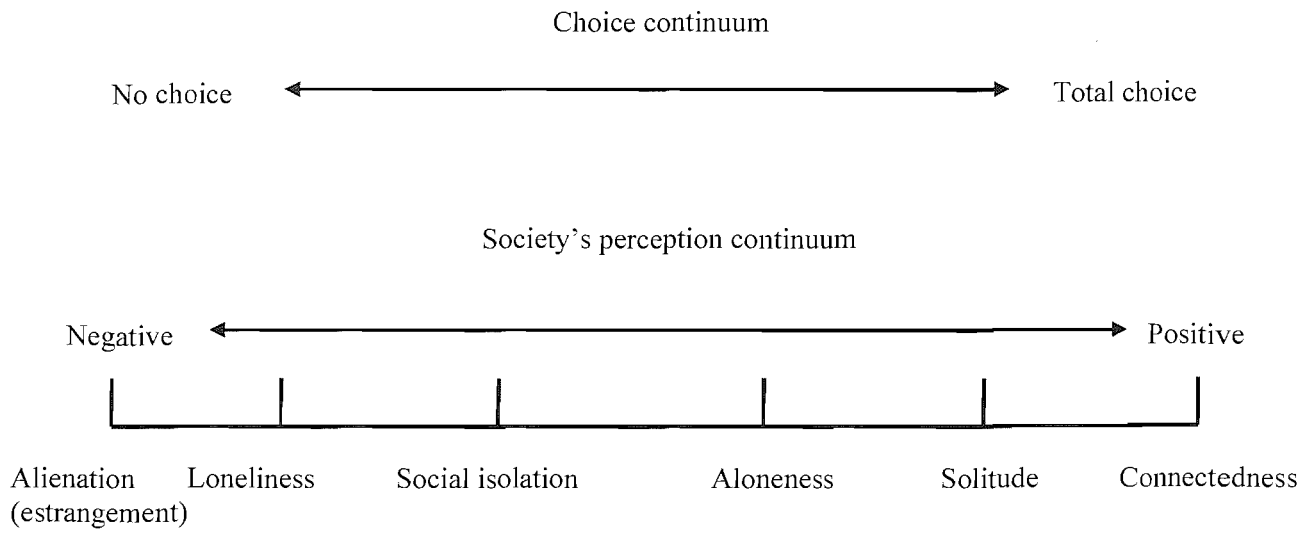

Figure 1. Alienation-connectedness continuum.
(Killeen, 1998).

2.5 Classification of Social Support

2.5.1 Tangible and Intangible Support

Heitzman and Kaplan (1988) categorised social support into tangible and intangible support. The former includes instrumental and informational components, and emotional and appraisal support constitute the intangible support. Although the significance of the emotional aspect of social support has been highlighted in several studies, instrumental support is particularly relevant to the adjustment in physically ill patients (Gottlieb, 1984).

2.5.2 Perceived and Received Support

A further development in the process of defining social support is the division of this construct into two frequently used dimensions, namely perceived and received support. Perceived support constitutes an individual's perception of the provision of or the existence of the sources of support. Received support, as the name indicates, is an estimate of support actually provided or received. It can also be defined as the support which is utilised in the face of crisis or need. It could be the view of the

recipient of support, the provider of support, an independent observer, or a combination of more than one of these.

Both these categories should ideally be positively associated. However, a low (Milbrath, 1979) or no correlation has been found between the two (McCormick, Siegert, & Walkey, 1987). Received and perceived support may have beneficial effects on individuals in different ways. While received support may help by providing targeted support in the time of need, perceived support operates rather indirectly by taking an overall view of the potential available support or external resources one may have. The perception of being loved and cared for, and the anticipation that help will be available if the need arises, has its own benefits. Since the perception of the availability of social support enhances one's sense of self-efficacy and minimises the effect of stressors (Sarason & Sarason, 1994), the role of perceived support in reducing physiological stress responses may be of greater importance than received support, and may provide a link between the objective environmental stimuli and physical health (Kiritz & Moos, 1974).

A study on cardiac patients and their spouses revealed that perceived support had a greater impact on the adjustment to the first cardiac event than received support (Helgeson, 1993). Wethington and Kessler (1986) proposed two explanations for the superiority of this index. First, people who perceive that the support would be available if needed may seek and hence elicit more support from their network than people who think otherwise. Second, the perception of available social support alters the individual's appraisal of the situation in which the need for social support arises rather than actually making the situation better. In a study which aimed to discriminate between the roles of received and perceived support on stress, received support from the spouse was found to be significantly associated with low distress, but this effect disappeared when perceived support was added to the model, suggesting that the perception of the availability of support can determine the experience of stress (Folkman, Schaefer, & Lazarus, 1979; Lazarus & Launier, 1978). This finding also suggests that the possible effects of received support on stress responses are mediated by perceived support. Moreover, the occurrence of stressful events may interact with perceived support in relation to the levels of stress experienced. This was supported in a large-scale national survey of married people,

where Wethington and Kessler (1986) also found that the effect of perceived support was greater in the presence of a stressful event than in its absence, suggesting the buffering effect of social support (buffering model of social support will be discussed later in the chapter). However, received support, particularly instrumental support, has been positively correlated with adjustment to physical illnesses (Gottlieb, 1984). A possible explanation for this association can be that the level of assistance by significant others is a function of recipient's crisis severity (Thoits, 1982) and limitations of physical functioning predict relative increases in the levels of social support (Moyer & Salovey, 1999).

Another synonymous term to received support called enacted support was introduced by Tardy (1985). It is defined as the actual actions performed by others to assist a person. Further in research on the role of perceived support and the factors which contribute to this perception, an interesting concept of veridicality of social support was introduced and tested by Antonucci and Israel (1986). Veridicality of social support refers to the congruence of perception or agreement between the recipient and provider about whether social support is received or provided respectively. This concept is different from perceived social support as it also takes into account the provider's view and hence addresses the issue of reciprocity and validity by others. There is evidence that veridicality was associated with feelings of closeness (or vice versa) but not with well-being (well-being included life satisfaction, happiness and lower level of negative affect). However, it was found that well-being was more efficiently predicted by the perception of reciprocity, which was the level of support exchanged as reported by the principal respondent. One limitation of this veridicality study was that the quality and quantity of support *per se* were not determined, and the emphasis was on the matching between the reported levels of support. These results suggest that closeness may be influenced by veridicality but overall well-being may be more influenced by one's subjective perception of support regardless of whether or not it was actually received. In another study, although the discrepancy between the recipient and provider's assessment of social support increased gradually from baseline at breast cancer surgery to 3 and 13 months later, it did not predict levels of psychological distress on the part of the patients (Moyer & Salovey, 1999).

2.5.3 Structural and Functional Support

The structural versus functional support is one of the most widely used categorisations, and was introduced by House and Kahn (1985). The structural aspects of social support include the properties of the social network e.g., size, range, density, boundedness, proximity, homogeneity and reachability. Whereas, functional support refers to the function served by the structural support components i.e., the provision of social support. The reasons for using the structural indices are their simplicity and objectivity. However, this index is often criticised for its simplicity since it provides limited information and objectivity may not provide information on the quality of support. Therefore, it may not be a reliable and valid measure of social support (Stokes & Wilson, 1984). Although the number of social ties can be seen as a crude measure of one's social integration on the assumption that the presence of more people means more support, it can be misleading as people in the network may also be a source of conflict and stress (Due, Holstein, Lund, Modvig, & Avlund, 1999). Another study endorsed these results suggesting that the presence of more people in the household was positively correlated with depression in breast cancer patients (Nausheen & Kamal, 2007). This shows that considering the classical indicators of social support such as network size may be of less utility when assessing a link between social support and health outcomes.

It is critical to distinguish network size from the precise source of social support because some relations e.g., family, despite being a vital part of one's social network are usually not chosen by the individual and hence may not be a source of adequate social support. Seeman and Berkman (1988) studied the correlations between structural characteristics of social networks, and instrumental and emotional support which are two important functional indices of social support. They found that both instrumental and emotional indices of social support were only weakly correlated with the network size. Both proximal and distant ties were important with reference to emotional support while only the former were important for instrumental support. However, adequacy or satisfaction with support was not significantly determined by either network size or its proximity. An interesting finding in this study was that the presence of a confidant, and not of a spouse, was associated with perceived support adequacy, suggesting caution on the use of marital status as a

measure of social support. However, the elderly sample of this study may restrict the generalisibility of the results.

Loneliness has been inversely correlated with the structural indices of social support (Cutrona & Peplau, 1979; Russell, 1996), functional social support (Jirka, Schuett, & Foxall, 1996), quality of social relationships (Borys, Perlman, & Goldenberg, 1985) and family function (Kim & Baik, 2002). However, some evidence suggests that feelings of loneliness are more closely associated with the quality rather than the quantity of social relationships (Akerlind, Hornquist, & Hansson, 1987). Levels of and satisfaction with emotional and tangible supports are inversely correlated with loneliness (Kim, 1999), and problems and conflicts in social relationships (de Jong-Gierveld, 1987; Jirka et al., 1996).

These facts point to the conclusion that the nature of the relationship among different categories of social support is complex, and the recipient's own conceptualisation and assessment of social support is more important in order to determine its effectiveness. Moreover, the terms *network size* and *social support* are distinct, and hence should not be used interchangeably.

2.5.3.1 Marital status.

Marital status is another structural dimension which has been used as a proxy for social support. Researchers used the commonly held view that married people are more likely to have higher social support than unmarried people. In a study of the effects of social support on loneliness in women with different marital status, Essex and Nam (1987) found that married and never-married women were the least lonely while formerly-married were the loneliest. Results of another study suggested that these differences were more pronounced in unmarried men than in unmarried women (Pinquart, 2003). Steptoe, Owen, Kunz-Ebrecht, and Brydon (2004) found that the levels of loneliness were lower in married than single or divorced middle-aged men and women, and were positively correlated with social isolation and low emotional support. Social isolation was assessed by structural support indices of marital/relationship status, number of relatives outside the household, and frequency of visits to friends and relatives. An interesting study examined social support by

using both males and females as providers and recipients to investigate its effects on cardiovascular reactivity to stress in the laboratory. Social support provided by women reduced cardiovascular changes for both men and women facing stress, as compared with nonsupportive women. Social support from men did not (Glynn, Christenfeld, & Gerin, 1999). These findings suggest that gender may play a complex role with reference to social support and health.

According to the dual-path model of the relational theory of loneliness, Weiss (1975) described two different types of loneliness: emotional loneliness resulting from emotional isolation which is a loss of a source of emotional fulfillment; and social loneliness which results from the absence of a social network and/or its components. Although some studies failed to find these specific effects of different types of loneliness, van Baarsen (2002) interestingly found that the loss of the partner produced both emotional and social loneliness.

Asserting the importance of marital status, there is interesting evidence that the fluctuations in the quality of the marital relationships can have detrimental effects on the mental health, particularly of women. Lieberman (1986) however, argued that it would not be realistic to equate poor marital relationships with lack of social support, and suggested that marital relationships are a source of stress and support. It is important in this respect that if the partner's support is not perceived to be sufficient, other confiding sources may not provide an effective substitute (Brown, 1978).

Marriage may provide an opportunity to maximise the social arena in the form of relations-in-law and possibly children, and being married has been associated with lower levels of loneliness (Carr & Schellenbach, 1993). Since marital status can have a salutary effect on the well-being through the provision of social support, the relationship between being married and lonely may also be mediated by the support one receives from their partner (Barron, Foxall, Von Dollen, Jones, & Shull, 1994). This highlights the significance of the role of quality of marriage in its link with loneliness as the beneficial effects of the presence of people or social support may be annulled by conflicts with its providers.

In conclusion, despite the suggested controversial role of marriage in the provision of social support, this index has been used frequently, mainly due to the ease of measurement.

2.6 Negative Effects of Social Support

The negative effects of social support are not only confined to the unavailability or insufficiency of social support but also to the presence of the surplus or detrimental aspects of social relationships.

2.6.1 Conflictual Relationships

Conflict is an integral part of social relationships as people in the social network can be a source of social support as well as strain. Drawing from the prospect theory of economics (Kahneman and Tversky, 1979) and the larger effects of losses than gains, Diener and Oishi (2005) proposed that the negative effects of social relationships possess the tendency to outweigh those of the positive ones. They also gave evidence from research done by Gottman (1994) in which negative marital experiences were perceived more frequently than positive experiences, despite being equal in number.

The dual aspects of social relationships must be taken into account to assess the quality of the social relationships comprehensively. Rook (1992) suggested the possibility that the positive effects of social interactions may be superseded by the negative effects. This view was supported in a study which suggested the contrasting effects of positive and negative interactions. Pagel, Erdly, and Becker (1987) studied the spouse caregivers of patients with Alzheimer's disease and found that the upsetting aspects were positively correlated with depression whereas, helpfulness was unrelated to the levels of depression at baseline and after 10 months, after controlling for age and sex of the caregiver. Barrera (1980) drew a distinction between the members of one's social network who are a source of the positive social support and those who are not. He categorised the providers of negative support in the conflicted network, and asserted that the size of the conflicted network is positively correlated with several psychological (Sandler & Barrera, 1984) and

physical (Rook, 1984) symptoms unlike the positive network which has a beneficial effect on the symptoms.

Conflicts in marital relationships and the resulting distress have also been associated with objective indicators such as cardiovascular morbidity and mortality (Orth-Gomer et al., 2000). Rook (1992) highlighted several conceptual and methodological questions which need to be answered in research on supportive and problematic social exchanges, and suggested that social relationships may be studied as a complex construct and their dual nature should be taken into account for their role in the psychological and physical well-being. She also identified an important possibility of threshold effects of social support and discussed the findings regarding the beneficial effects of social relationships which were more prominent when comparing at least one supportive confidant versus no supportive relations.

Koopman, Hermanson, Diamond, Angell, and Spiegel (1998) assessed aversive social support in addition to positive social support and defined it as characterising little help, too many demands and criticism. They found that aversive social support was associated with greater mood disturbance.

2.6.2 Relational Strain

Relational demand or strain is a distinct aspect of social relationships and should not be confused with lack of social support. Due et al. (1999) designated it to be a negative dimension of the functional aspect of social relations and defined it as the extent to which functions of social relationships cause emotional or instrumental strain.

2.6.2.1 Overprotection.

Rook (1992) discussed how the detrimental effects of social exchanges may arise by an increased vulnerability of an individual to stress which their loved ones may experience, and may result from providing support in the time of crisis or from inadvertent behaviors such as interference with the medical regimens, modeling unhealthy behaviors and being overprotected. In a sample of men recovering from

congestive heart failure and myocardial infarction, Garrity (1973) found that the more concerned the family was about a man's health, the fewer hours he worked after the attack. Likewise, Lewis (as cited in DiMatteo & Hays, 1981) reported that patients from over-protective families were less likely to return to work. These findings demonstrate the significance of perception with reference to the role of social support and highlight the important role of need i.e., social support and its need may interact with each other to have the beneficial effects.

To conclude, the complex concept of social support has come a long way from a general to specific construct. Since different components and aspects of social support may predict specific outcomes in health psychology, a need for a careful operationalisation of social support is warranted in order to compare the findings in this area and to weigh the significance of this construct. So far, the literature has shown that different indices of social support may yield dissimilar findings. It is imperative to define and categorise social support in order to reach conclusions regarding the significance of its role with reference to physical and psychological health. Structural-functional and perceived-received indices of social support reveal useful information which may differentially predict health-related outcomes.

2.7 Measurement of Social Support

2.7.1 Overview

The literature on social support is saturated with a wide range of self-reported tools. Due to the lack of specificity and variation in the process of operationalisation as discussed in the above section, it becomes difficult to compare the results of studies which used various different measures. O'Reilly (1988) reviewed the available instruments and addressed the methodological issues faced in the measurement of social support. He reviewed 24 functional support and 9 structural support measures. Despite some of the common elements in the function of social support, he found the appropriate conceptual definition of the construct in only 14 out of the total 33. He also found that the items of the questionnaires lacked the clarity of the concept and derived the level of social support from the network format i.e., structural indices. As a result, although these indirect indices were found to be

associated with different health-related outcomes, the connection between the investigators' definition and the operationalised measures was weak or non-exist in some cases. The weakest type of instruments in terms of the reliability and validity were the ones which were relying on a limited number of items and using a broader definition such as availability of a confidant to seek help in dealing with life. Therefore, it was concluded that the construct of social support needs to be broken down into operationally defined components to facilitate objective measurement.

Another important issue which was raised by O'Reilly was whether the instrument was for a general or a specific population. The latter may be more effective in seeking information regarding the issues of that particular population and hence may depict a clearer picture of the degree of the role of social support with respect to health-related aspects.

Finally, it is important to distinguish between everyday support or the general level of social support and the support provided in critical times. O'Reilly identified problems with measuring both types as everyday support could be taken for granted which could hinder the measurement. Since it is not usually measured prior to the crisis, the latter could be contaminated by emotional aspects associated with the crisis situation. He also criticised the use of the diverse indicators of social participation like club and church memberships, which are components of structural support and reflect misconceptions and nonclarity in defining the construct of social support.

Moreover, the reliability and validity of the instruments turned out to be weak in this review and it was suggested that more rigorous measures were needed to establish these indices. Validity measurements were limited to the face validity in most of the instances and where they applied, resulted in only modest evidence. Also, in some cases, it resulted in nonsupportive evidence towards the validity of the instruments. Reliability measurement was more promising than validity in the case of the functional support instruments but not in the case of the structural indices of social support, where most of the data was missing. However, there were major shortcomings in some cases such as using someone from one's social network to

verify the levels of social support, which may not be a true indicator of available social support as perceived by the recipient.

Another important issue is the possible overlapping among the measures of different categories of social support. Although the categories of emotional, instrumental and informational support are conceptually different from one another, it is difficult to distinguish them in naturalistic settings because they are not independent of each other (Cohen & Wills, 1985).

Sarason, Shearin, Pierce, and Sarason (1987) indicated that it was important for social support measures to correlate among themselves in order to facilitate the comparability of the findings and to ascertain their validity. They compared different measures of social support and the selection of those measures was based on different theoretical perspectives on the definition of social support. They found that received support and structural characteristics of the network were not highly correlated. However, both of these measures correlated moderately to perceived social support. Moreover, received support and structural support were less strongly correlated with loneliness than perceived support. Also, these correlations were stronger for women than for men. In their paper, they highlighted that the mode of collecting information on social support is important and may, in some instances, yield different results. However, in their review, the mode of the assessment of social support did not yield any significant differences. Both questionnaire and interview techniques evoked similar information regarding the social support. An important point made was that the yes/no format of the questionnaires or interviews had the most sensitive range in the low to moderate range of social support, whereas 0-9 or 1-6 point Likert scales differentiated at higher levels. An account of some of the widely used social support questionnaires is given in Table 1.

Table 1. Some of the widely used social support questionnaires.

Questionnaire	Type of social support assessed	Definition of social support
Social Support Questionnaire (SSQ ; Sarason et al., 1983)	(1) Structural support (2) Functional support	(1) Perceived available support (2) Satisfaction with perceived available support
Social Network List (SNL; Stokes, 1983)	Structural support	Size, density and number of friends, relatives and confidants
Inventory of Socially Supportive Behaviours (ISSB; Barrera, Sandler, & Ramsey, 1981)	Structural support	Frequency of received supportive behaviours in the past month
Family Environment Scale (FES; Moos & Moos, 1981)	Functional support	Amount of perceived support from family
Interpersonal Support Evaluation List (Cohen, Mermelstein, Kamarck, & Hoberman, 1985)	Functional support	Perceived availability of tangible support, appraisal support, self-esteem support and belonging support
Perceived Social Support from Friends and Family (PSS-Fr, PSS-Fa; Procidano & Heller, 1983)	Functional support	Perceived extent to which family and friends fulfil the individual's need for support, information and feedback
Inventory Schedule for Social Interaction (Henderson, Duncan-Jones, Byrne, & Scott, 1980)	Functional support	Perceived availability and perceived adequacy for each of two dimensions: attachment and social integration
The Quality of Relationships Inventory (QRI; Pierce, Sarason, & Sarason, 1991)	Functional support	Amount of support, conflict and depth for each of the person nominated

Note. Adapted from Sarason et al. (1987).

2.7.2 Limitations of Self-Report Measurement

The measures employed to assess social support, the absence of social support or the degree of loneliness, primarily used verbal and/or self-report methods. These methods are most commonly used in psychosocial research owing to their cost effectiveness and easy administration. The literature on social support, which is saturated with a large number of self-reported tools measuring a wide range of aspects of this construct, provides researchers a variety to choose from. However, since these measures are primarily based on self-reports, the findings in this area are contaminated by the limitations of this particular mode of measurement. These limitations are similar to those of any other self-report measures.

2.7.2.1 Response biases.

The response biases relevant to the measurement of social support include social desirability, presentational bias and the Hawthorne effect. These stem from the motivation to present oneself in a favourable or agreeable light and manifest in the form of altered response on self-report or explicit[1] measures. This mode is sensitive to these biases because it provides an opportunity to alter the responses if such motivation exists.

The degree of these biases depends to a great extent on the construct's self-presentation potential or social sensitivity (Fisher & Katz, 2000) i.e., the respondents are motivated and hence are more likely to *fake* on the self-report measures if the construct being assessed holds a value in the social or cultural system. There is evidence that some values are more socially desirable than others e.g., a consumer research survey found that values like warm relationships with others were the most important to Americans along with self-respect, security and a sense of accomplishment (Beatty, Kahle, Homer, & Misra, 1985). Interestingly, some personality characteristics may also be relevant in this respect. Lieberman (1986) addressed these issues with the assessment of social support in his commentary "social support – the consequences of psychologising." He quoted Brown's (1978)

[1] The term *explicit* means overt and refers to self-reports. It is used to denote the nature of the mode of measurement, and to create a comparison and understanding of the term *implicit*, which will be discussed in the next section.

stance that some people, although embedded in social relationships, claim that they never required any help from the relations in order to deal with their problems. Moreover, the knowledge regarding the purpose of the studies may influence the self-reported responses. Therefore, the responses based solely on the respondents' report may provide insufficient and sometimes misleading information. Also, in order to conform to the social norms the possibility that the motivation to fake the responses on the self-report measures of social relationships may result in altered response is likely to happen. Paulhus (1984) suggested two essential components of social-desirability bias: self-deception, where the response is honest but reflects an overly favourable light; and impression management, which involves the conscious motivation to alter the responses in order to make them more socially acceptable or impressive. The former being an intrinsically motivated trend is associated with personality characteristics such as self-esteem and optimism (Winters & Neale, 1985).

On a concluding note on the biases affecting self-reports, Loving and Agnew (2001) suggested that research can be contaminated on both theoretical and applied levels i.e., the biased data leading to the development of compromised theories and the inefficient interventions based on the biased data may result in persistence of social problems.

2.7.3 Implicit Measurement

In attempting to address the inherent weaknesses of self-report measurement of social support, I propose to measure it by an implicit measure to investigate if it provides an effective alternative or more useful substitute to the conventional self-report (also called the explicit measures). Implicit measures have been frequently used in the recent years to measure socially sensitive issues such as prejudice, stereotypes, attitudes, etc. The purpose of these measures is to assess the sensitive or bias-prone constructs without having to directly ask the participants. Various implicit techniques and tools have been tested in social psychology. A summary of the existing implicit measures is given in Table 2.

Table 2. A summary of the existing implicit measures.

Measure	Task	Previously used for
Stroop task (Stroop, 1935)	To name the colour of the cards on which critical and neutral words appear. The response latency and error rate are higher for cards with critical words than for the ones with neutral words	Alcohol cognitive bias (Cox, Yeates, Reagan, 1999)
Word-fragment completion (Warrington & Weiskrantz, 1968)	To supply missing letters to form a complete word	Racial prejudice (Dovidio, Kawakami, Johnson, Johnson, & Howard, 1997), self-esteem (Hetts, Sakuma, & Pelham, 1999)
Reaction-time visuospatial attention task (Simon, 1969)	To organise the stimulus words by assigning *positive* or *negative* categories to them. Incongruent trials take longer than the congruent ones	Attitudes (De Houwer & Eelen, 1998)
Priming procedures (Meyer & Schvaneveldt, 1971)	To respond to the associated versus unassociated concepts. Response latencies are longer in the latter than in the former	Racial prejudice (Fazio, Jackson, Dunton, & Williams, 1995; Gaertner & McLaughlin, 1983)
Preference for one's own name-letter (Nuttin, 1985)	To rate alphabets on their attractiveness. Name-letters are rated as more attractive than no name-letters	Self-esteem (Greenwald & Banaji, 1995; Koole, Dijksterhuis, & van Knippenberg, 2001)
Linguistic Intergroup Bias (LIB) (Maass, Salvi, Arcuri, & Semin, 1989)	To describe the drawings depicting stereotype-congruent and -incongruent behaviours. The latter results in more concrete description than the former which results in abstract descriptors	Prejudice (Von Hippel, Sekaquaptewa, & Vargas, 1997)

(Cont.)

Measure	Task	Previously used for
Implicit Association Test (IAT) (Greenwald, McGhee, Schwartz, 1998)	To assign compatible versus incompatible stimuli to the target and attribute categories. The strength of association between the target and attribute is assessed by calculating the response latency differences	Racial attitudes (Phelps et al., 2000), self-esteem (Greenwald & Farnham, 2000), weight identity (Grover, Keel, & Mitchell, 2003), personality (Asendorpf, Banse, & Mucke, 2002)

2.7.3.1 Implicit Association Test (IAT).

The IAT which was originally developed by Greenwald and his colleagues in 1998 at the University of Washington, USA to measure racial attitudes is the most frequently used implicit test. It has been adapted to measure implicit prejudice, attitudes, self-esteem and personality. Greenwald and his colleagues (1998) defined implicit attitudes as introspectively unidentified (or inaccurately identified) traces of past experience that mediate favourable or unfavourable feeling, thought, or action toward social objects. Since the judgements regarding these attitudes are, due to the related issues, only under the control of automatically activated evaluation, this reaction-time tool taps them without the performer's awareness of that causation (Greenwald & Banaji, 1995). The IAT works on the unified theory of implicit social cognition, where the *Me* node is the central piece in the social knowledge structure and is connected with different social concepts. These social concepts carry either positive or negative valence. The strength of all these links varies and is assessed by the time taken by the participant to respond to these associations (Greenwald et al., 2002).

2.7.3.2 What is implicit in the IAT?

Taking into consideration the nature of the IAT, the word *implicit* implies that the construct is being measured without allowing the respondent the opportunity to

alter the responses despite the presence of the motivation to do so. It is important to note that although it does not necessarily reflect unawareness i.e., even when conditions permit awareness, this process is fast, associative, highly robust (and is therefore affected by both aging and neurological damage) (Gilinsky & Judd, 1994). Also, it involves weakened ability to control thoughts, feelings and motives (Banaji, Lemm, & Carpenter, 2001). There are different dual-process theories explaining the existence and nature of the two systems in the human brain i.e., implicit and explicit systems also called system 1 and system 2, respectively by the cognitive theorists. These theories agree on the basic premise and functions of the two systems i.e., thinking and reasoning operate from these two systems. The implicit system does not include awareness and hence is difficult to control. The explicit system on the other hand, is based on deliberation and is flexible in its controllability (Evans, 2003). However, there are differences regarding the question of whether or not the constructs being assessed on this test are unconscious. In the literature, the term *implicit* has been used to refer to those processes which operate without the responder's conscious awareness, and *automatic* to those processes that operate without the responder's conscious control (Banaji et al., 2001). On the other hand, some of the dual-process theorists characterised the implicit (also referred to as heuristic) processes as preconscious but based on prior experiences and beliefs (Evans and Over 1996). The idea that the IAT is tapping into the unconscious bears similarity with the concept of the Freudian slip, and has been criticised on account of its synonymity with *attitudes* which are also defined as the beliefs which operate outside human awareness. Fazio and Olson (2003) argue that this synonymity makes the term *implicit* redundant when used in relevance to measuring attitudes. However, the extended use of the IAT to measure personality has been based on the assumption that accessibility to the self is limited through the self-reported method (Asendorpf et al., 2002), implying the involvement of the unconscious.

Despite this difference regarding the unconscious-preconscious issue, there is agreement among the dual-process theorists on the view that the implicit system operates outside awareness. It is crucially important to view consciousness and awareness as different but highly related concepts, where one may occur in the

absence of the other. Referring to the MODE model[2] (Fazio & Olson, 2003) to explain the implicit measurement, implicit tests are considered as significantly free from presentational biases due to the lack of the opportunity to deliberate the responses. An alternative single-system perspective proposed by Osman (2004) which was based on Cleeremans and Jimenez's (2002) dynamic graded continuum (DGC) framework, suggests that implicit processing makes one end of the thinking and reasoning continuum. Furthermore, consciousness has a different functional role on various points of this continuum. The stability or length of time a representation remains active during processing is one of the important properties determining the involvement of awareness. According to this framework, implicit processes involve an individual's ability to consciously access behaviour but not the ability to control it. Given that reaction-time tests are based on the *as fast as possible* responses, the automatic responses are made in the pre-conscious state prior to the realisation regarding the occurrence of the response. Greenwald's stance on what the IAT actually measures is:

"If one assumes that association strengths measured by the IAT are consciously accessible, then the difference between self-report and IAT measures can be understood as the difference between direct and indirect measures of association strength" (Greenwald et al., 2002, p. 18).

Explaining the IAT with Festinger's theory of cognitive consistency (1957; originally called the theory of cognitive dissonance), individuals are motivated to act according to their beliefs, values and perceptions. In the case where two inconsistent pieces of information are presented, people are likely to experience a psychological conflict or dissonance which interferes with the ability to act or respond. On the IAT, when the two concepts are inconsistent with one another, there is a cognitive conflict in the face of forced compliance which delays the response on the test. On the other hand, when the concepts are in harmony with each other, the response is smooth and hence comparatively faster.

[2] MODE is an acronym for motivation and opportunity as determinants of whether the attitude-to-behaviour process is primarily spontaneous or deliberative in nature.

The MODE model can also be applied to the prediction of spontaneous, deliberate, or mixed behaviour as a function of attitudes and beliefs. Mixed processes are of particular relevance to implicit measures as they comprise both automatic and controlled components. The latter requires both motivation and opportunity for the cognitive effort on the part of the respondent.

2.7.3.3 Predictive validity of the IATs: literature review.

Despite low correlations with explicit and other implicit measures of the same constructs, IAT has shown satisfactory predictive validity. Poehlman, Uhlmann, Greenwald, and Banaji (2005) reviewed 61 studies in their meta-analysis on predictive validity of the IAT, and concluded that although self-report measures outperformed the IAT in the areas of brand-related choices and political preferences, IAT measures showed better predictive validity in the domains of stereotyping, prejudice and physiological responses or behaviours which are difficult to control consciously. Bosson, Swann, and Pennebaker (2000) found that a self-esteem IAT consistently related to the impressions of self-esteem conveyed in essays. On a similar IAT, confirmatory factor analysis showed that implicit and explicit measures of self-esteem were measuring two distinct but weakly correlated factors (Greenwald & Farnham, 2000). In a study on the assessment of attitudes towards stigmatised (e.g., smoking) and nonstigmatised (e.g., eating vegetables) behaviours, Swanson, Rudman, and Greenwald (2001) found that smokers had greater attitude-behaviour consistency in their explicit attitudes towards smoking than in their implicit attitudes. Interestingly, vegetarians showed this consistency for vegetables at both implicit and explicit levels. A study on implicit and explicit weight identity and attitude toward overweight found that although men and women were equally consistent on their implicit and explicit anti-fat attitudes, men identified themselves as lighter on the IAT-weight identity than on the explicit measure, while women's implicit weight identity was positively correlated with their weight status, explicit weight appraisal and implicit self-attitude. These findings were supported by the fact that men seldom attend weight-loss help and women are at greater risk of developing eating disorders (Grover et al., 2003).

Another study on self-esteem and social anxiety revealed that implicit self-esteem was high in both high and low social anxiety groups yet the former showed significantly higher discrepancy between esteem of self versus others. On the basis of these results, de Jong (2002) attributed social anxiety to this negative self-favouring bias in comparison to others rather than low self-esteem. Marsh, Johnson and Scott-Sheldon (2001) hypothesised that implicit and explicit attitudes toward condom use and implicit identification with the use of condoms would differentially predicted the spontaneous and deliberate use respectively in real life. The score on this IAT was not correlated with deliberate condom use i.e., with a steady partner, but as predicted, it correlated with the spontaneous use with casual partners. The self-identity IAT (identification of *self* with condoms versus identification of *not-me* with condoms) did not correlate with condom use behaviour with any of the partners. It could be argued that since condom use in real life was based on self-reports, the absence of correlations between the implicit and criterion measures could have been influenced by the same presentational artifacts. On the other hand, explicit attitudes did correlate with the use of condom with steady partners. An important point was that the *non-condom* category on the self-identity IAT included several neutral objects (e.g., different images of markers, batteries), but no single overriding concept category label that connected them.

So far, the IAT proves to be a useful implicit tool and the findings on predicting behaviours which are not under conscious control of an individual have been promising (Fazio, Jackson, Dunton, & Williams, 1995). Some recent studies used physiological criterion measures to establish the predictive validity of the IATs. Egloff and Schmukle (2002) found that an IAT-anxiety predicted the ratings of the experimenter regarding the participant's anxiety level and the changes in performance after going through a stressful task in a laboratory experiment. The explicit measures were unable to predict these criteria. Since the IAT elicits automatic and partly uncontrolled responses, it is reasonably logical to assume that its scores may correlate with physiological processes which also occur automatically and in general out of one's deliberate control. In a study of this pattern, Phelps et al. (2000) measured the activity in the amygdala, a subcortical structure which is involved in the processing of negative emotions, in response to Black versus White faces. The strength of amygdala activation in the left-superior region was correlated

with the IAT measuring race evaluation and startle eyeblink potentiation bias (another indirect measure) and not with the explicit expression of race attitudes measured by a self-report scale. Moreover, a large region of activation extending from the right region to the inferior insular cortex was also correlated with the IAT score. The insular cortex has links with the amygdala and is active in the assessment of emotional responses. In another study, Asendorpf et al. (2002) found stronger evidence for this double association between implicit and explicit measurement and corresponding criterion behaviour. In a laboratory induced shyness situation, participants' spontaneous shy behaviour (as indicated by facial adaptors, body adaptors and tense body posture) was associated with the implicit, but not explicit, shyness measured by the IAT, while the controlled shy behaviour (as depicted by speech and illustrators (e.g., emblems)) was correlated with the explicit, but not implicit, measure of shyness. This association between spontaneous shy behavior and the IAT was confirmed in a faking study of this series where the participants were asked to present themselves as *not shy*. This also confirms that the IAT effect is not controllable and hence is difficult to fake. The fact that the IAT is difficult to fake has also been shown by some previous researchers (e.g., Banse, Seise, & Zerbes, 2001; Egloff & Schmukle, 2002). For example, Kim (2003) found that the participants were unable to fake more pro-Black attitudes by responding faster on the IAT even when they were instructed to do so. Although the participants succeeded to slow down their responses in the *Black + unpleasant* block, yet they could not speed up their responses on the *Black + pleasant* block.

The IATs have also shown satisfactory incremental validity (i.e., the IAT predicts variance in relevant criteria in addition to explicit measures of the same construct) beyond the predictive validity of explicit measures. Egloff and Schmukle (2002) found that the IAT-anxiety predicted changes in experimenter-rated anxiety and changes in performance after stress that explicit measures were unable to predict.

2.7.3.4 Implicit social support.

Since self-report measurement of constructs is influenced by response biases, it is tempting to speculate that the measurement of social support and/or loneliness may not be free from these influences. There is evidence supporting that social

desirability is positively associated with adequacy of social support (Cramer, 2000). Sarason et al. (1987) found that social desirability explained at least 4 per cent of the variance in satisfaction with perceived available support and the social network list. Due to the issues stated in the previous sections in detail which are associated with the self-report measures, it is tempting to assume that employing the techniques which assess sensitive constructs on a level which is accessible automatically without involving any self-report may overcome the limitations of self-report measures of social support. Based on the notion proposed by Fitness and Fletcher (1993), emotions associated with relationships are associated with a number of cognitive appraisals. This relationship schema was studied by Banse (1999) by using the experimental priming technique and was based on the idea that the activation of a cognitive unit activates the related units. Because of this activation or priming process, the activation of the related units occurs faster than the unrelated units (Anderson, 1995).

Implicit measurement of (the lack of) social support is a novel concept and no implicit measures of social support are available. To the best of my knowledge, research in this area has been based on the use of conventional explicit or self-report measures.

2.8 Social Support and Physical Health

Social support plays an important role in well-being, and social relationships have been found to be strongly associated with positive emotions (Bradburn, 1969) and the levels of happiness (Diener & Seligman, 2002). Research on applying the deficit model of partner loss (Strobe & Strobe, 1987) to the well-being of recently bereaved people provided evidence that the relationship between having close social relationships and well-being is causal (Strobe, Strobe, Abakoumkin, & Schut, 1996). In general, the role of social support in health-related outcomes has been associated with its role in stress-associated coping. The qualitative indices of social support such as need for support and satisfaction with support have been found to be strong predictors of physical and mental-health symptomatology including depression (Barrera, 1981). However, some studies have shown that an overall quantitative and qualitative picture of one's social relationships (social integration: Cutrona, 1990) is

an effective predictor of mortality (Berkman & Syme, 1979; House, Robbins, & Metzner, 1982; Schoenbach, Kaplan, Fredman, & Kleinbaum, 1986).

2.8.1 Outcome Variables in the Field of Social Support and Physical Health

DiMatteo and Hays (1981) in their review of studies on social support and physical illness gave an account of outcome variables in this area. The possible effectiveness of the role of social relationships in physical illness can be determined by *physical recovery* manifested by increased longevity, greater physical mobility, reduction in the need for medication, symptom amelioration and quicker recovery; *social role recovery* manifested by greater productivity, reduction in the use of health services and greater compliance or cooperation with a health regimen; and *socioemotional recovery* manifested by greater life satisfaction and happiness, greater harmony in interpersonal relationships, increased ability to cope emotionally with illness, restored self-esteem, reduced anxiety, reduced fear, reduced stress, and increased morale and hope for survival are among many outcomes studied.

2.8.2 Historical Perspective

Psychosocial aspects have been associated with physiological processes since the beginning of the history of medicine. Hippocrates proposed that the imbalance of bodily fluids was responsible for determining mood. Although he did not find evidence for this theory, this notion paved the path for the future research on the link between the *psyche* and *soma*. The initial work on the role of social forces was mainly in the area of sociology. The concept of social support in psychology emerged during the past few decades as more work was done, and researchers in social and medical sciences discovered the significant role of social support networks in physical health. Syme, Hyman, and Enterline (1965) explained this significance by stating:

"Social aetiology of disease attempt to systematically examine variations in the incidence of particular diseases among people differentially located in the social structure and attempt to explore the ways in which their position in the social

structure tends to make them more vulnerable, or less, to particular diseases" (p. 178).

The precise emphasis on the role of social support with reference to health emerged in the early 1970s with the work of an epidemiologist, Cassel, and a social psychiatrist, Caplan. Cassel started his work by concentrating on the effects of urbanisation on the incidence of tuberculosis, digestive diseases and mental illnesses. He argued that the changes in the immediate environment can lead to altered resistance for different diseases. For example, crowding and hence inappropriate communication within one's social environment, can lead to a state that he referred to as loss of equilibrium (Cassel, 1974). The question as to why some people remain unaffected by this state depends on their resistance to the behavioural or environmental exposures which include the protective effect of the psychosocial factors and the identification of the role of social relationships.

Caplan (1974) carried on with Cassel's theme, and identified the need of clarifying and determining the nature of social support in the physical health milieu, and outlining a scheme for its classification.

There has been extensive research in the area of health psychology on how social support may influence the well-being and physical health of individuals. As described earlier in this chapter, despite a great number of studies in this area in the 70s and 80s unfortunately this concept has lacked a definitional specificity. Several important questions needed to be answered before its role in health could be explored. What exactly is meant by social support? Who does it come from? What quantity is sufficient to benefit physical state? Is it the quantity or quality of social support that matters the most? How can the individual differences in the perception of social support be summarised? What aspects of illnesses are affected by it? Is benefit of receiving social support equal to the harm its absence may cause? These are some critical questions connected with operationalisation of the concept of social support.

Welin, Larsson, Svardsudd, Tibblin, and Tibblin (1992) summarised some of the early theories supporting possible reasons for the association between social

factors and physical health. One is the vulnerability hypothesis which asserts that social factors or a strong social network protects against noxious stimuli which might otherwise cause disease and death. The alternative drift hypothesis asserts that those affected by disease drift downward socioeconomically and tend to lose contact with friends and relatives. This association between socioeconomic status and physical conditions has been supported by research. In a classic study, Spitz (1945; 1947) studied 130 infants in two institutions with similar conditions except that in one, the care-givers were nurses, and in the other, mothers. The ones who had been looked after by the nurses showed more susceptibility towards disease, and retardation in growth, talking and walking later than the ones looked after by mothers. Simple acts of contact like touching have also been associated with patients' lower heart rates and rhythms (Lynch et al., 1974; Lynch, 1977). A deficiency of emotional support can even result in physical deformities. In a study, maternal rejection was associated with abnormalities like dwarfism without any signs of malnutrition (MacCarthy & Booth, 1970).

The advanced scientific and empirical research in this area of social support started in late 1970s when epidemiologists began to see the association between social support and health, using epidemiological data from archival prospective designs. One such study used the 1965 Human Population Laboratory Survey of 6928 Alameda County residents and found lower levels of mortality and morbidity nine years after the individuals had reported *better connectedness (*Berkman & Syme, 1979). This association was independent of self-reported physical status at baseline. These reserachers developed and used the Social Network Index which identified four major sources of social contact; marriage, contacts with close friends and relatives, church membership, and informal and formal group associations. Results showed that residents with ties provided by any of the sources had lower mortality rates than the ones without such ties. These finding were also adjusted for age. Married residents had lower relative risk of mortality than separated, widowed, single and divorced residents, and this risk was higher in men than women. However, the differences in mortality rates between people who scored high and low on the combined measure of contacts were greater for women than for men. Also, although each of the four sources of social contact predicted mortality independently, the differences for marital status, friends and relatives were larger than for church and

other group associations, which is in accordance with the conclusions drawn by O'Reilly (1988) in his review discussed earlier in the section on measurement of social support. The scores on the Social Network Index were also associated with ischemic heart disease, cancer, cerebrovascular and circulatory diseases, and other causes of death. Two major limitations of this study were the low validity of self-reported health status indicators and uncertainty about the outcome variable which was either illness incidence or survival time between the disease onset and death.

Despite the controversies with the use of marital status as a measure of social support, the results on the significance of marital status as a predictor of mortality and morbidity have also been shown in studies. Bereaved people complained more about physical and psychological symptoms particularly in the first year of bereavement (Maddison & Viola, 1968). However, the effect of being married on mortality has been found to be larger in men than in women (Gardner & Oswald, 2004). Also, this beneficial effect of being married is more pronounced in younger than older people. Living with a partner may be associated with receiving high emotional support in younger but not older cancer patients (Schwarzer, Forster, Schulz, & Taubert, 2001). In another study, younger breast cancer patients reported higher social support from the family including husbands than their older counterparts (Nausheen & Kamal, 2007).

Several correlational studies on social support and physical health were done in the following years. House, Landis, and Umberson (1988) found similar findings to Berkman and Syme (1979) with an index of social networks including both availability and activity of social relationships, taking into account the siblings and children. Although these studies found associations between social support and physical well-being and health, social support was assessed as a broad concept and the measurement relied largely on the structural indices e.g., church membership or number of relations, hence lacking a direct assessment of the quality of the relationships in question.

Following the contemporary trend of research, House et al. (1982) studied mortality in a 9-12 year follow-up period. They improved the methodology employed by Berkman and Syme (1979) by using more valid biomedical measures of

morbidity to detect the possible underlying effect on health problems, and a wider range of social relationship measures to have a clearer picture of the role of social relationships in mortality. They found that marital status, organisational involvements and social activities (e.g., movies, sports, etc.) were inversely correlated with mortality in men, while in women, passive/solitary leisure activities (e.g., watching television, reading, etc.) were positively associated with mortality, after controlling for age and other risk factors. An interesting finding in this study was the nonlinear and nonmonotonic pattern of results i.e., the mortality level was the lowest at moderate social relationships and it increased with the increasing level of social involvement. However, no potential explanation for this finding was provided by the authors. Satisfaction with relationships was surprisingly not found to be associated with mortality. Overall the findings suggested that the worst consequences in health were related to a lack of any meaningful relationships and the inverse association of social relationships with mortality was stronger in men than in women.

In a smaller-scale epidemiological study, Blazer (1982) investigated whether social support predicted mortality in a sample of 331 elderly after a 30-month period. A gradual refinement and specificity of the term social support can be seen as *perceived social support* was used as a component of social support along with roles and availability attachments, and frequency of social interactions. Results indicated that all three parameters of social support significantly predicted 30-month mortality, after controlling for age, sex, race, socioeconomic status, physical health status, self-care capacity, depressive symptoms, cognitive functioning, stressful life events and cigarette smoking. Low perceived social support, roles and attachments predicted mortality even when the other two parameters of social support were controlled. Unlike other contemporary findings suggesting that being unmarried and socially isolated were associated with higher rates of tuberculosis, schizophrenia, accidents and mortality (Berkman & Syme, 1979; Faris, 1934; Kohn & Clausen, 1955; Tillman & Hobbs, 1949), marital status was not associated with mortality in this sample. Findings also revealed that as physical health deteriorated, the perception of social support and social interaction also deceased, after the effects of initial health status were controlled for, suggesting that the relationship between social support and health is bidirectional.

Schoenbach et al. (1986) investigated the relationship between a social network index and survival in the residents of the Evans County, Georgia. This study did not however replicate the previous findings (Berkman & Syme, 1979; House et al., 1982). The most striking effect of social networks on mortality was found in older adults. Unmarried white people were at higher death risk than married ones. However, in blacks, it was the case only for males < age 60. Church participation was correlated with decreased mortality in people ≥ age 60 except in black males. No clear pattern was found for the friends and close relative index. This study highlights the importance of beneficial effects of social network in older adults. It is important to note that these results were obtained after statistically controlling for the cardiovascular disease risk factors, which was unprecedented and may explain this different pattern of results relative to previous studies.

To conclude, it has been demonstrated that health is related to the availability of supportive ties e.g., the number of ties in a social network, the frequency and quality of contact with network members, and the differential presence of kin or friends in these networks (e.g., Cohen, Doyle, Skoner, Rabin, & Gwaltney, 1997; Cohen & Perl, 2003; Turner-Cobb, Sephton, Koopman, Blake-Mortimer, & Spiegel, 2000).

2.8.3 Proposed Mechanisms of the Effect of Social Support on Health

As shown in the above section, social support appears to be associated with psychological well-being and physical health. There are two models which explain the possible ameliorating effect of social support on physical health. Cohen and Wills (1985) reviewed studies to assess the efficiency of these models, and found evidence for both models. Each of these models is discussed below:

2.8.3.1 Main effect model.

This model explains the direct or main effect of social relationships, and postulates that the effect of social support on health is beneficial as it provides increased social integration and stability of relationships. It also dispenses emotional, instrumental or informational aid and keeps the recipient away from negative

experiences. Cohen and wills (1985) discussed the possibility of a threshold of social contact in order to exert a meaningful effect on well-being i.e., some evidence suggested that the nature of the main effect of social support is nonlinear which occurs when the comparison is made between people who have very few or no social contacts and those who have moderate to high levels of social support. However, they concluded that the evidence in favour of this hypothesis was not conclusive.

2.8.3.2 Buffering effect model.

Based on the notion that improving and strengthening social support may be more feasible than reducing the exposure to the stressors (Cassel, 1974), Cohen and Wills (1985) reviewed the effectiveness of the stress buffering effect of social support. They suggested that the beneficial effects of social support on health are dispensed in times of crises or stress, and discussed that the nature of stress involves helplessness and possible low self-esteem, which warrants protective factors to shield the individual when faced with it. Social support is one of those factors and intervenes at the two possible points in the process from a stressful episode to the vulnerability towards physical illness. First, it affects the appraisal process which occurs between the stressful event and the cognitive reaction to it. This alteration in the perception of the magnitude of the stressor depends on the internal and external resources available to cope with it. Second, social support may facilitate the reevaluation of the nature of the stressor and altering the maladaptive responses to it. This happens between the appraisal of the stressful event and the onset of the physiological process (Cohen & McKay, 1984, see Figure 2).

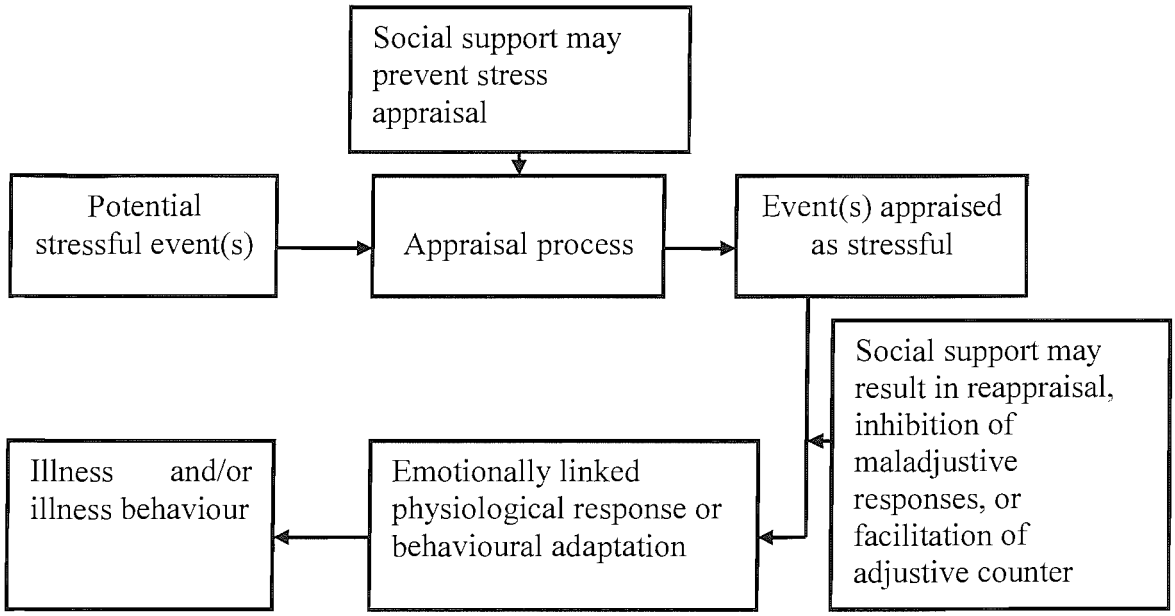

Figure 2. Two points at which social support may interfere with the link between stressful events and physical illness.
(Cohen and Wills, 1985).

Cohen and Wills (1985) suggested that social support acts as a moderator in the relationship between stress and well-being, where it buffers the individual against the harmful effects of stress. Therefore, in the face of stress, people who show higher levels of well-being are the ones who receive or report greater social support from their social relationships.

Taylor (1995) adopted the model of stress, coping and health, and nominated social support to be construed as an external resource variable which may affect the stress appraisal and hence coping outcomes by buffering its adverse effects on health. She proposed that social support can provide a means of affecting appraisal and problem-focused coping by helping the individual redefine an event and suggesting solutions, and by affecting emotion-focused coping by providing empathy and targets of emotional expression.

An important thing with regards to the measurement of the buffering effect of social support is that it is efficiently determined only when the support measured meets with the requirements of the stressor (Cohen & Wills, 1985). Support in the

form of advice, aid and reassurance is an important thing in a time of crisis. Building on the vulnerability hypothesis, this buffering effect of social support was observed in highly stressed individuals, where social relationships provided a protective effect and minimised the negative effects of stress (Rook, 1987). The supportive evidence for this model was found in a study with breast cancer patients, where it was found that having more people in one's social network was associated with less mood disturbances for those who had experienced greater life stress. Also, having greater aversive social support was associated with mood disturbance for the high life-stress group (Koopman et al., 1998).

Another large-scale semi-prospective study investigating the effect of psychosocial factors on the severity of cervical cancer tested this stressor-support-coping model, having distress and tumour grade as outcome variables but did not find evidence to support this model (Tiersma et al., 2004).

According to the dual-path model of attachment theory developed by Weiss (1975), since social support operates through a different pathway than marital status towards well-being, the buffering effect theory may not stand true. The buffering effect model asserts that in the face of stress (e.g., bereavement in this case), social support protects the bereaved from the harmful effects of the stress. In contrast, Weiss suggests that different sources of support lead to physical and mental symptomatology via different mediators. As mentioned earlier, lack of social support creates social loneliness and lack of a spouse creates emotional loneliness, both leading towards the negative effects of the lack of these support sources (Weiss, 1975). Evidence was found for this theory in a study where a comparison group of married people were individually matched to the widowed ones. The mediating role of emotional loneliness was found between marital status, and somatic and depressive symptoms in widowed individuals, while social loneliness played the role of a mediator between social isolation and symptomatology (Strobe et al., 1996).

2.8.4 Pathways/Mechanisms

So far I presented evidence for the fact that a lack of support from social relations or loneliness is linked with and may cause vulnerability of physical

illnesses. Two important potential pathways have been proposed in this context including behavioural and physiological pathways which will be discussed in the next section. At the basic level both these pathways depend on the same psychological or cognitive pathway which asserts that the perception of a social situation (or a lack of social support) may depend on or lead to adverse psychological states such as low self-efficacy and self-esteem, and depression/distress (Berkman, Glass, Brissette, & Seeman, 2000) (see Figure 3).

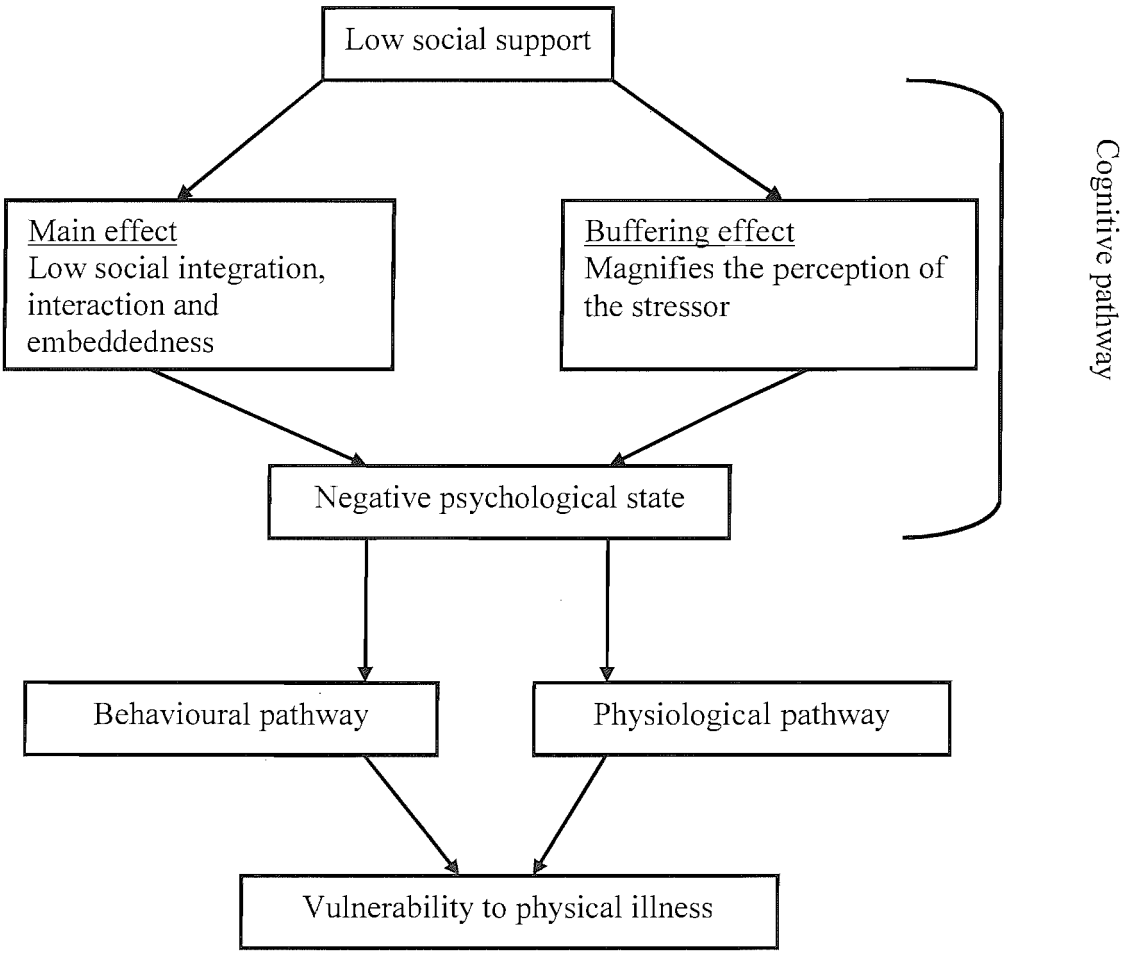

Figure 3. Pathways to physical illness.

2.8.4.1 Cognitive pathway.

In addition to any direct effects of lack of support on health (e.g., unavailability of transportation to the hospital leading to deteriorated physical

condition/illness), both of the main pathways may depend on the same psychological pathway which asserts that, a lack of social support may cause negative psychological states such as loneliness, stress, depression, anxiety, etc. (main effects) or magnify the level of an external stressor and induce these negative psychological states (buffering effect). In both conditions, the negative state may in turn be responsible for the increased vulnerability of the individual towards physical illness through either behavioural or physiological pathways (see Figure 3).

There are two essential components of the basic psychological approach. First is the main premise, as mentioned above, that certain psychological states result from insufficient levels of social support, and are capable of and may be responsible for making physical changes in the body leading towards physical illness (Denollet et al., 1996; Ramirez et al., 1989). There is evidence that these negative psychological states, which can be a result of loneliness, may be associated with subjective health complaints even in the absence of objective physical symptoms (Russo et al., 1997; Watson & Pennebaker, 1989).

Second, this psychological *imbalance* or *negativity* may stem from another important cognitive component i.e., the perception of and attitude towards a particular social episode or social relationship determine the strength of the resulting psychological states. If a social interaction is not perceived as satisfying and fulfilling then it is likely to provoke more negative feelings than when it is perceived on the contrary. The perception regarding the availability of support from one's social network is important as it can buffer against the stressors. It can also happen directly where social support provides an individual with reassurance, strength, or assistance which has a beneficial main effect (Cohen & Wills, 1985).

2.8.4.2 Behavioural pathway.

Low or insufficient social support and the consequent negative psychological states can lead to a vulnerability to physical illness through either of the two major pathways: behavioural and physiological (see Figure 3). If social support affects physical health through the behavioural pathway then individuals with little social support should manifest poorer health-related behaviour than people who have

greater social support. Berkman and Syme (1979) found that health practices significantly mediated the association between social networks and mortality i.e., socially-isolated people are more likely to engage in poor health practices such as smoking, drinking, binge eating leading to obesity or under-nutrition, lack of physical activity etc., which then predict an increased vulnerability towards physical diseases and/or mortality. Marital status as a proxy for social support has also been linked with unhealthy practices. A study on non-small-cell lung cancer found that the proportion of patients who continued smoking after surgery and hence was less likely to survive, was unmarried (Saito-Nakaya et al., 2006).

Moreover, people with fewer social contacts are less likely to use preventive services like health insurance, dental and medical check ups, etc. The utilisation of these preventive services has been correlated with lower mortality rates. Studies on cancer found that unmarried patients are more likely to be diagnosed at a later disease stage, and hence are less likely to receive definitive treatment (Goodwin, Hunt, Key, & Samet, 1987) and to be treated by surgery (Greenberg et al., 1988).

However, some contrary evidence suggests that certain negative psychological states which are associated with subjective health complaints even in the absence of objective physical symptoms (Russo et al., 1996) can also lead to excessive utilisation of the health services (Dennis, 2004).

2.8.4.3 Physiological pathway.

According to a body of research on the physiological or biological pathways between social support and physical health, stress or negative psychological states induced by insufficient levels of social support may lead to bodily changes which in turn make an individual more susceptible to physical illness. These bodily changes may occur through the stimulation or suppression of the nervous, immune, or endocrine systems, prolonged activation of which can lead to the development of various physical and psychological disorders (Cohen, 2004). The stress initiates the information-processing pathways in the central nervous system (CNS) and the periphery. This triggers: (1) a fight-or-flight stress response in the autonomic nervous system (ANS), or (2) a more perverse response produced by the hypothalamic-

pituitary-adrenal (HPA) axis. The fight-or-flight response is mediated by the sympathetic nervous system (SNS) which stimulates catecholamine hormones e.g., adrenaline and noradrenaline (Daruna, 2004). Noradrenaline and adrenaline can trigger the secretion of cytokines such as vascular endothelial growth factor (VEGF) (Lutgendorf et al., 2003), which plays a role in various illness processes (described in Chapter 4). Lutgendorf et al. (2003) also proposed the mediational role of noradrenaline and adrenaline in the relationship between social support and VEGF. The catecholamines can also alter natural killer (NK) cell activity. Levy et al. (1990) found that perceived emotional support in an intimate relationship, social support from physicians, and using social support as a potential stress buffer predicted higher NK cell activity in stage I and II breast cancer patients six weeks after diagnosis. NK activity is of importance in tumour control and hence in survival of cancer patients (Suck, 2006). However, what degree of social support and immunological changes translate into the onset, severity, or progression of disease is still unknown. The buffering effect of social support may minimise the stress-related effects on the immune system and endocrine changes associated with tumour proliferation (Kiecolt-Glaser & Glaser, 1992).

The stress-induced up-regulation of the HPA axis is mediated by the hypothalamus which produces corticotrophin-releasing factor and arginine vasopressin, both of which stimulate the secretion of pituitary hormones e.g., adrenocorticotropic hormone (ACTH). ACTH stimulates the release of glucocorticoids e.g., cortisol which have an important function related to the immune system and the regulation of stress reactivity.

2.9 Chapter Summary

This chapter highlighted the merits and demerits of different categories of social support, and concluded that functional indices of social support provide comprehensive information regarding the levels of social support and hence are more likely to predict health-related outcomes than the indices of structural support. The controversies and inconsistencies in the literature around the definition, conceptualisation, and significance of the role of social support in physical health-related outcomes may be due to the limitations associated with the conventional

explicit or self-report measures of social support and loneliness. There is a need to overcome this issue which can be met by incorporating theories from other areas of psychology and borrowing techniques such as implicit measurement, in order to establish the links in health psychology.

This chapter also discussed the pathways of the beneficial effects of social support on health. The cognitive pathway between provision of social support and physical health determines whether the effect of social support is a main effect or a buffering effect. It also includes a cognitive component which shapes the way in which the presence or absence of social support is perceived, leading to the salutary effects of social support on health either through one or both of the two major pathways: behavioural and physiological.

This chapter provided the necessary background on social support, and physical health in order to study social networks and the support drawn from them with reference to cancer in the following chapters. The literature discussed here on implicit measurement of psychosocial constructs will facilitate the adaptation and validation of an implicit measure of loneliness.

Chapter Three: Social Support and Cancer

3.1 Aims of the Chapter

This chapter discusses the relationship between social support and cancer. The first part includes an overview of the biological aspects of cancer and the magnitude of the prevalence of cancer. It also discusses the role of social support in cancer-related outcomes. In order to reach a conclusive stance regarding the precise significance of the role of social support in progression of cancer, the second part of this chapter includes a systematic review of the literature on this topic.

Part I

3.2 Cancer: The Disease

Cancer is an ancient perplexing medical condition which is usually fatal in its natural course. Although work towards finding a cure for this family of diseases is in progress, recent research in psychology hinted at the possible role of psychosocial factors suggesting that these nonmedical variables might influence or even contribute towards determining the course of cancer. There is evidence which suggests that both medical and psychosocial variables contribute to health status and survival of patients with cancer (e.g., Kreitler, Kreitler, Chaitchik, Shaked, & Shaked, 1997).

A cancerous tumour or neoplasm is defined as "an abnormal mass of tissues the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after the cessation of the stimuli which evoked the change" (Kumar, Cotran, & Robbins, 1997, p.133). The categorisation of a tumour is done on the basis of its clinical properties. A tumour is benign when its characteristics are considered relatively innocent i.e., it remains localised, can not spread to other sites, and is generally removed and hence cured by a local surgical procedure. Whereas, malignant tumours also referred to as cancers, exhibit the properties of invasion and metastasis[3]. A malignant tumour is developed through the

[3] A growth of abnormal cells distant from the site primarily involved by the morbid process (Dorland's pocket medical dictionary, 2004).

process of carcinogenesis which is a multi-step mechanism resulting from the accumulation of errors in vital regulatory pathways. This process is initiated in a single cell, which then multiplies and acquires additional changes that give it a survival advantage over its neighbours. The altered cells must be amplified in number to generate billions of cells that constitute a cancer (King & Robins, 2006). The process of progression involves the additional changes occurring after a cancer has formed, where cells continuously require oxygen and nutrients which can only be supplied by angiogenesis[4]. There is ample evidence from animal models suggesting that the cells transfected with angiogenic stimulators develop faster and larger (Zhang, 1995). Also, anti-angiogenic treatments have been proven to be useful in the treatment of cancers and in enhancing the efficacy of chemotherapeutic treatment (Folkins et al., 2007).

Most of the cancers exhibit the following six general characteristics (Hanahan & Weinberg, 2000): (1) self-sufficiency in growth signals; (2) insensitivity to anti-growth signals; (3) evading apoptosis; (4) limitless replicative potential; (5) sustained angiogenesis; and (6) tissue invasion and metastasis.

3.2.1 Prevalence of Cancer

Cancer is a very common disease. There were an estimated 10 million new cases of, 6.2 million deaths due to, and 22 million patients living with cancer (within 5 years of diagnosis) worldwide during the year 2000. These estimates represent 22 per cent increase in incidence and mortality from 1990. The most common cancers in terms of incidence are lung (12.3%), breast (10.4%) and colorectum (9.4%). The cancers of lung (17.8%), stomach (10.4%) and liver (8.8%) are among the most common causes of death. In men cancers of lung, stomach and colorectum have the highest rate of incidence while lung, colorectum and liver have the highest mortality rate. In women cancers of breast, cervix uteri and colorectum have the highest incidence, and breast, stomach and colorectal cancers have the highest rate of mortality (Parkin & Bray, 2006).

[4] A process which leads to rapid tumour growth and invasion, and involves growth of new blood vessels with the sprouting of new capillaries from the existing blood vessels (Voronov et al., 2003).

In the UK, 276,678 persons were diagnosed with cancer in 2003. Four, most prevalent types which account for over half of all new cases were breast (16%), lung (13%), colorectal (13%), prostate (12%) and others (46%). In 2005, there were 153,491 deaths from cancers of lung (22%), colorectal (10%), breast (8%), prostate (7%) and others (53%) (Cancer Research UK, 2007a).

3.3 Social Support and Cancer

Hippocrates's (400 BC) classification of *bodily humours* associated complex psychological states with physiological imbalance. Galen (AD 200) extended Hippocrates's theory of humours to psychology and suggested that certain temperaments were linked with particular humorous imbalances and physical symptoms. He wrote that women with melancholic temperament were more susceptible to *swellings* of the breasts than sanguine or cheerfully optimistic women (as cited in Dunn, 1996). Although there has been a debate about the exact psychosomatic aspects of cancer since the mid 1700s (Gendron, 1759), it has been proposed that the *mind over body* phenomenon can also be applied to cancer (Daruna, 2004). Therefore, psychosocial factors have long been suggested to have a role in this disease. There has been an enormous amount of research on psychosocial factors and cancer-related outcomes. The factors which have been studied in this context include psychological (e.g., depression), social, and personality and individual characteristics. The outcomes include both psychologically and physically orientated variables. The psychological outcomes include mental well-being, emotional adjustment and quality of life (QoL), while the physical outcomes include onset, severity and progression of cancer.

Social support is in the list of a few important variables with potentially promising evidence in psycho-oncology along with other psychosocial factors including helplessness, repression, depression and stressful life events (Garssen, 2004; Levenson & Bemis, 1991; Spiegel & Giese-Davis, 2003; Spiegel & Kato, 1996). In a study on psychological and medical predictors of health status 3 and 5 years post-surgery, and survival 5 years post-surgery in breast cancer, adjustment with respect to sexual relationships and disease stage were the most important predictors of health status and survival. For state of health after 3 years, the

predictors with the larger contributions were psychological, and those with the smaller contributions were medical. However, after 5 years, the contribution of psychological variables became smaller than that for 3 years. Adjustment with sexual relationships significantly predicted 43 per cent of the variance towards the course of the disease at both time points (Kreitler et al., 1997). Despite convincing findings like this, there are differences in the methodological quality of the studies in this area which make it difficult to reach conclusions regarding the significance of the role of social support in cancer. It is important to note that the literature on the role of social support in cancer progression seems more convincing than in cancer onset (Garssen & Goodkin, 1999). For example, in a large-scale longitudinal Dutch study on the role of personality factors including social support in the development of primary breast cancer, only anti-emotionality (i.e., an absence of emotional behavior or a lack of trust in one's own feelings) was significantly associated with an increased risk of having breast cancer (Bleiker, van der Ploeq, Hendriks, & Ader, 1996). This evidence was supported by a systematic review of studies on several psychosocial factors and the development of breast cancer in which Butow and her colleagues (2000) found no evidence for social support as a predictor of the onset of breast cancer. Interestingly, the results of this review were positive for the anti-emotionality factor of personality, replicating Bleiker's finding.

In a prospective study on social networks as predictor of ischemic heart disease (IHD), cancer, stroke and hypertension, Vogt, Mullooly, Ernst, Pope, and Hollis (1992) found that social network scope (a measure of the number of different domains in which a person has social contacts) predicted incidence of only IHD in a 15-year follow-up. Other aspects of social support such as social network frequency and size did predict 5-year IHD incidence but this association was no longer evident with longer periods of follow-up. This trend shows that some aspects of social support may predict different long- and short-term disease outcomes. No significant correlation was found between social support and cancer incidence/onset. Since these findings established that social support may not have a direct role in the onset of cancer, a semi-prospective study tested the possibility of the buffering effect of social support in a sample of women with breast cancer and benign breast disease, coming in for cancer screening. Social support included both the availability of sources of intimate and nonintimate emotional and instrumental support. Although no direct

association was found between social support and diagnosis of breast cancer, patients who reported to have a major stressful event in the past 2 years and had no intimate emotional support were more likely to have a diagnosis of breast cancer than those who had good intimate emotional support, after controlling for age (Price et al., 2001).

Although a few studies found a significant relationship between social support and severity of cancer at diagnosis, their semi-prospective designs prevented the inference of causality. In such a study on the relationship between social ties, stage of disease, and survival in a population-based sample of black and white newly diagnosed breast cancer patients, a summary measure of structural support was found to be modestly correlated with advanced breast cancer in black women (Reynolds et al., 1994). Another population-based study on social support and risk of colon cancer found that minimal emotional support was strongly associated with both local and advanced disease stage among blacks. No such association was found for their white counterparts (Kinney et al., 2003). The nonsignificant results were supported by two other studies conducted in Italy and USA where social support, loneliness (Giraldi, Rodani, Cartei, & Grassi, 1997) and number or amount of contact of dependable supports (Weihs et al., 2005) were not associated with disease severity in breast cancer.

In a study with a semi-prospective design on loneliness and the incidence of breast cancer, loneliness prior to a mammogramme screening was higher among patients whose diagnosis was positive for breast cancer than those who were disease-free (Fox, Harper, Hyner, & Lyle, 1994). It is important to note however that the patient delay i.e., time interval between symptom onset and diagnosis, has neither been considered nor controlled for in these studies. Patient delay may prove to be an important factor in the link between social support and severity of cancer as it has been associated with disease stage in different types of cancer including cancers of colon and rectum. It has also been associated with demographic factors such as gender. Young, Sweeney, and Hunter (2000) found that male colorectal cancer patients are more likely to delay seeking medical help than females and hence are less likely to be diagnosed at an early stage of disease. Since some research suggests that unmarried people are more likely to be diagnosed at more advanced stages of the

disease (Goodwin et al., 1987), and hence possibly have poorer prognosis, the role of patient delay may be more relevant to research on social support and cancer severity than anticipated or reported.

So far, I summarised the evidence on the role of social support in cancer-related outcomes including onset and severity of cancer. While unconvincing findings were reported with regards to cancer onset, mixed findings on cancer severity warrant further research. On the basis of the literature reported so far, it may be concluded that the relationship between social support and severity of cancer at diagnosis may be more convincing in specific populations.

3.3.1 Marital Status

The use of marital status as a proxy measure of social support is common in the literature on social support and cancer due to one major reason: it is a simple measure to administer and in most instances this information can be obtained from the medical records of the patients without their personal involvement in the study.

In a 10-year prospective study on breast cancer patients, Neale, Tilley, and Vernon (1986) found that the difference in mortality between married and widowed women started to get larger after 4 years from diagnosis. In this study being married was found to be a significant but weak predictor of survival in patients, after adjusting for age, socioeconomic status, disease stage and patient delay. This study used two groups to categorise marital status: married and widowed. In another study on breast cancer, the quality of the marital relationship was taken into account by assessing the satisfaction with spousal support in order to rule out the possibility of any negative spousal interaction involved. The results showed that the likelihood of relapse was lower for married patients only in the group of patients who reported gaining more satisfaction from support (Declerck, Brabander, Boone, & Gerits, 2002), suggesting an interaction between marital status and support satisfaction.

Most of the other studies merged the *single*, *divorced* and *widowed* categories into one category, which makes it difficult to estimate the precise contribution of a particular marital state in predicting disease progression. It is possible that the effect

is stronger for any one of these than others. Methodologically speaking, it is also important to distinguish the categories *single* or *never married* from *widowed, divorced* or *separated* as single people may be more socially isolated because the people in the latter categories may have offspring and other kin-based contacts which are not available for single people. Alternatively, single/never married people may have developed a larger social circle as they have not been able to rely on a partner.

In a study on bladder cancer, married patients were found to have better survival than single patients, independent of age, gender, race, disease stage and lymph node status. Widowed patients also had significantly worse survival than married patients. However, the results did not reach the conventional level of statistical significance in the case of divorced/separated patients (Gore, Kwan, Saigal, & Litwin, 2005). Krongrad, Lai, Burke, Goodkin, and Lai (1996) used the 1973 to 1990 database of the Surveillance, Epidemiology and End Results (SEER) programme, and found significantly longest survival in married prostate cancer patients, after controlling for age, race, stage and treatment. Divorced and separated men had the worst survival rate preceded by single and widowed men respectively, replicating the results reported by Goodwin et al. (1987) where being unmarried was associated with poorer survival than being married. However, they also merged the *single*, *widowed* and *divorced* categories into *unmarried*, and considered several types of cancer collectively. There is evidence that cancers of different primary sites are aetiologically different, may vary in prognosis and hence have different lengths of survival associated with them. Grouping them together may present a misleading picture.

A comprehensive study by Lai and colleagues (1999) overcame this issue by studying the effect of marital status on survival with 255,605 late-stage patients of various sites separately. The results showed that the survival varied not only by marital status but also by primary site. Survival was not affected by marital status in cancers with poor prognosis: for instance in men, cancers of liver, lung, stomach, oesophagus and pancreas had significantly shorter survival than the cancers of oral cavity, larynx, prostate, lymphoma, myelomas and leukaemias, and it did not differ as a function of marital status in the former group. In the latter group, married men had better survival than unmarried men. A similar pattern was replicated for women

i.e., in cancers which have a median survival of longer than 1 year, married women had significantly longer survival than their unmarried counterparts. The overall survival combining all sites was significantly worse in unmarried than married men and women. However, the magnitude of relative risks was smaller for women. All the analyses were adjusted for age, race and treatment.

Despite significant findings regarding the beneficial effects of being married, the quality of marriage may be a moderator in the link between marital status and health, and marital distress is associated with worse health more strongly in women than in men (Whitton et al., 2007). Although women more frequently nominate friends and other people as their social network while men usually name their wives as their main source of social support (Kiecolt-Glaser & Newton, 2001), in a study on social support and survival in metastatic melanoma, marital status was significantly associated with survival but social support was not, suggesting that the contribution of marital status in the prognostic effects of social support is minimal (Butow, Coates, & Dunn, 1999). However, the interaction of marital status with social support was not tested in this study.

There are a few proposed mechanisms linking marital status with cancer progression. Since the use of marital status in this context is based on the assumption that being married means having higher social support, mechanisms for social support and physical health may also hold true for marital status. Moreover, since loneliness has been associated with compromised immune function (Levy et al., 1990) and living alone or without a partner is associated with increased mortality (Goodwin et al., 1987; House et al., 1988), there is the likelihood that the mechanisms of this link may be similar to those for social support. Considering the behavioural pathway, there is evidence that married people have better health habits e.g., smoking, alcohol intake (Weihs et al., 2005) and physical activity (Kroenke, Kubzansky, Schernhammer, Holmes, & Kawachi, 2006) than their unmarried counterparts. There is also a significant pattern for unmarried people to be diagnosed at later stages of the disease (de Graeff et al., 2001) and hence they are less likely to receive definitive or potentially curative treatment. There is also a possibility that unmarried people have a lack of emotional gratification (Lai et al., 1999). Osborne, Ostir, Du, Peek, and Goodwin (2005) found that unmarried women, who had no

known comorbidities and were from the highest socioeconomic status, were still at a higher risk of mortality than married women, suggesting that this relationship between being unmarried and worse cancer outcomes may not be moderated by socioeconomic status or financial limitation.

It may also be speculated that being married does not have any benefits towards better health but there are certain personality (or other) characteristics which are associated with either being married or the choice to be married and health.

Krongrad et al. (1996) discussed the following hypothetical models of the mechanisms linking marital status and mortality: (1) brain-cancer connection model: psychosocial factors moderate cancer biology. The evidence for this model is insufficient for cancers with poor prognosis e.g., prostate cancer, supporting Lai's (1999) conclusions regarding the role of primary site of cancer; (2) lead time bias model: lead time refers to the time between diagnosis and mortality which is extended by low patient delay. This model was not significant in Krongrad's sample as the effect of marital status persisted even after controlling disease stage; (3) social support and depressed mood model: this is supported by the findings showing that loss of a spouse increases psychological morbidity particularly depressive symptoms which increases the risk of death (e.g., Williams, 2005).

In summary, many studies in psychosocial oncology provide evidence for social support as an important factor which may potentially play a significant role in cancer-related outcomes. However, it is important to remember that developments in treatment can make a difference to prognosis, viz. poor prognosis may shift to good prognosis, and this can then alter the potential role of social factors.

3.4 Methodological Critique

In recent years, greater attention has been paid to the psychosocial aspects of cancer in order to improve the QoL of cancer patients who now have longer survival spans than in the past, and to explore the possibility of these aspects having an influence on health-related outcomes. Various methodological designs employed by researchers in this area have their own merits and de-merits. The research on social

support and progression of cancer has been extensive. However, due to methodological flaws including the inconsistencies in defining and categorising constructs, employment of correlational designs and lack of control over the relevant confounding variables, it is difficult to reach a consensus over the significance of the role of social support in progression of cancer. There have been only a few interventional studies investigating the effect of mainly psychological or psychologically-orientated interventions on disease progression in cancer patients (e.g., Kissane et al., 2007; Spiegel, Bloom, Kraemer, & Gottheil, 1989). These studies are not free from methodological biases: their small sample sizes, which make it difficult to reach the conventional levels of statistical significance, and differences in the nature of the interventions and types of cancer studied make it difficult to compare their findings. One of the challenges of researching in the field of psychosocial oncology is to merge the intricacies of the fields of medicine and psychology. The core purpose is to conduct research which is theoretically driven and clinically relevant without burdening the patient or disrupting their ongoing medical treatment (Redd, 1995).

Many of the traditional methods are quantitative in nature, placing emphasis on the reliable measurement of variables in the context of controlled investigation including experimentation. Other qualitative methods are concerned with the exploration and analysis of health or illness experience. Qualitative approaches are gradually becoming more accepted (Murray & Chamberlain, 1998).

The cross-sectional design is the most prevalent design in this area. However, the minimal control over the predictor variable employed in this design prevents causal inferences from the findings and gives rise to a phenomenon called ambiguous temporal precedence indicating a bidirectional nature of the relationship (Shadish, Cook, & Campbell, 2002). The problems associated with cancer (such as undetected premorbid states, difficulty in quantifying severity at any stage, differences in biology of different tumours and treatment) make it difficult to design studies that eliminate important alternative explanations. Correlations may be affected by other variables which influence both psychosocial characteristics and cancer (Sklar & Anisman, 1981). Therefore, causal inferences from cross-sectional data are limited but further clarification can be achieved to an extent by the semi-prospective design.

Also called quasi-prospective, a semi-prospective design is an approximation of a longitudinal prospective research design which assesses the outcome before and after a particular event. Such studies are frequently done during medical check-ups or diagnostic tests at disease-screening clinics. A criticism against this design is the fact that some people may well suspect that they have the disease even before a definite diagnosis is made which may affect their psychological state, responses to the questions asked during the study and hence the variable under investigation. Differential participation in the study may lead to the possibility of a non-representative sample. A possible weakness of this design may also come from the psychoneuroimmunological perspective which asserts that the central nervous system, the immune and the endocrine systems are tightly inter-connected. Therefore, the immune-system mediated disease such as cancer (and the inflammatory signals in its microenvironment) can have an effect on the psychological states even prior to its knowledge (or formal diagnosis) e.g., certain proinflammatory cytokines may have effects on the higher cognitive states (Raison, Demetrashvili, Capuron, Miller, 2005) and mood (Reichenberg et al., 2001). However, there are some merits of this design. Lack of a long follow-up prevents the results of the research from the contamination caused by participant drop-out, and events other than the treatment occurring between time 1 and time 2 which can cause a change in the variable under consideration (Sansone, Morf, & Panter, 2004). Finally, a semi-prospective design enables to test in a logistically simple and inexpensive manner the prognostic role of new factors, and upon confirming their effects, more complex prospective studies can be designed.

Longitudinal prospective designs involve measuring responses of a single sample over a long-term period, however they may or may not include this measurement on more than one occasions. The assessment of the predictor variable(s) may be prospective or historical (or archival) prospective, but the prospective longitudinal designs allow greater control over the sample, the variables measured and the times when the measurements take place (Coolican, 1991). Also, more importantly a prospective design, although not enabling causal inferences, rules out the bidirectionality of the relationship which is the major limitation of cross-sectional and semi-prospective designs.

The (semi-prospective and) prospective approach with multiple assessments of the variables surmounts the biggest disadvantage of cross-sectional studies, i.e., subject variance, by employing repeated measures on the same group of subjects over a substantial period, often a number of years. In this way genuine changes and the stability of some characteristics may be observed. If intervals between observations are not too large, major points of change can be identified (Coolican, 1991). However, the precise lack of the manipulation of the predictor variable(s) prevent from inferring the cause-and-effect relationship which can only be achieved by employing experiments and interventional studies, which are methodologically the most superior category of designs.

Experimental or interventional studies involve manipulation of the variables, which is done to ensure that the participants only differ in the treatment of that particular manipulated variable(s). Ethical issues as a consequence of interventions and/or experimentation become more important in psychosocial health research due to the involvement of a physically ill population. Sansone and colleagues (2004) discussing the methods in social psychology wrote: "When designing an appropriate comparison or control group, investigators must remember that it usually is unethical to assign people to an experience that does not at least meet the standard of care normally available. Participants can not receive medical or psychological treatments that are thought to be less effective than what would be available generally outside the study" (p. 451). However, these studies are conceptually and scientifically important because they are experimental demonstrations of a causal role of psychosocial variables in cancer-related outcomes (Cohen & Herbert, 1996). Clinically, these studies are important since they demonstrate possible health benefits of psychosocial interventions.

So far, I have discussed the methodologies in the field of psychosocial oncology and the inconsistent literature on social support, and cancer onset and progression. The following part of this chapter extends the current discussion, and includes a systematic literature review on social support and cancer progression in order to conclude on the exact significance of the role of different indices of social networks and support in the progression of cancer.

Part II

Systematic Review of the Literature on Social Support and Cancer Progression

3.5 Introduction

Although findings of some of the prospective studies on progression of cancer support the significance of the role of social relationships and the support drawn from them, there could be a few important reasons behind the inconsistent findings in this area. Firstly, as discussed in the previous chapter, several initial studies lacked a much-needed operational definition of the term social support. Also, there has been no uniformity in the definition of social support across the studies, which makes it difficult to compare the findings. This problem led to the second issue which is the use of various measures of social support. Thirdly, the populations have not been categorised on the basis of their prognostic potential. There is evidence that some cancers are more aggressive and show poorer prognosis e.g., lung or liver cancers have poorer prognosis than cancer of the breast, even after controlling for disease stage at diagnosis. Combining more than one type of cancer into one category without the scientific evidence for doing so may contaminate the results by masking the possible true beneficial effect of social support in one particular type of cancer. Since there is evidence that the significance of the role of marital status in different types of cancer may vary as a function of prognosis (Lai et al., 1999), the same may also apply to social support. Finally, the findings are difficult to compare due to varying number of confounding variables which have been taken into account in different studies. When studying more than one type of cancer, the set of relevant sociodemographic and biomedical variables may vary for each type. There are two possible approaches regarding this. One is that all relevant confounding variables must be controlled for in multivariate analysis regardless of their effect on the outcome in univariate analyses. This may particularly apply to important confounding variables such as cancer stage. The other approach advocates taking into account only those variables which turn out to be significant in the preliminary or univariate analyses on the sample of interest.

Some systematic reviews have been published on cancer progression which took into account several psychosocial predictors collectively (De Boer, McCormick, Pruyn, Ryckman, & van den Borne. 1999; De Boer, Ryckman, Pruyn, & van den Borne, 1999; Hoodin & Weber, 2003; Paton & Perez, 2006; Spiegel & Kato, 1996). Although these reviews included social support or social involvement in some form, due to the emphasis on several factors the issues related to this variable were not addressed in detail. Reifman (1995) reviewed longitudinal prospective studies on social relationships and recovery from heart disease and breast cancer which included seven studies on the latter. Blanchard, Albrecht, Ruckdeschel, Grant, and Hemmick (1995) reviewed the studies on social support, and cancer adaptation and survival. The studies included in this review were published between 1987 and 1993. However, the inclusion of the interventional studies which did not specifically focus on social support (e.g., Spiegel et al., 1989) makes its conclusions less relevant to the topic of social support. Ell, Nishimoto, Mediansky, Mantell, and Hamovitch (1992) listed the studies on social support and cancer progression, which had been published by that year, in order to support their findings. To the best of my knowledge, these are the only published reviews concentrating on social support (or the like) and its role in cancer progression. It is necessary to systematically organise and review all the studies on this topic in order to critically appraise the findings, and reach a conclusion regarding the significance of social support in the progression of this disease. Therefore, the following part of this chapter includes a systematic review of the studies published from 1970 to 2007 on the topic of social support and cancer progression.

3.6 Method

An exhaustive search for the articles was done on *PsycInfo*, *Medline* and *Web of Science* electronic databases by using, and combining the key words *cancer/tumor/tumour/neoplasm*, *progression*, *survival/mortality*, *social support/emotional support/instrumental support/spousal support*, *social relationships*, *social contact* and *social isolation/loneliness*. Hand search was done from reference lists of key papers.

The inclusion criteria for the articles were as follows: published in English language, in peer-reviewed journals between 1970 and July 2007, should have the above-mentioned keywords in the title or abstract. Only prospective studies with a longitudinal design were included. The studies with a cross-sectional design were excluded due to their inability to rule out bidirectionality. Also, the semi-prospective studies investigating the relationship between social support assessed before the diagnosis of cancer and the stage of disease at diagnosis did not qualify for this review as their outcome was severity of the disease. Also, the quantity or quality of social support may vary as a function of diagnosis, which in semi-prospective designs, occurs between the study entry and death or end of the follow-up period. The designs included in this review fell into one of the following two categories: longitudinal prospective and longitudinal prospective-superior. The latter includes the assessment of social support at more than one time point. This repeated assessment of variables during the follow-up period makes the design superior as the understanding of any variations in the levels of social support during the course of the study may reveal additional information, promote the understanding of the underlying mechanisms and minimise the possibility of the opposite causal effect i.e., disease severity leading to different patterns of seeking or eliciting social support.

The participants in the studies could be patients with any type of cancer including haematological and skin cancers, and although their participation or entry point in the studies could vary, it was to occur at one of the following: after the diagnosis, before the primary operation, after the primary operation, after a recurrence or metastasis, after admittance to hospital for treatment or follow-up. The studies measured the outcome by any one or two of the following criteria: (1) survival calculated by time to death or last follow-up, (2) disease-free survival calculated by time to recurrence or relapse, (3) progression calculated by time to recurrence or death whichever came first, (4) progression calculated by the time till change in the disease stage or tumour grade.

3.6.1 Defining Social Support

Since there are inconsistencies regarding significance of social support in progression of cancer, it is important to review the literature by taking into account the complexities of the construct. This may be a useful exercise in reevaluating the role of this predictor variable in the outcome and may work towards reaching a conclusive standpoint.

Although there has been a debate in the literature on the efficacy of the structural index of social support due to the limited knowledge this index offers, many studies in psychosocial oncology have either solely relied on this index or included it in addition to functional support. Since the manner in which social support has been categorised and measured may have an effect on the findings in this area, this review lists studies according to two major categories of social support: structural support and functional support. The former constitutes the quantity of support and includes properties such as the size, range and density of the social network. The latter refers to the quality, and includes instrumental, emotional and informational support (Berkman et al., 2000). The fact that unwanted or unsatisfactory support may lead to distress necessitates the measurement of the quality or functional aspects of social support (Krongrad et al., 1996).

3.6.2 Categorising Cancer

Due to the reasons that breast cancer is the second most prevalent type of cancer in general, the most prevalent type in women (Parkin & Bray, 2006) and the studies on breast cancer constitute a major part of the literature in this area, this review employs a further categorisation of the studies into *breast cancer*, *other type of cancer* constituting any one type of cancer other than breast cancer and *mixed cancers* including studies with more than one type of cancer.

3.7 Results

The titles and abstracts of the resulting 997 source studies were carefully read. Thirty-two studies were shortlisted. Studies were further excluded on the basis

of pre-determined inclusion criteria. Four studies which aimed to assess social support as a predictor of cancer incidence in healthy people and studied the consequent survival (Iwasaki et al., 2002; Reynolds & Kaplan, 1990; Vogt et al., 1992; Welin et al., 1992) were excluded as this review did not focus on onset or development of cancer. Two additional studies were excluded because they defined and measured social support either as a component of coping strategy (Grulke et al., 2005), or as a function of self-esteem (De Boer et al., 1998). Three studies were excluded because of insufficient information on the measurement of social support (Colon, Callies, Popkin, & McGlave, 1991; Rodrigue, Pearman, & Moreb, 1999; Tiersma et al., 2005). Studies on paediatric cancers were not included as they did not measure the levels of social support available to the patient *per se* but the family function and marital satisfaction of the parents as predictors of cancer progression (e.g., Dobkin et al., 2000). Studies on other psychosocial outcomes e.g., QoL were not included. However, those which studied social support as part of QoL, but analysed it separately, were included. Studies on the relationship between marital status and cancer were not included.

Twenty-three studies fulfilled the inclusion criteria and hence were included in this review (see Figure 4 for the flow chart showing data collection, and Table 3 for characteristics and results of the studies).

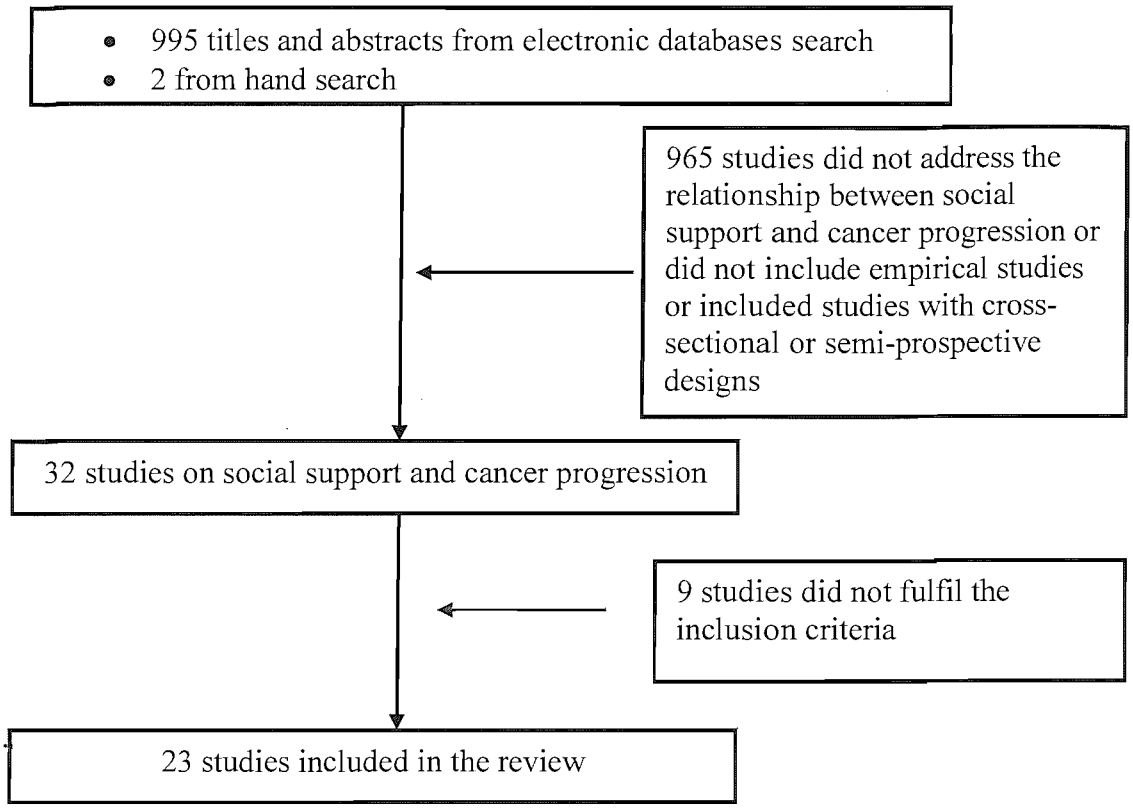

Figure 4. Flow chart depicting data collection.

Table 3. Characteristics and results of reviewed studies.

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
BREAST - STRUCTURAL SUPPORT						
Funch and Marshall (1983). USA. Longitudinal prospective	*N* = 208 Age of sample not reported All females 20 years§ Survival from diagnosis to death	Localised, regional	Number of people in the social network, organisational involvement. Assessed in retrospect for 5 years preceding the study entry	Age, SES *(marital status)*	Stage, past heath status	Results showed that higher level of organisational involvement was significantly associated with survival
Waxler-Morrison et al. (1991). Canada. Longitudinal prospective	*N* = 118 4 years Age of sample not reported All females Survival to last follow-up or death	I-IV. Age ≤ 55 years (pre-menopausal)	Number of supportive people, frequency of contact, employment status, a composite measure called size of social network including marital status, contact with friends/relatives and church membership	Age	Stage, nodal status, histological tumour grade, estrogen receptor status	Lower frequency of contact with friends, number of supportive people and friends, and being unemployed were associated with increased relative death rate. Having a large social network size was associated with greater relative death rate than medium social network size
*Ell et al. (1992). USA. Longitudinal prospective	*N* = 294 35 - 85 years All females Follow-up not stated §	I-V (in situ – metastasis)	Social integration	Marital status *(SES = income, education & occupational status, age, personal sense of control)*	*(Stage, functional status)*	Nonsignificant

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
Reynolds et al. (1994). USA. Longitudinal prospective (population-based sample)	*N* = 1011 20 - 79 years All females 5 years§	Early (in situ, I, IIN0), late (IIN1, III, IV)	Number and frequency of social contacts, church group membership, community groups membership, perceived sources of emotional support and instrumental support, a composite score of network size including the first 4 indices and marital status	Age, race, location (or State)	Stage, comorbidity	Fewer sources of perceived emotional support and fewest number of friends/relatives were associated with an increased death rate
Maunsell et al. (1995). Canada. Longitudinal prospective	*N* = 224 Age of sample not reported All females 7 years§ Survival from initial treatment to death or end of follow-up	Localised or regional	Number and types of confidants	Age *(treatment centre, marital status, years of schooling as an indicator of SES, stressful events and psychological distress in the time preceding the diagnosis)*	Presence of invaded axillary nodes, adjuvant radiation, adjuvant systemic therapy (hormone or chemotherapy) *(tumour size, stage, estrogen receptor status, type of surgery, weight)*	Having one or more confidants was associated with longer survival than having no confidants, followed by patients who had used 2 or more types of confidant. The longest survival was associated with the nomination of either physician or nurse as one of the categories

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
Weihs et al. (2005). USA. Longitudinal prospective	*N* = 90 51.6 years (10.4) All females 8-9 years§ Survival to recurrence or death or end of follow-up	II, III	Number of dependable and nonhousehold relationships, frequency of contact	*(Age, ethnicity, education level, marital status)*	Prognostic index consisting of tumour size, lymph node stage, histological grade *(treatment aggressive ness)*	The number of relationships predicted decreased mortality. There was a trend towards the prediction of recurrence which was not significant
Kroenke at al. (2006). USA. Longitudinal prospective-superior	*N* = 1753 46 - 71 years All females 12 years§† Survival from diagnosis to death or end of follow-up. Analysed the relationship between (1) social support before diagnosis and survival, (2) change in social support between before and after diagnosis and survival	All stages	Social isolation score including number and frequency of social contacts, church group membership, community group membership and marital status. Availability of a confidant and frequency of contact with them	Age	Time between diagnosis and assessment of social support, stage, chemotherapy, tamoxifen, radiation, estrogen-receptor status, age at menarche, oral contraceptive use, birth index (calculated by age at menopause - age at child birth), menopausal status, age at menopause, use of	Socially isolated patients before diagnosis were more likely to die from all-cause and cancer-specific mortality. Analysing the specific components of the social isolation index, lack of close relatives, friends and children was associated with a higher risk of breast cancer and all-cause mortality. No significant results for community or church group membership or having a confidant. Analyses based on post-diagnosis measures were nonsignificant due to low power after exclusions but yielded similar effect estimates

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
					hormone replacement therapy, smoking status, BMI, physical activity, protein intake	
BREAST - FUNCTIONAL SUPPORT						
*Ell et al. (1992). USA. Longitudinal prospective	*N* = 294 35 - 85 years All females Follow-up not stated§	I – V	Perceived adequacy of emotional support	Marital status *(SES including income, education and occupational status, age, personal sense of control)*	*(Stage, functional status)*	Perceived adequacy of emotional support was found to be a protective factor predicting survival
Giraldi et al. (1997). Italy. Longitudinal prospective	*N* = 95 51 years (9.5) All females 6 years§	Local, loco-regional	Received social support, loneliness	*(Fighting spirit)*	*(Tumour stage, lymph node status, infiltrating histotype of tumour, estrogen receptor)*	Nonsignificant. T-tests showed no significant differences in the social support scores for the groups of healthy, alive, or dead patients
Butow et al. (2000). Australia. Longitudinal prospective	*N* = 99 57 years (12) All females 5.5 years§ Survival from study	Metastatic	Need for social support, received social support	Age, education, occupation, ethnicity, marital status	Site of metastasis (liver, lung or pleura), appetite loss, treatment	Nonsignificant

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
	entry to death or censored at last date of follow-up					
Soler-Vila et al. (2003). USA. Longitudinal prospective (population-based sample)	*N* = 322 26 - 79 years All females 10 years§	Early (0 and I), late (II-IV)	Adequacy of perceived emotional support	Age, marital status, health locus of control, isolation, education, annual family income, occupational rank, insurance coverage, alcohol consumption, smoking	Stage, menopausal status, BMI, comorbidity, histologic grade, type of treatment *(nuclear grade, estrogen and progesterone receptor status, genetic alterations)*	Lower adequacy of perceived emotional support was associated with a higher risk of death from cancer. Stage specific analyses revealed that the perceived emotional support-survival correlation was strong and significant in women with late-stage (II-IV) disease but not in women with early stage (0-I)
Osborne et al. (2004). Australia. Longitudinal prospective	*N* = 62 (n = 14 for cancer-related deaths) 56.4 years (11.8) All females 6.1-7.9 years§†	First primary cancer	Perception of and need for confidant support and affective support	Age	Tumour size, lymph node status, histological type, histological grade, type of treatment (surgery or chemotherapy)	Nonsignificant

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
Lehto et al. (2006). Finland. Longitudinal prospective	*N* = 101 54.2 years (8.45) M = 1%, F = 99% 8.4 years§ Survival from diagnosis to date of relapse and further to the date of death or date of last follow-up	Localised or regional	Perceived social support including emotional/informational support, practical support and love	Age, education *(working status, family income)*	Number of positive nodes, tumour size, grade 3 in ductal carcinoma, baseline adjuvant treatments *(hormonal receptors, type of baseline surgery)*	A high level of perceived social support was significantly associated with shorter survival in over-all survival analysis. Social support did not predict event-free survival
MIXED - STRUCTURAL SUPPORT						
Cassileth et al. (1985). USA. Longitudinal prospective	*N* = 359 (1) 60.3 years (11.5); (2) 52.2 years (14.7) M = 83, F = 117 2 years§ Analysed (1) survival from study entry to death; (2) time to relapse	(1) Regional or metastatic disease to determine the time of survival; (2) Stage I or II melanoma or stage II breast cancer to determine the time to relapse	Number and frequency of social contacts, and marital status merged together	-	-	Nonsignificant. Nonsignificant results after 8-year follow-up of the same groups (Cassileth, Walsh, Lusk, 1988)

Study, country, year and design	*N*, mean age (*SD*)/age range, of males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
*Ell et al. (1992). USA. Longitudinal prospective	*N* = 294 35 - 85 years % not reported Follow-up not stated§	Colorectal and lung cancers	Social integration	*(SES including income, education and occupational status, marital status, age, personal sense of control)*	Stage, functional status	Nonsignificant
Goodwin et al. (1996). USA. Longitudinal prospective	*N* = 646 62.4 years M = 71%, F = 79.8% 10 years§ Survival from study entry to death or last follow-up	Colorectal, prostate, breast (in situ, local, regional, distant). Older cancer patients aged ≥ 65	Number and frequency of contacts, church membership, marital status	Age, gender, family income, means of transportation, ethnicity, cognitive status, cancer knowledge, education	Stage, treatment, patient delay, comorbidities, physical activity, functional status *(availability of a family doctor)*	Nonsignificant. Analyses for each cancer site produced similar results with wider confidence intervals due to small sample size
Burns et al. (2005). Australia. Longitudinal prospective-superior: social support was assessed at: (1) study entry, and (2) 12 weeks after study entry	*N* = 163 62.9 years M = 47.2%, F = 52.8% 7 years§ Survival from study entry to mortality or end of follow-up	Breast, Haema-tological, prostate, other (advanced stage, locoregional or distant)	Number and type of confidants for sharing emotional support	Marital status *(Sex)*	Primary site of cancer, extent of disease or stage, treatment setting, treatment, performance status, general health status	Death risk was lower in patients with having 4 and more or less than 2 confidants as compared to having 2-3 confidants. Patients with shorter survival nominated their family members as confidants than those with longer survival. Longer survival was predicted by having friends as confidants. Nonsignificant for 12 weeks after study entry

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
MIXED - FUNCTIONAL SUPPORT						
*Ell et al. (1992). USA. Longitudinal prospective	*N* = 294 35 - 85 years % not reported Follow-up not stated§	Colorectal and lung cancers (I-V)	Perceived adequacy of emotional support	*(SES including income, education and occupational status, marital status, age, personal sense of control)*	Stage, functional status	Nonsignificant
OTHER - STRUCTURAL SUPPORT						
*Saito-Nakaya et al. (2006). Japan. Longitudinal prospective	*N* = 238 Age of sample not reported M = 59.9%, F = 60.9% 8 years§†	Non-small cell lung cancer (I-III)	Number of confidants	Age, sex, smoking status before and after surgery *(educational level, depression)*	occasion of diagnosis, stage, serum albumin *(histological type, type of surgery, performance status, pain, dyspnea, BMI)*	Nonsignificant
Villingshoj et al. (2006). Denmark. Longitudinal prospective	*N* = 770 Age of sample not reported M = 52.5%, F = 47.5% 11 years§ Survival from study entry to death or end of follow-up	Colorectal cancer (all stages)	Frequency of contact with the people in the social network before and after the surgery	Sex, age	Stage, recurrence, comorbidity	Increased contact with children was associated with a higher mortality rate compared to unchanged contact before and after cancer surgery

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
OTHER - FUNCTIONAL SUPPORT						
Stavraky et al. (1988). Canada. Longitudinal prospective	*N* = 224 Age of sample not reported M = 74.6%, F = 25.4% 1 year§	Lung (regional II and III, advanced IV).	Need for social support, received support	*(Age, education, sex, employment)*	Stage, pathological diagnosis *(comorbidity)*	High need for sympathy and devotion was associated with higher odds of death
Herndon II et al. (1999). USA. Longitudinal prospective	*N* = 206 61 years M = 74%, F = 26% 2 years§ Survival from study entry to death or end of follow-up	Non-small cell lung cancer (advanced stage)	Quality, and need of affective and confidant support	*(Age, gender, marital status, employment status, income level, educational level)*	*(Functional and physical performance status, recurrence, histology, site of metastasis, presenting symptoms, weight loss, albumin level, haemoglobin)*	Univariate analysis nonsignificant
Butow et al. (1999). Australia. Longitudinal prospective	*N* = 125 55 years (14) M = 62%, F = 38% 2 years Survival from study entry to death or censored at the date of last follow-up	Melanoma (metastatic)	Need for social support, received social support	Age, sex, education, occupation, ethnicity, marital status	Site of metastasis, treatment	Nonsignificant

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
Naughton et al. (2002). USA. Longitudinal prospective	*N* = 70 62 years (9.5) M = 71%, F = 29% Follow-up not stated§ Survival from study entry to death	Small-cell lung cancer (no mention of stage. Presence of brain and liver metastases noted. Performance status was measured)	Perceived social support (comprising of informational, tangible, emotional support and positive social interaction)	Age, gender, race, QoL subscales (physical functioning, role functioning, emotional functioning, social functioning), overall QoL, sleep quality, depression, treatment group	Performance status, presence of brain and liver metastases, performance status, symptoms	Nonsignificant
Frick et al. (2005). Germany. Longitudinal prospective	*N* = 99 54.7 years (9.7) M = 57.6%, F = 42.4% 1 year§ Survival from the autologous peripheral blood stem cell transplantation (PSBCT) to death or end of follow-up	Haematological cancers (acute myeloid leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple	Perceived positive support from family and friends, perceived problematic support from family and friends	Depression, participation in psychotherapy *(Age, marital status)*	Performance status (to indicate one of the following: complete remission, partial remission, no change, progressive disease), interferon treatment *(Diagnosis i.e., type of malignancy)*	Nonsignificant for perceived positive support in univariate analysis. Perceived problematic support predicted survival when categorised by quartile and comparing extreme groups. Nonsignificant but a trend for perceived problematic support when categorised by quartile

Study, country, year and design	*N*, mean age (*SD*)/age range, % males and females, length of follow-up & survival	Type of Cancer and stage	Social support index	Tested sociodemographic factors	Tested biomedical factors	Results
		myeloma, other)				
Pinquart et al. (2007). Germany. Longitudinal prospective	*N* = 50 54.4 years (14.8) M = 46%, F = 54% 2 years§ Survival from study entry to death or end of follow-up	Acute myelogenous leukaemia	Perceived social support (comprising emotional, instrumental, confidant support, and social integration)	Age	Functional status, treatment, cytogenetic risk factor	Lower levels of perceived social support predicted mortality
*Saito-Nakaya et al. (2006). Japan. Longitudinal prospective	*N* = 238 Age of sample not reported M = 59.9%, F = 60.9% 8 years§†	Non-small cell lung cancer (I-III)	Satisfaction with confidants	Age, sex, smoking status before and after surgery *(educational level, depression)*	Occasion of diagnosis, stage, serum albumin *(histological type, type of surgery, performance status, pain, dyspnea, BMI)*	Nonsignificant

Note. *Studies which included both structural and functional support, §All-cause mortality, †cancer-specific mortality, BMI body mass index, sociodemographic and biomedical variables which were considered but not included in the final multivariate analyses are in italicised text.

3.8 Quality Assessment

The quality of the studies was determined by using the framework for assessing the internal validity of prognostic studies proposed by Altman (2005). The categories and subcategories of this framework are given in Table 4. The minimum and maximum possible scores on this list of criteria are 11 and 28, respectively. The studies were grouped as methodologically sound or *good* if they scored ≥ 80 per cent. Sixteen studies passed this criteria and 7 scored < 80 per cent.

Table 4. Quality-assessment framework.

Feature	Qualities sought	Scoring
Sample of patients	1. Inclusion/exclusion criteria defined	1 = No, 2 = Yes
	2. Sample selection explained	1 = No, 2 = Yes
	3. Clinical and demographic variables described	1 = No, 2 = Yes
	4. Representative	0 = No information given 1 = The characteristics of participants and non-participants were found significantly different in the comparison OR 1 = Less than 75% participants agreed to take part 2 = More than 75% participants agreed to take part, but there was no comparison between participants and nonparticipants 3 = More than 75% participants agreed to take part and the comparison showing that the sample is representative OR 3 = ≥ 90% participants agreed to take part OR 3 = Any %age of participants agreed to take part and the comparison showing that the sample is representative

(Cont.)

Feature	Qualities sought	Scoring
	5. Size - Appropriate[5]	1 = No, 2 = Yes
Outcome	1. Fully defined	1 = No, 2 = Yes
	2. Appropriate	1 = Survival including recurrence i.e., recurrence was not measured during follow-up period 2 = Survival and recurrence separately OR 2 = Progression measured by the grade or stage
	3. Known for all or a high proportion of patients (≥ 80%)	1 = No, 2 = Yes
Prognostic variable	1. Fully defined	1 = No, 2 = Yes
	2. Precisely measured	1 = No, 2 = Yes
	3. Available for all or a high proportion of patients (≥ 80%)	1 = No, 2 = Yes
Analysis	1. Appropriate analyses	1 = No, 2 = Yes
	2. Statistical adjustment for relevant variables	1 = None controlled 2 = Some controlled 3 = All or most of the important ones controlled

[5] Power in survival analysis is enhanced by larger sample sizes and covariates with stronger effects. Therefore, based on a calculation for sample size in survival analyses, a sample size of 12 for each covariate included is recommended by Eliason (1993).

3.8.1 Results of Quality Assessment

The review included the studies on social support and progression of cancer which are presented in Table 1. The table is categorised according to the type of cancer, and each category of cancer is subcategorised into structural and functional support. The studies were scored on the basis of their methodological rigour in the quality assessment procedure on the basis on pre-determined criteria (see Table 4). The findings of studies (n = 16) which scored at or above 80 per cent were rated as good or methodologically sound studies (Burns, Craft, & Roder, 2005; Butow et al., 1999; Butow, Coates, & Dunn, 2000; Goodwin, Samet, & Hunt, 1996; Herndon II et al., 1999; Kroenke et al., 2006; Lehto, Ojanen, Dyba, Aromaa, & Kellokumpu-Lehtinen, 2006; Maunsell, Brrisson, & Deschenes, 1995; Naughton et al., 2002; Osborne et al., 2004; Reynolds et al., 1994; Saito-Nakaya et al., 2006; Soler-vila, Kasl, & Jones, 2003; Villingshoj, Ross, Thhomsen, & Johansen, 2006; Waxler-Morrison, Hislop, Mears, & Kan, 1991; Weihs et al., 2005). Table 5 includes the numbers and percentages of: (1) studies with significant results for the relationship between social support and cancer progression, and (2) methodologically sound studies with significant results for this relationship. Table 5 also depicts the percentage of good studies which did not find significant evidence for the relationship between social support and cancer progression.

3.8.1.1 Populations.

Twenty-seven findings reported in this review were published in 23 articles. Forty-eight per cent of these findings were on breast cancer, 33 per cent were on any other type of cancer and two per cent were on mixed cancers.

3.8.1.2 Follow-up.

The follow-up period in the studies ranged from 1 year to 20 years. The mean follow-up period was 6.7 years. The follow-up periods for breast cancer, other cancer, and mixed cancers categories were 8.5 years, 4.4 years and 6.3 years, respectively.

3.8.1.3 Ratio of sample size with control variables.

Most of the studies defined all relevant sociodemographic and biomedical variables. However, many of them did not control for all of the important ones in the main analysis (see Table 3). The major difference in the scores on quality assessment was related to the control of relevant confounding variables. The average number of sociodemographic and biomedical variables controlled in the studies were two and three, respectively. The appropriate number of variables included in the statistical tests in survival analyses is based on maximum likelihood methods which are only reliable with larger samples.

3.8.1.4 Statistical analyses.

Most of the studies employed the standard survival analyses. Cox Proportional-Hazards Model was the most frequently employed statistical analysis which was used by 87 per cent of the studies included in this review. Two studies used multiple regression analyses (Funch & Marshall, 1983; Stavraky, Donner, Kincade, & Stewart, 1988) and one used the Mantel-Cox Statistic which is not a multivariate analysis (Cassileth, Lusk, Miller, Brown, & Miller, 1985).

3.8.1.5 Social support and cancer progression.

The relationship between social support and cancer progression was addressed in 23 studies. Ten studies were done in USA, 3 in Canada, 4 in Australia, 2 in Germany, and 1 each in Italy, Finland, Japan and Denmark. Since some studies used both structural and functional indices of social support, they were counted once for each of the index. Therefore, in total 27 findings in all types of cancer were included in this review out of which 9 provided significant evidence for this relationship, and were methodologically sound and of good quality (Burns et al., 2005; Kroenke et al., 2006; Lehto et al., 2006; Maunsell et al., 1995; Reynolds et al., 1994; Soler-Vila et al., 2003; Villingshoj et al., 2006; Waxler-Morrison et al., 1991; Weihs et al., 2005). Eight studies of the similar calibre failed to find this relationship

(Butow et al., 2000; Butow et al., 1999; Goodwin et al., 1996; Herndon II et al., 1999; Naughton et al., 2002; Osborne et al., 2004; Saito-Nakaya et al., 2006[6]).

The structural support indices which were assessed included number of people or supportive people in social network (Funch & Marshall, 1983; Goodwin et al., 1996; Reynolds et al., 1994; Waxler-Morrison et al., 1991), frequency of contact with people in social network (Goodwin et al., 1996; Reynolds et al., 1994; Villingshoj et al., 2006; Waxler-Morrison et al., 1991), number of confidants possibly for emotional support (Burns et al., 2005; Maunsell et al., 1995; Saito-Nakaya et al., 2006), types of confidants possible for emotional support (Burns et al., 2005; Maunsell et al., 1995), number of dependable and nonhousehold relationships (Weihs et al., 2005), frequency of contact with dependable and nonhousehold relationships (Weihs et al., 2005), employment status (Waxler-Morrison et al., 1991), organisational involvement (Funch & Marshall, 1983), church group membership (Goodwin et al., 1996; Reynolds et al., 1994), community groups membership (Reynolds et al., 1994), sources of emotional support and instrumental support (Reynolds et al., 1994). The structural indices also included composite measures such as social network including marital status, contact with friends/relatives and church membership (Reynolds et al., 1994; Waxler-Morrison et al., 1991), social integration (Ell et al., 1992[7]), social isolation including number and frequency of social contacts, church group membership, community groups membership and marital status (Kroenke et al., 2006), and an index including number and frequency of social contacts, and marital status (Cassileth et al., 1985).

Functional support indices included perceived adequacy of emotional support (Ell et al., 1992[8]; Soler-vila et al., 2003), perceived confidant support and affective support (Osborne et al., 2004), perceived social support including emotional/informational support, practical support, love, and positive interaction (Lehto et al., 2006; Naughton et al., 2002; Pinquart, Hoffken, Silbereisen, & Wedding, 2007), perceived positive support from family and friends (Frick, Motzke, Fischer, Busch, & Bumeder, 2005), received social support (Butow et al., 1999; Butow et al., 2000; Giraldi et al., 1997; Stavraky et al., 1988), perceived problematic

[6] Two findings.
[7] Two findings.
[8] Two findings.

support from family and friends (Frick et al., 2005), loneliness (Giraldi et al., 1997), quality of affective and confidant support (Herndon II et al., 1999), satisfaction with confidants (Saito-Nakaya et al., 2006), need for social support (Butow et al., 1999; Butow et al., 2000; Stavraky et al., 1988), and need for confidant and affective support (Herndon II et al., 1999; Osborne et al., 2004).

With regards to structural support, 67 per cent of good quality studies found significant results concerning the relationship with cancer progression. Interestingly, the studies on functional support were less convincing. Twenty-one per cent of studies found the evidence in favour of the association between functional indices of social support and cancer progression, but only 13 per cent of these findings were reported in good quality studies. Since most of the studies on this topic were on breast cancer, it is not surprising that a greater number of significant findings were found in the studies on this type of cancer in comparison to the *other* and *mixed* categories of cancer. All 5 of the good studies on structural support and breast cancer progression found significant evidence, while only 25 per cent for functional support. Overall, 22 per cent of good studies on breast cancer found no evidence for social support having any relationship with breast cancer progression in comparison to 67 per cent of good quality studies which found significant results. It is important to note that counter-intuitive evidence was found in one of the good quality studies, where higher level of functional support was associated with increased risk of breast cancer mortality (Lehto et al., 2006).

In studies which included any one type of cancer except breast cancer, the evidence was more convincing for functional support as none of the structural support studies found significant results. Although the number of studies employing functional support indices was greater than the ones with structural support (ratio of 7:2), only two studies on functional support found significant evidence. A study on structural support and colorectal cancer progression found that increased frequency of contact with children was associated with a higher mortality rate compared to unchanged contact with the children before and after cancer surgery. Looking at total social support, none of the good quality studies found significant evidence in this category of cancer. However, 83 per cent of good quality studies yielded nonsignificant results.

Considering *mixed cancers* category, there was only one study on functional support while four studies measured social support by using structural support indices. Twenty-five per cent of the latter found significant results, while no study found significant evidence for functional support. The significance of total social support was supported in 50 per cent of good quality studies on mixed cancers, while an equal 50 per cent of good quality studies found no such evidence.

These results show that the evidence for the significant role of overall social support in cancer progression is not convincing in cancer, except in breast cancer, due to almost equal number of studies showing significant and nonsignificant results.

As far as the two categories of social support, structural and functional support are concerned, results were more convincing for the former than the latter. Nine good quality studies employed structural support indices and six of them found significant evidence for their role in cancer progression (see Table 5).

Table 5. Number (and percentages) of studies with significant results and good quality studies with significant results for different types of cancer.

Type of cancer	Structural support (%)	Structural support Good quality (%)	Functional support (%)	Functional support Good quality (%)	Total social support (%)	Total social support Good quality (%)
Breast	6/7 (86)	5/5 (100)	2/6 (33)	1/4 (25)	8/13 (62)	6/9 (67) - *2/9 (22)*
Other	0/2 (0)	0/2 (0)	2/7 (29)	0/4 (0)	2/9 (22)	0/6 (0) - *5/6 (83)*
Mixed	1/4 (25)	1/2 (50)	0/1 (0)	0/0 (0)	1/5 (20)	1/2 (50) - *1/2 (50)*
Combined	7/13 (54)	6/9 (67)	3/14 (21)	1/8 (13)	10/27 (37)	7/17 (41) - *8/17 (47)*

Note. Percentages of nonsignificant results found in good quality studies are in italics.

3.9 Discussion

3.9.1 All Cancers

The results of this systematic review hinted towards the significance of the role of social support in progression of cancer. Considering all the findings on cancer, 7 out of 17 good quality studies on structural and functional support found significant evidence for their role in cancer progression. As compared to this, an almost equally convincing 8 out of 17 methodologically sound studies found no significant evidence. Surprisingly, the overall percentage was more convincing for structural than for functional support. The structural support indices which were significant with reference to cancer progression included the following: number of people or supportive people in social network (Kroenke et al., 2006; Reynolds et al., 1994; Waxler-Morrison et al., 1991); frequency of contact with people in social network (Kroenke etal., 2006; Waxler-Morrison et al., 1991); number of confidants possibly for emotional support (Burns et al., 2005; Maunsell et al., 1995); having nurses, doctors and friends for support had a beneficial effect while having family had no significant effect (Burns et al., 2005; Maunsell et al., 1995); number of dependable and nonhousehold relationships (Weihs et al., 2005); being unemployed (Waxler-Morrison et al.,1991); having sources of emotional support (Reynolds et al., 1994); and composite measures of social network (Waxler-Morrison et al., 1991) and social isolation defined as number and frequency of social contacts, church and community groups membership and marital status (Kroenke et al., 2006).

Nonsignificant results were found in good studies for number of people or supportive people in social network (Goodwin et al., 1996), number of confidants possible for emotional support (Saito-Nakaya et al., 2006), and church group and community groups membership (Kroenke atl., 2006). Results were significant in the opposite direction for structural support index of frequency of contact with the people in the social network (Villingshoj et al., 2006).

Functional support was found to be significantly associated with cancer progression in only 21 per cent of the findings. Results of good studies were significant for perceived adequacy of emotional support (Soler-vila et al., 2003),

while nonsignificant results were found in good studies for the following: perceived confidant support and affective support (Osborne et al., 2004); perceived social support including emotional/informational support, practical support and positive interaction (Naughton et al., 2002); received social support (Butow et al., 1999; Butow et al., 2000); quality of affective support (Herndon II et al., 1999); satisfaction with confidants (Saito-Nakaya et al., 2006); need for social support (Butow et al., 1999; Butow et al., 2000); and need for confidant and affective support (Herndon II et al., 1999; Osborne et al., 2004).

Results were unexpectedly significant in the opposite direction for the index of perceived social support including emotional/informational support, practical support and love (Lehto et al., 2006).

It is important to note that all the nonsignificant results on functional support and cancer progression were found in studies which included metastatic cancers except Osborne et al. (2004) and Saito-Nakaya et al. (2006) where the cancers were primary and all stages, respectively. It has been discussed earlier in this chapter that social support may play a more important role in cancer progression at early stages of the disease. Although a study done by Soler-Vila et al. (2003) suggested to the contrary, with adequacy of emotional support associated with survival in late but not in early stage breast cancer.

Structural support was found to be significantly associated with cancer progression in 67 per cent of good studies, which is five times more than the evidence found for functional support. Since this finding contrasts with what has been postulated in the literature (as discussed in Chapter 2), there could be a few explanations for this pattern of results in the context of the topic of the current review. Firstly, despite the fact that structural support provides limited information, its assessment is simpler and more straightforward than that of functional support due to the complexities associated with the conceptualisation and operationalisation of the latter. These issues related to the assessment of functional support, if not addressed properly, may result in misleading findings. Secondly, patients may have a wide circle of friends and relatives from whom social support may be available i.e., they report to have high structural support. However, they may not report to have

sufficient social support (i.e., report low functional support) due to individual differences in their ability to seek social support such as they may lack behaviours which are associated with eliciting social support include talking to someone to get additional information or discuss feelings, seeking professional help, or asking friends or relatives for advice and making a plan of action and following it. These behaviours are critical to eliciting functional aspects of social support from the social network. Therefore, reliance on only structural support indices may, at least in some instances, yield misleading information which might have been responsible for counter-intuitive results with respect to cancer progression (e.g., Villingshoj et al., 2006). Thirdly, there are certain personality styles which may undermine the buffering potential of interpersonal support. For instance, Lepore (1995) found an interactive effect of social support and cynicism in cardiovascular reactivity. Also, Lehto et al. (2006) explained their unexpected results regarding higher perceived social support and shorter survival in breast cancer by speculating that nonexpression of negative emotions, which was inversely correlated with perceived social support in their sample, might have been responsible for the unfavourable effect of high perceived social support on cancer progression. Finally, a significant nonlinear pattern of results regarding structural support has been reported in two studies (Burns et al., 2005; Waxler-Morrison et al., 1991) where having low and high scores on structural support indices were associated with a higher risk of mortality than having a medium score. This supports the pattern of results found by House et al. (1982) in their longitudinal study on structural support indices and mortality. It is difficult to explain this U-shaped pattern of the results. It may be possible that people confused the extended network with close relations. In relation to the effects of fewer friends, it is possible that having too many friends reflects superficial relations which may not provide adequate or needed social support. Hammer (1983) explained the core and extended networks in relation to health and illness, and suggested that an index of extended network should be used which is a large reservoir of distant relationships from which new friends and helpers can be recruited as the smaller core network changes, in order to distinguish between the two with reference to predicting physical health outcomes.

3.9.2 Other Cancers and Mixed Cancers

No strong evidence for the role of social support in progression of cancers other than breast cancer was found in the present review. In *other cancer* category, none of the good studies found the evidence as compared to 83 per cent of studies which found nonsignificant results. These studies were on non-small cell lung cancer (Herndon II et al., 1999; Saito-Nakaya et al., 2006[9]), small-cell lung cancer (Naughton et al., 2002), melanoma (Butow et al., 1999) and colorectal cancer (Villingshoj et al., 2006). Nonsignificant evidence was found in cancers of non-small cell lung (Herndon II et al., 1999; Saito-Nakaya et al., 2006[10]), small-cell lung (Naughton et al., 2002) and melanoma (Butow et al., 1999). Counter-intuitive results were found in the study on structural support and mortality in colorectal cancer (Villingshoj et al., 2006). More convincing results regarding functional support in comparison to structural support have been found in this category. However, none of the methodologically sound studies using functional support indices found significant results. The pattern of the findings in this category supports the results found by Lai et al. (1999) in their extensive study on marital status and survival, suggesting that survival varied by primary site of cancer and was not affected by marital status in cancers with poor prognosis, after adjusting for race, age and treatment. Burns et al. (2005) also found evidence in their study on structural support and survival in mixed cancers including breast, haematological, prostate and others, supporting that survival varied by primary cancer site. This evidence hints that early stage cancer may be better for studying the effects of psychosocial factors and some types of cancer may be more influenced by these factors via the neuro-hormonal-immunological pathway (Kiecolt-Glaser & Glaser, 1995, 1999; Garssen, 2004). Therefore disease-related variables may be better predictors of progression particularly at advanced stage of the disease. A study by Ell and colleagues (1992) also found that stage was the only significant predictor of survival among patients with more advanced disease but not in breast cancer. Due to these differences in cancer types and its stages, social support may be more useful at certain stages and types of cancer. It may also be speculated that there are differences in the ways patients seek and receive social support at different stages of the disease. It is

[9] Two findings.
[10] Two findings.

therefore, crucial to consider this factor before reaching a conclusion. So far the results on progression of cancer (and survival) have not been conclusive as to which specific stage social support affects the most.

Several studies included in this review found significant evidence for disease-related variables. For instance, disease stage at diagnosis was the best predictor of (Funch & Marshall, 1983) or significantly associated with survival (Cassileth et al., 1985; Goodwin et al., 1996; Stavraky et al., 1988; Villingshoj et al., 2006; Waxler Morrison et al., 1991). Other disease outcomes were also associated with survival. Inadequate treatment was a significant predictor of reduced survival in older adults in *mixed cancers* category (Goodwin et al., 1996). Pathological nodal status (Waxler Morrison et al., 1991), prognostic index (based on tumour size, lymph node, stage and histological grade) (Weihs et al., 2005) and site of metastasis (Butow et al., 2000) were also significantly associated with shorter survival.

In *cancers of mixed sites* category, 50 per cent of good quality studies found significant evidence for structural support while the same percentage failed to find it. Despite a smaller number of studies in this category as compared to *breast cancer* and *other cancer* categories, the evidence was stronger for structural than for functional support, replicating the pattern found for breast cancer.

3.9.3 Methodological Issues

There are some methodological issues which are relevant to research in this area. The studies with survival or mortality as their outcome used all-cause mortality which warrants taking into account all the important biomedical variables which may be relevant to survival such as baseline comorbidity, or general physical health status. In studies where these were not statistically adjusted for, mortality following the diagnosis and treatment can not be solely attributed to cancer. There is evidence that comorbidity is significantly associated with survival (Villingshoj et al., 2006) and cancer stage, which is otherwise a powerful predictor of survival, may not remain so in patients with three or more comorbidities (Santariano & Ragland, 1994). However, some evidence suggests that social support is related with all-cause mortality, in people without initial cancer, independent of physical health (Cohen,

1988). Another related issue is regarding the recurrence or relapse of the disease during follow-up period which is significantly associated with survival (Villingshoj et al., 2006). Although some studies took into account the time between study entry and recurrence (e.g., Cassileth et al., 1985), only one study (Villingshoj et al., 2006) controlled for it in the main survival analyses. Weihs et al. (2005) found that recurrence was not a reliable predictor of survival and therefore did not include it in the main analyses. It can be argued that the time lapse between the recurrence and its detection may vary, therefore recurrence may not be a reliable index of disease progression.

Since social support was most frequently assessed only at study entry which in most of the cases, was after diagnosis, the question of whether the levels of social support reported at that time are indicative of the support the person usually gets is open to discussion. Nevertheless, assessing social support after the diagnosis may be a better predictor of survival than the assessment before the diagnosis (Waxler-Morrison et al., 1991). The assessment of social support at any of the critical times such as before and after surgery particularly mastectomy, can also be seen with similar scepticism, as it is a time in which patients may be more psychologically and emotionally vulnerable than at any other time, and the reported levels of social support may be biased. Also, predictors of survival may change during the course of the disease. For example, Burns et al. (2005) found that having 0-1 or 4+ confidants and having friends as confidants were associated with longer survival in cancer patients when these variables were assessed at study entry. When these indices were assessed at 12 weeks after study entry, they found that survivors shared their feelings with doctors more than nonsurvivors and number of confidants was no longer predictive of survival unlike at study entry.

Some aspects of patients' lives which may have a potential contribution towards the levels of social support e.g., marital status, may change during the follow-up period, which necessitates the assessment of these measures at more than one time points during the follow-up period.

Patient delay is an important variable in health-related research and may be important with reference to cancer progression. It may be relevant not only due to the

fact that patients who are diagnosed at a later disease stage are less likely to receive curative treatment and/or surgery (Greenberg et al., 1988) but also because the time at which the decision to seek medical help may be associated with some aspects of patients' social life e.g., studies on cancer found that unmarried patients were more likely to be diagnosed at a later disease stage (Goodwin et al., 1987). Despite the potential relevance of patient delay, only two studies (Goodwin et al., 1996; Reynolds et al., 1994) assessed and analysed this variable. Interestingly, the results of these two studies did not show any significant results. Reynolds et al. (1994) also found that the most isolated women were not more likely to be diagnosed at a later disease stage than the women with most social connections.

Finally, attention should be paid to the instruments in the measurement of social support. Questionnaires may not be a reliable tool to measure the exact extent of perceived social support. Moreover, the use of different social support measures employed by studies makes it difficult to compare their findings.

3.10 Conclusion

This systematic review aimed at identifying and summarising the evidence for the significance of two important indices of social support in cancer progression. It is important to note that no allowance was made for publication bias in this systematic review. The findings suggested that the evidence for the relationship between social support and cancer progression is significantly strong for breast cancer as shown by methodologically sound studies, but not convincing for other types of cancer or in studies which combined different types of cancer. However, these findings should be viewed in the context that a larger number of studies have been conducted on breast cancer as compared to other types of cancer. Structural support indices were found to be more consistently associated with cancer progression than the indices of functional support in all types of cancer, particularly in breast cancer. Disease-related variables such as severity, treatment, nodal status and site of metastasis were found to be significant predictors of cancer progression, and it is suggested that these variables must be considered when conducting studies on the role of psychosocial factors in cancer-related outcomes including progression.

3.11 Chapter Summary

There is a large number of studies on psychosocial factors and cancer-related outcomes. Due to the progress in cancer treatment, more people are now living with cancer than ever before which makes it more important to improve their QoL, and investigate the role of relevant psychological and social factors which may also influence survival in cancer.

Since different types of social support and their need change during the course of cancer, it is important to determine when and which index of social support is more efficient in predicting cancer progression. The available theoretical and empirical literature suggested that the index of functional support may be a better correlate of psychological, and physical health-related outcomes than structural support. However, the results of the present systematic review suggested on the contrary i.e., the prognostic role of structural support is more important, at least for cancer progression. The results of this review also suggested that the significance of the role of social support in cancer progression may vary as a function of type and stage of disease i.e., the beneficial effects of social relationships may not contribute to longer survival in cancers of poor prognosis and advanced stage.

Chapter Four: Psychoneuroimmunological Pathways between Social Support and Cancer

4.1 Aims of the Chapter

This chapter is an extension of the previous chapter on social support and cancer progression. It focuses on the bidirectional communications between brain and immune system in the context of social stress, and discusses the implications of these communications for cancer by considering the evidence from animal and human studies. This chapter emphasises proinflammatory cytokines and stress hormones as possible neuroimmunological pathways which may be linking the stress associated with the lack of social support with the progression of cancer.

4.2 Bidirectional Brain-Immune System Communications

PNI is the study of the bidirectional interrelations between the CNS and the immune system (Ader, 1980), and tries to reveal the underlying mechanisms linking psychosocial factors with health-related outcomes. It has been recognised that the nervous and immune systems share a common biochemical language and communicate through a circuit consisting of neurotransmitters, neuroendocrine hormones, cytokines[11] and their receptors (Blalock & Smith, 2007). All this happens as a bidirectional feedback loop between the two systems (Reiche, Nunes, & Morimoto, 2004).

The tight interconnections between the immune and nervous systems make it possible for the cellular immune system to become dysregulated in response to psychosocial stress (Mravec et al., 2006) via the endocrine system (Steel, Carney, Carr, & Baum, 2004). This dysregulation occurs through neurotransmitters such as noradrenaline, serotonin, dopamine, and acetylcholine; neuropeptides such as enkephalins, substance P, vasoactive intestinal peptide, corticotropin releasing factor (CRF), and neuropeptide Y; neurohormones such as growth hormone, ACTH, and

[11] Cytokines are soluble proteins secreted by various cells both at the periphery by macrophages and lymphocytes, and in the brain by astrocytes and microglia. They can act on the cell itself (autocrine) or on other nearby cells (paracrine) by binding to specific receptors and signal mainly between immune cells.

prolactin; and adrenal hormones such as corticosteroids and adrenaline, and their receptors that are situated on lymphocytes and macrophages (Reiche et al., 2004).

The major neural pathways by which stress can have an effect on the immune system are the HPA axis and the ANS, particularly the SNS. The activation of the HPA axis leads to the release of pituitary peptides such as ACTH, enkephalins and endorphins. ACTH activates the release of glucocorticoids (e.g., cortisol) from the adrenal cortex. CRF, which stimulates the activation of the HPA axis also activates the SNS, and in turn releases noradrenaline in the brain and the periphery (see Figure 5).

Experimental studies on stress have shown that plasma adrenaline can affect immune function by affecting the lymphocytes and monocytes. Also, catecholamines such as adrenaline and noradrenaline are reported to be immunosuppressive. Corticosteroids which are produced as a result of stress are considered to be immunosuppressive for the lymphocytes and macrophages, affect the pattern of their circulation, and alter the production of many cytokines. The production of cytokines is divided into two broad categories depending on the functional profile of the secreting T-helper cells: type 1 helper cells (Th1) generally mediate the cellular immune response through the activities of cytotoxic lymphocytes, NK cells and macrophages and include production of the cytokines interferon gamma (IFN γ), tumour necrosis factor-alpha (TNF-α), and interleukin (IL)-2; type 2 helper cells (Th2) enhance immune reactions mediated by antibodies, and include production of ILs-4, 5, 6 and 10.

So far, I discussed the effect of neurological functioning on the immune system. Due to the bidirectional nature of these signals, the communication from the immune system to the brain is also possible, which acts as part of normal homeostatic process. For instance, peripheral inflammation leads to penetration of circulatory cytokines into the brain, in the areas where blood-brain barrier is absent. This can result in alteration in brain cytokines, hypothalamic hormones and behaviour (commonly known as sickness behaviour). The vagus nerve has been suggested to transmit this immune-to-nerve conversion of information (Gidron, Perry, & Glennie, 2005).

The main question from a PNI perspective is what is the precise mechanism underlying the possible relationship between social support and cancer progression?

4.2.1 Implications of Brain-Immune System Communications for Cancer

There is evidence suggesting that the mediators of SNS including acetylcholine, noradrenaline and adrenaline activate cellular pathways within tumours that lead to their growth and progression. In a recently published review, Antoni and his colleagues (2006) discussed the evidence regarding the effects of stress on tumour progression, placing emphasis on neuroendocrine influences on the tumour microenvironment and suggested that the preganglionic neurons originating from the SNS (which originates from the brainstem itself) terminate in the ganglia near the spinal column. It is from these ganglia that the postganglionic fibres run to the effector organs, and have an effect through their neurotransmitters noradrenaline and adrenaline. These catecholamines (and glucocorticoids) influence tumour-cell expression of genes that control cell proliferation, invasion, angiogenesis, metastasis, immune invasion and the secretion of proinflammatory cytokines. This has been supported by experimental evidence demonstrating that injections of adrenaline promoted metastasis in breast cancer (Antoni et al., 2006), and in *in vitro* studies, noradrenaline increased colon cancer cell migration. This effect was inhibited by beta (β)-blockers (Masur, Niggemann, Zanker, & Entschladen, 2001).

The immune-to-brain pathway, possibly important in cancer is the tumour-related inflammation and vagus nerve. The vagus nerve receives afferent information from several visceral regions including the oesophagus, heart, gastrointestinal tract, liver, pancreas and colon. This information regarding visceral inflammation and levels of circulatory cytokines is communicated to the brain via penetration of these cytokines into the brain. The resulting high levels of brain cytokines could be relevant to cancer progression (Gidron et al., 2005).

4.3 Social Support, Stress, Neuroimmune Pathways and Cancer

It has been suggested that certain sustained or repetitive negative psychological states which either result from the absence of social support and

possible subsequent loneliness (main effect model), or get worse as a result of a lack of social support in the face of stress (buffering effect model) can influence the progression and spread of cancer via neuroimmunological pathways (Andersen, Kiecolt-Glaser, & Glaser, 1994; Gerin, Milner, Chawla, & Pickering, 1995), particularly via the dysregulation of the ANS and the HPA axis. The evidence for this has been found in laboratory studies on the adverse effects of psychosocial stress on cardiovascular reactivity (Nausheen, Gidron, Gregg, Tissarchondou, & Peveler, 2007). Studies have shown that the neuropeptide oxytocin inhibits the stress-induced up-regulation of the HPA axis (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). Since oxytocin is released as a result of positive social interactions (Uvnas-Moberg & Petersson, 2005), these findings suggest the stress buffering effects of social support. Moreover, stress caused by external social and behavioural factors possibly interact with biological factors, and in turn alter the neuroendocrine and immune systems leading to vulnerability, onset, or progression of physical disease (Engel, 1971). For instance, moderate life stressors e.g., housing relocation have been associated with low natural killer cell cytotoxicity (NKCC) (Lutgendorf et al., 2001). Cytotoxicity is an important immune function of NK cells in which alien cells, including cancer cells, are killed. Low levels of social support have also been linked with the dysfunction of various immune parameters such as low number of NK T cells (Bouhuys, Flentge, Oldehinkel, & van den Berg, 2004).

The current existing models in psycho-oncology place an emphasis on immunosuppression or compromised immunity as mediating between psychological factors and cancer progression (e.g., Antoni et al., 2006), suggesting that psychosocial stress may adversely affect the tumour through the stimulation of the HPA axis and the suppression of cell immunity leading to metastasis. The SNS can activate a secondary pathway which involves the release of its neurotransmitters which regulate the levels of proinflammatory cytokines resulting in disease progression. There is evidence that a variety of stressors alone can induce proangiogenic cytokine secretion on peripheral and central levels e.g., hippocampal levels (Dhabhar & McEwen, 1996) (see Figure 5), which plays a precipitating role in the progression of cancer.

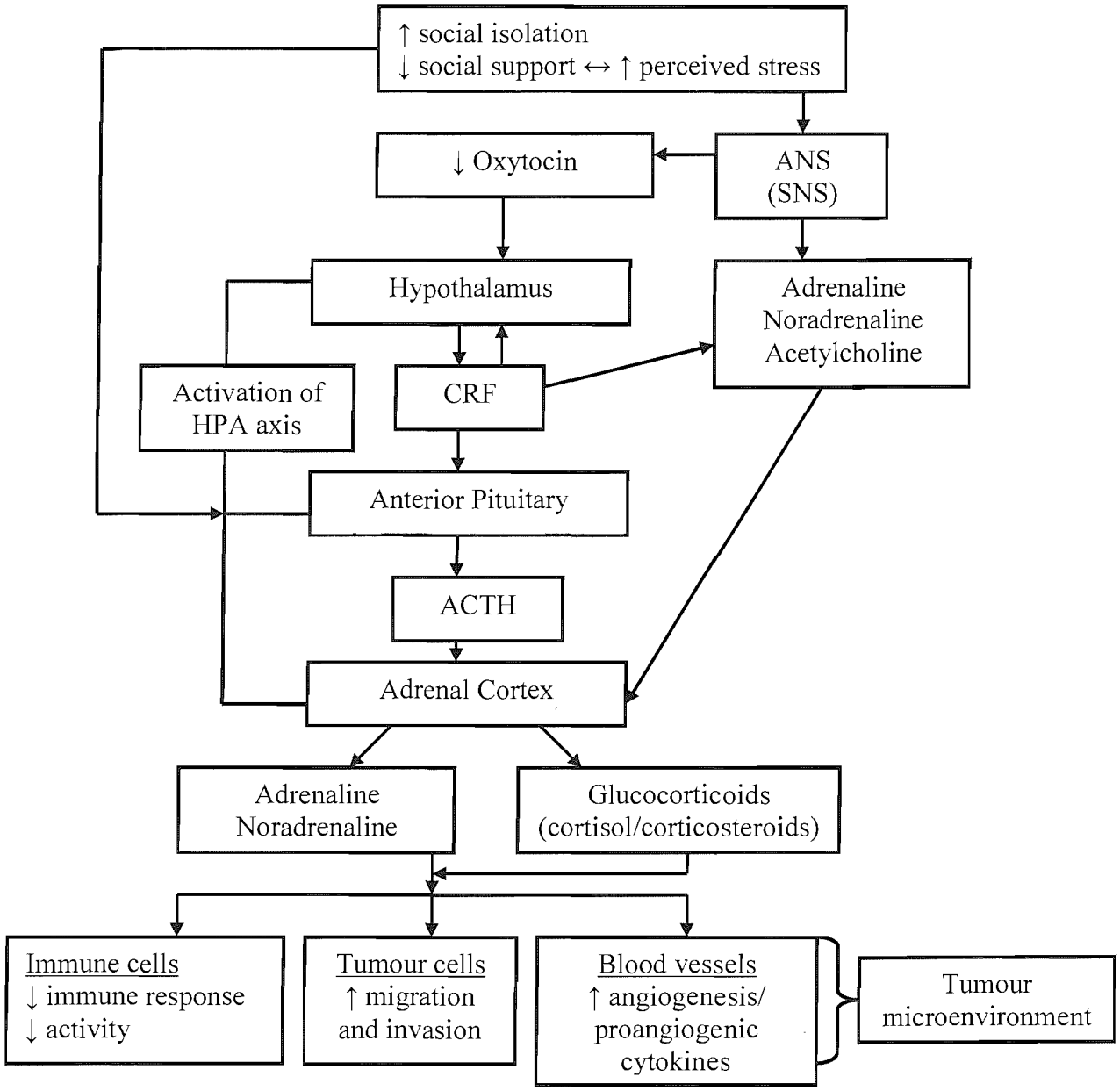

Figure 5. Effects of social isolation stress on tumour microenvironment. (Antoni et al., 2006; DeVries, Glasper, & Detillion, 2003).

Riley (1981) analysed the mechanism of stress-induced tumourigenesis in C3H/HE mice using rotation as a stressful stimulus. He found a significantly increased rate of tumour incidence in a stressed group carrying an oncogenic virus. He also found a linear relationship between the stressful stimulus and blood corticosterone levels. The latter plays a role in immunosuppression which can in turn lead to increased tumour growth if a tumour is present. However, two main limitations exist in such older models. First, cancer is a cluster of dozens of pathologies, which result from multiple aetiological processes, many of which are

unique to certain forms of cancer. Second, immunosuppression plays a partial role in cancer progression. In fact, over-activity of certain immunological signals, particularly proinflammatory cytokines, may be more important in cancer progression (e.g., Voronov et al., 2003). Furthermore, several studies have linked psychosocial states and traits with changes in such cytokines (e.g., Maes et al., 1998). Hence proinflammatory cytokines may be more important mediators in the relationship between psychosocial factors like social support and cancer in humans.

The following section discusses the evidence on the relationship between some important cytokines and a stress hormone oxytocin, and social support, hypothesising their role as possible mediators of the link between social support and progression of cancer. Cytokines and certain stress hormones are associated with the functions of the immune system, and have been linked with cancer severity, progression and prognosis. The following section will particularly address and cite the existing literature on two issues: First, the link between proinflammatory cytokines and oxytocin (an important stress hormone which will be discussed later in this chapter), and psychosocial factors. Second, the possible mediating role of cytokines and oxytocin in the link between psychosocial factors, and cancer progression.

4.3.1 Proinflammatory Cytokines and Psychosocial Factors

Miller, Cohen, and Ritchey (2002) proposed a glucocorticoid-resistance model to explain the capacity of a synthetic glucocorticoid to suppress the in vitro production of the proinflammatory cytokines including IL-1β, IL-6 and TNF-α. They postulated that chronic stress stimulates the secretion of hormonal products of the HPA and sympatho-adrenomedullary (SAM) axes in response to which the white blood cells commence a counter regulatory response, and downregulate the function of glucocorticoid receptors. When this continues, the capacity of the immune system to respond to the anti-inflammatory action of cortisol is affected, resulting in an increase in the inflammation and worsening of the existing diseases. This group studied the parents of cancer patients and parents of healthy children to examine the levels of the proinflammatory cytokine response to the chronic stress of having a child with cancer. They found that parents of children with cancer reported more

psychological distress and had significantly less glucocorticoid-regulated suppression of IL-6 production than parents of healthy children. Furthermore, the LPS[12]-stimulated blood cultures of the parents of ill children exhibited lower average levels of IL-6, and greater average levels of TNF-α, than parents of healthy children. These findings suggested glucocorticoid resistance of the immune system and excessive inflammation in chronically stressed parents.

Coussons-Read, Okun, Schmitt, & Giese (2005) found that the levels of psychosocial stress were positively associated with serum levels of IL-6, TNF-α, and inversely associated with the levels of the anti-inflammatory cytokine IL-10, suggesting the role of psychosocial stress in the dysregulation of the immune and endocrine systems.

Similarly, cytokines have also been associated with social engagement. In a study which investigated the biological pathway of the relationship between social relations and coronary heart disease (CHD), the serum concentrations of several inflammatory markers including IL-6 were measured. The study found that the structural index of social support was significantly inversely correlated with IL-6 in men. This finding was adjusted for confounders including age, smoking, blood pressure, cholesterol ratio, BMI, medication, diabetes, cardiovascular disease (CVD), depression and socioeconomic status (Loucks et al., 2006). In another study on the interplay of social engagement, sleep quality and plasma IL-6 in a sample of aging women it was found that having more trusting and satisfying relationships with others, and concern for the welfare for others predicted lower levels of plasma IL-6. There was also an interaction effect between social relationships and the quality of sleep in this study, with women with the highest levels of plasma IL-6 being those with both poor social connections and sleep quality (synergistic interaction). The reason for the similar pattern of effect of both the variables may point towards the involvement of HPA axis dysfunction in both of them (Friedman et al., 2005). Higher plasma levels of IL-6 have also been associated with psychosocial stress and lower levels of social support in several medical conditions (e.g., late pregnancy; Coussons-Read, Okun, & Nettles, 2007).

[12] LPS stands for lipopolysaccaride which acts as the prototypical endotoxin - a portion of a bacteria. In immunology, the induction of LPS is the exposing of the subject to a toxin to measure functional immunity.

A possible association between social support and another major inflammatory cytokine, TNF-α, was revealed in a study by Grossi, Perski, Evengard, Blomkvist, and Orth-Gomer (2003) on the immune, endocrine and metabolic correlates of burnout in working women. They found that lower levels of social support at work were associated with higher burnout (emotional exhaustion, depersonalisation and low personal accomplishment). Burnout was associated with higher plasma levels of TNF-α, after controlling for confounders like depression. Although the relationship between social support and TNF-α was not reported in this paper, the possibility of the latter being a mediator between social support and burnout can be argued on the grounds that it is released in response to psychosocial stress (Maes et al., 1998), and its higher levels may induce fatigue, exhaustion, depression and other sickness behaviours relevant to burnout (Yirmiya, 2000).

The adaptivity of proinflammtory cytokines depends on the context in which they are elevated. Greater chronic systemic production of proinflammatory cytokines can have a negative effect on health, and is associated with chronic negative emotions like depression and anxiety (Schiepers, Wichers, & Maes, 2005). However, their greater early local production at a wound site may have beneficial effects for healing as it leads to the up-regulation of the adhesion molecules and is therefore important for inflammatory cell recruitment and tissue repair (Marucha, Kiecolt-Glaser, & Favagehi, 1998). Kiecolt-Glaser et al. (2005) tested 42 healthy married couples to assess how spousal support and conflict resolution modulated wound healing, and the levels of local and systemic production of IL-6, TNF-α and IL-1β in high- and low-hostile behaviour couples. Results showed that the production of these cytokines at the blister site was lower, which had an adverse effect on wound healing, following a marital-conflict interaction compared to after social support interactions, and increased more steeply after the social support interaction than after the conflict interaction. Compared with low-hostile behaviour couples, high-hostile couples showed greater increases in circulating levels of plasma IL-6 and TNF-α following a conflict discussion than a social support interaction. Since the increase in local cytokine production over time was assumed to be a function of their synthesis at the wound site by local cells, there were no reliable relationships between the local and systemic levels of the cytokines. Thus, while high-hostile couples responded

with greater increases in systemic inflammatory cytokines to conflict, this was not seen in the local injury site, suggesting a non-adaptive response.

The above section included the evidence from correlational studies on the relationship between social support and different cytokines. In addition to these studies, there are studies on animals which are particularly note-worthy as they are experimental and thus hint at a causal link between social-isolation stress and the secretion of proinflammatory cytokines. Studying the response to endotoxin challenge in the face of social isolation in piglets, it was found that naturally increasing levels of peripheral and central TNF-α were diminished in response to repeated social isolation (Tuchscherer, Kanitz, Puppe, & Tuchscherer, 2006). However, the levels of the hormones ACTH and cortisol were not significantly affected by isolation treatment. These results suggest that the enhanced function of the immune system in the face of a toxic challenge can be compromised due to social isolation. A study by the same research group elaborated the results suggesting that the HPA axis activity after the induction of a toxic challenge was not affected by the repeated isolation but it was only the social isolation prior to the administration of the toxin which diminished the plasma TNF-α response. Furthermore, in the same study, increased levels of TNF-α in the spleen of the pigs were associated with the decreased glucocorticoid receptor (GR) binding in the hippocampus. These findings suggested that social-isolation stress may cause long-term effects on proinflammatory regulation in the periphery and in the brain following immune challenge, and TNF-α may also modulate central responsivity to cortisol, again in line with glucocorticoid resistance.

Shapira, Houri-Haddad, Frolov, Halabi, and Ben-Nathan (1999) studied the impact of social isolation on the outcome of infectious diseases in mice. They injected the socially-isolated and socially-housed (control) mice with heat-killed P gingivalis on the third day of treatment, and subcutaneous chamber fluid was analysed for leukocyte number, TNF-α and IFN-γ. The levels of TNF-α in socially isolated animals, which should have been increased ideally in response to the infectious agent, were significantly lower as compared to the controls, particularly on the fifth day. These findings replicate the previous finding (Tuchscherer et al., 2006), suggesting that the levels of TNF-α in response to the induced infectious agent were

downregulated in socially-isolated animals. Thus, social isolation reduced the ability of the immune system to respond adequately to immune challenges.

4.3.2 Cytokines, Psychosocial Factors and Cancer

Tumour enlargement, progression and metastasis take place with the aid of the process of angiogenesis. Multiple cytokines may determine the course of cancer by the production of angiogenic action. The cells in the tumour microenvironment or tumour cells produce these cytokines. Tumour cells secrete a vascular permeability factor called the VEGF which is one of the most powerful proangiogenic cytokines. It is produced by a variety of other cells including endothelial cells, neutrophils, platelets, tumour-associated inflammatory cells and mononuclear cells, and is regulated by a number of other cytokines including IL-6, hormones and growth factors and noradrenaline (Lutgendorf et al., 2002). Lutgendorf and her colleagues (2002) found that levels of social well-being (assessed as part of QoL) in preoperative ovarian cancer patients were inversely correlated with the plasma levels of VEGF. Patients who reported a greater distance from their friends had significantly higher levels of VEGF whereas, patients with greater support from friends, neighbours and family had lower levels of VEGF, after controlling for cancer stage. Marital status and the living condition i.e., living with a spouse or children versus living alone, were not associated with the levels of VEGF. It may be suggested that noradrenaline is involved in this association between social support and VEGF. It is supported by the fact that VEGF can be induced by noradrenaline, and lower levels of neuroendocrine hormones i.e., adrenaline, noradrenaline and cortisol have been associated with social support (Lutgendorf et al., 2002). Based on the hypothesis that the stress-related mediators such as noradrenaline, adrenaline, isoproterenol and cortisol regulate the production of this cytokine by tumour cells, the secretion of VEGF by two ovarian cancer cell lines was examined in an in vitro study. Lutgendorf et al. (2003) induced the effective dosages of stress-related hormones which were equivalent to the levels which would be produced in the body in the face of stress-related catecholamine secretion. As a result, VEGF induction in both SKOV3 and EG cell lines was most significantly enhanced at 3 hours. Also, the effects of noradrenaline were more pronounced than the effects of adrenaline, although adrenaline had significant effects on EG cells. Since social support has been

associated with lower levels of these stress hormones and stress reduction has been associated with their decreased levels, these findings suggest that these hormones may be a possible pathway between social-isolation stress and higher levels of VEGF in serum and at tumour site.

Another cytokine, IL-6, is related to disease progression in cancer, and has been found in patients unresponsive to chemotherapy (Scambia et al., 1994). Costanzo et al. (2005) found that high social attachment was significantly associated with lower levels of IL-6 in peripheral blood in 36 advanced ovarian cancer patients, after controlling for age and disease stage. Social attachment comprised of six provisions including guidance, reliable alliance, reassurance of worth, social integration, attachment and opportunity to provide nurturance. Lower serum IL-6 was associated with seeking instrumental support at diagnosis along with better clinical status and less disability at one year in women with gynecological cancer (Lutgendorf, Anderson, Sorosky, Buller, & Lubaroff, 2000).

Another study examined if psychosocial factors including mood, depression, physical well-being and dimensions of QoL were associated with serum levels of VEGF in colorectal cancer patients pre and postoperatively. Findings revealed that pre and postoperative VEGF were negatively correlated with physical well-being, QoL and positive affect, and positively correlated with depression. Multivariate analyses showed that preoperative anxiety, depression and functional well-being were independent predictors of postoperative VEGF levels (Sharma, Greenman, Sharp, Walker, & Monson, 2007). As most of these studies were conducted in humans, they did not enable full control over various variables and their cross-sectional designs did not allow causality.

Experiments conducted in animals provide such control and possibly allow causal inferences. In a very important and unique series of studies in rodents, Wu and colleagues (1999-2001) directly examined the PNI of social isolation and cancer progression. They found that socially isolating mice led to enhancement of tumour invasion, to liver metastasis and to shorter survival time in mice given colon 26-L5 carcinoma cells compared to non-isolated controls receiving the same tumour (e.g., Wu et al., 2000; 2001). Furthermore, they found that production of plasma TNF-α

and expression of hepatic TNF-α messenger ribonucleic acid (mRNA) were elevated in the isolated mice with or without tumour burden. Increased TNF-α level was particularly discernible in the liver of tumour-bearing mice. Elevated positive staining for TNF-α was immunohistochemically observed within and around tumour mass in the liver from isolated tumour-bearing mice, compared with group-housed mice with tumours (Wu et al., 1999). They also found that liver cells treated with TNF-α exhibited a marked promotion of the tumour invasion factors (e.g., matrix metalloproteinase (MMP)-2 and -9) in socially isolated mice. These findings suggest that TNF-α may mediate the adverse effects of social isolation on cancer progression in animals.

In human studies however, a different pattern was found where the increased levels of TNF-α were associated with tumour regression and increased survival (Nakamoto, Inaqawa, Takaqi, & Soma, 2000). It was found that TNF-α induced cell apoptosis within the angiogenic vasculature. Marucha, Crespin, Shelby, and Andersen (2005) prospectively measured the changes in social activities and relationships at the time of diagnosis, during surgical treatment and after 12 months, and hypothesised that disruptions in social relationships across the follow-up period would be associated with lower levels of plasma TNF-α. The results indicated that breast cancer patients who reported increased structural support i.e., higher levels of leisure, home and social activities, exhibited stronger TNF-α responses than those who decreased involvement. It is important to note that these effects were more pronounced when functional support i.e., partner satisfaction was taken into account. Taking the above evidence, it is interesting that apart from the fact that the level of TNF-α could be a function of social factors, it has a dual physiological role in tumours, which is referred to as a double-edged sword (Aggarwal, 2003). It acts towards both tissue destructive reactions and recovery. On one hand it kills tumour cells, while on the other hand it facilitates tumour cell proliferation, angiogenesis, invasion and metastasis. Moreover, it was found that its local high dose (administered regionally) targets tumour blood vessels but when produced chronically it may act towards tumour promotion (Balkwill & Mantovani, 2001). This finding suggests that the direction of the complex relationship between social support and TNF-α in humans with cancer may be unclear, and that measuring blood TNF-α level alone may not be informative.

4.3.3 Oxytocin and Social Support

Oxytocin is a neuropeptide hormone which is produced in the hypothalamus, and is active both centrally and peripherally. It is released in response to positive social bonding and interactions (Uvnas-Moberg & Petersson, 2005) and downregulates the HPA axis. The HPA axis activation is a response to stress, that includes three primary stress hormones: CRF, ACTH and cortisol (or corticosterone). CRF is released from the hypothalamus as a response to stress, which in turn stimulates the secretion of ACTH from the anterior pituitary gland. ACTH then triggers the release of glucocorticoids (cortisol) from the adrenal cortex. Oxytocin has been associated with suppressed HPA axis activity, and specifically with lower levels of plasma ACTH and cortisol (DeVries et al., 2003). Given the relation of oxytocin with social bonding (Carter, 1998), social recognition (Ferguson, Young, & Insel, 2002) and interpersonal trust (Zak, Kurzban, & Matzner, 2004), this hormone could be a mediator linking social relationships with the suppression of the HPA axis. Grewen, Girdler, Amico, and Light (2005) tested the hypothesis that positive partner interactions would have an enhancing effect on oxytocinergic activity. They found that greater partner support in a warm contact episode in the laboratory was associated with higher plasma oxytocin in both men and women. Furthermore, greater partner support predicted higher oxytocin and lower noradrenaline, and oxytocin was found to be a partial mediator of the effect of partner support on noradrenaline in women. Vasopressin is another important component of the neural and endocrine systems along with oxytocin. Fries, Ziegler, Kurian, Jacoris, and Pollak (2005) studied the neuroendocrine consequences of the absence of social bonding in orphanage-reared children and found low levels of oxytocin and vasopressin in their urine.

In a study of the effect of social support and oxytocin on cortisol, mood and anxiety responses to psychosocial stress in humans, participants were randomly assigned to receive intranasal oxytocin or placebo, and either social support from a friend during the stressor or no social support. The results showed that oxytocin had an anxiolytic effect, and the combination of oxytocin and social support exhibited the lowest cortisol levels (synergistic interaction) during the stressor (Heinrichs et al., 2003). Taylor and colleagues (2006) tested two different hypotheses regarding the

relationship between oxytocin and social functioning. First, the level of oxytocin increases in response to stress, and facilitates relaxation and affiliative behaviours, therefore its elevated levels suggest or may even induce increased social bonding and higher social support. Second, oxytocin may be a potential impetus to social interaction since it has been associated with relationship stress and higher level of oxytocin indicates problems in social relationships (Turner, Altemus, Enos, Cooper, & McGuinness, 1999). They found that oxytocin was associated with elevated HPA axis activity, and its level was elevated in women with problems in social relationships assessed by decreased contact with friends and family and dissatisfaction with the partner relationship. Given the cross-sectional nature of the study design, it is impossible to discern the direction of the effects between oxytocin and social relations in this study. Experimental studies could partly resolve these contradictions.

Similar to the cytokines, animal experiments attempt to enable a causal inference to explain the direction of above-mentioned relations between oxytocin and social relations. In a study on the effect of chronic intranasal oxytocin administration on the functioning of the HPA axis in adult female squirrel monkeys, blood samples showed that oxytocin-treated monkeys had lower ACTH concentrations compared to saline-treated monkeys after 90 minutes of social-isolation stress. This study shows the anti-stress effect of oxytocin following social isolation (Winslow & Insel, 1991). In a similar study, the influence of centrally and peripherally administered oxytocin on the behaviour of rat pups during social isolation was studied. Central administration of an oxytocin antagonist blocked the decrease in ultrasonic vocalisations following central but not peripheral administration of oxytocin. This suggests that oxytocin regulates the stress response to social isolation via its central receptors (Insel & Winslow, 1991).

Oxytocin can also block the stress-induced increases in cortisol and facilitate wound healing. Detillion, Craft, Glasper, Prendergast, and DeVries (2004) found evidence for this in hamsters, where treatment of isolated hamsters with oxytocin blocked stress-induced increases in cortisol and led to faster wound healing. Moreover, they found that treating pair-housed hamsters with an oxytocin antagonist delayed wound healing. These findings suggest that social interactions buffer against

stress and have a positive physiological or health-related effect by an oxytocin-induced suppression of the HPA axis.

4.3.4 Oxytocin and Cancer

It has been established that oxytocin plays an important role in inhibiting the HPA axis (DeVries et al., 2003) and it may mediate the health enhancing effects of social interactions (Uvnas-Moberg, 1998). In tumours, several studies suggest that oxytocin has an important anti-proliferative role (Cassoni, Sapino, Negro, & Bussolati, 1994; Cassoni, Sapino, Papotti, & Bussolati, 1996; Cassoni et al., 1997; Cassoni, et al., 2000), though other studies did not find this result (Cassoni, Sapino, Stella, Fortunati, & Bussolati, 1998). In cancer, oxytocin inhibits the growth of epithelial cells (e.g., breast and endometrial) and neuronal or bone tumours (Pequeux et al., 2004), and it may be speculated that oxytocin may mediate the relationship between social support and slower cancer progression by having an anti-proliferative effect.

4.4 Chapter Summary

A number of findings support the view that proinflammatory cytokines and hormones (oxytocin) are associated with psychosocial factors, particularly social relationships. Moreover, it is established that these cytokines and hormones also play an important role in tumour growth, invasion and metastasis, and oxytocin may have anti-proliferative effects in some cancers. However, there are exceptions in the case of TNF-α due to its complex dual role in cancer. The tumour microenvironment is complicated, and tight interconnections between the immune, nervous and endocrine systems may make it possible for the cellular immune system to downregulate or for inflammatory markers to be upregulated in response to stress inflicted by the lack of social support. The clinical evidence for the beneficial actions of the anti-cytokine therapies is growing considerably (Bataille et al., 1995). Several clinical trials in the treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease and cancer itself have shown that cytokine antagonist therapies are helpful towards the prevention of the processes which are also associated with cancer progression e.g., inhibition of cytokine production and angiogenesis (Maini & Taylor, 2000).

Although the research on the role of these cytokines and hormones, and psychosocial factors in cancer patients has been mainly correlational, it holds long-term implications with reference to cancer prevention and treatment. The findings reviewed in this chapter will provide the impetus and scientific basis for planning Study 3 of the present thesis. This study will be based on the tenets of proposed model of social support and cancer, as depicted in Figure 6.

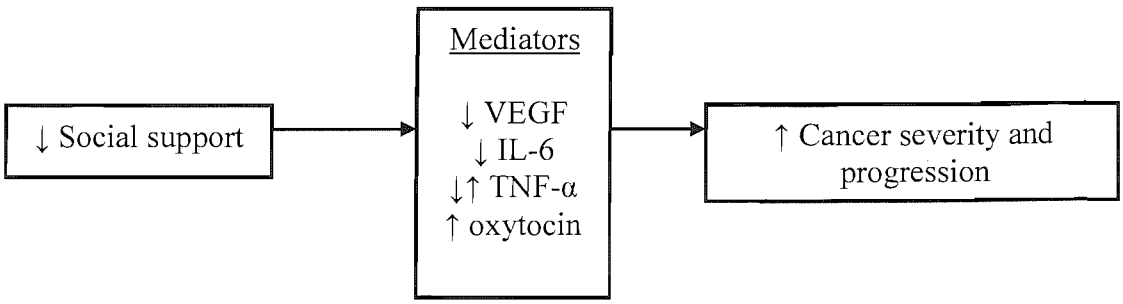

Figure 6. Proposed model of social support and cancer.

Chapter Five: Study One - Adaptation and Validation of an Implicit Measure of Loneliness

5.1 Aims of the Study

This study aims to adapt an Implicit Association Test (IAT) to measure loneliness, and establish the concurrent, construct and criterion-related validity of this tool by assessing its correlation with the explicit or self-reported measures of loneliness, social support and QoL, respectively.

5.2 Introduction

The IAT (Greenwald et al., 1998) has been used to measure implicit attitudes (Hummert, Garstka, O'Brien, Greenwald, & Mellott, 2002), stereotypes (Grover et al., 2003), personality (Asendorpf et al., 2002) and self-esteem (Greenwald & Farnham, 2000). The IAT is a computerised reaction-time test which assesses the relative strength of associations by comparing the performance on two pairs of concepts. Although respondents do not lack awareness that the IAT is being administered, it assesses psychosocial constructs indirectly without any verbal self-report. The two important criteria for determining the validity of the IAT are its capacity to correlate with conventional self-report measures, and to predict outcome variables (Greenwald, Nosek, & Banaji, 2003; Poehlman et al., 2005). This study addresses these criteria. However, there is evidence suggesting that the correlations between the implicit and explicit measures depend to a great degree on the level of the social sensitivity of the construct which may also be a function of age and cultural norms. When assessment involves issues that are sensitive or prone to presentational bias, low correlations between implicit and self-report measures of similar constructs may be expected. This is due to demand characteristics, evaluation apprehension, and self-deception (Greenwald & Farnham, 2000). Greenwald et al. (2003) found implicit-explicit correlations to be as low as .11 and .29 when measuring socially sensitive issues such as attitudes towards the aged and racism but found higher correlations such as .69 for comparatively less threatening attitudes such as choice of the election candidate.

5.2.1 Social Support, Loneliness and QoL

Previous research has shown that loneliness and lack of social support are significantly correlated with low QoL (Ekwall, Sivberg, & Hallberg, 2005; Tovbin, Gidron, Jean, Granovsky, & Schnieder, 2003) which is a major outcome variable in health and well-being (Frost & Sloan, 2002; Schwartz & Sprangers, 2002). Some research also highlighted the significance of functional support over structural support. For example, one of such studies examined the relationships between health-related QoL, perceived social support, social network size and loneliness among college students (Arkar, Sari, & Fidaner, 2004). They found that QoL was positively correlated with perceived social support and inversely correlated with loneliness. The size of the social network was not significantly correlated with QoL. However, perceived social support from a significant other and family significantly predicted QoL. This suggested that QoL may be more strongly determined by the quality and not the quantity of social relationships. Another study found that emotional support and functional aspects of social support were important in examining health-related outcomes (Ashing-Giwa, 1999). Helgeson (2003) proposed that structural support shows a linear relationship with QoL whereas, the functional aspects of support may demonstrate the stress buffering effects.

These findings regarding the significance of functional support may be less relevant to some populations. For example, in caregiving men and women aged 75 years or older, a small or non-existent social network was significantly associated with low QoL (Ekwall et al., 2005).

The evidence on the relationship between social support, loneliness, and QoL is in line with theories in health psychology. Moreover, the magnitude of these correlations has been strong. Therefore, social support has also been studied as an essential component of QoL in predicting health-related outcomes (Herndon II et al., 1999; Yoshida, Sato, Akagawa, & Hiasa, 2001). It is due to this strong evidence suggesting that QoL is a strong correlate of social support that it is included in the present study as a criterion, in order to establish the criterion-related validity of the IAT-Loneliness.

5.2.1 Definitions of the Constructs

As discussed in Chapter 2, social support can be categorised into two broad types: structural support and functional support. The former constitutes the quantity of support and includes properties such as the size, range and density of the social network. The latter refers to the quality of social support, and includes instrumental (tangible), emotional and informational support (Berkman et al., 2000). A related concept, loneliness has been described as a product of social isolation and can be defined as a subjective experience resulting from an unpleasant or inadmissible lack of (the quality of) certain social relationships (de Jong-Gierveld, 1987). Although a lack of social support does not necessarily implicate loneliness, there is evidence that loneliness is inversely correlated with quantity (Cutrona & Peplau, 1979) and quality of social relationships (Borys et al., 1985), and being married (structural support) (Carr & Schellenbach, 1993). Loneliness is also positively correlated with problems and conflicts in social relationships (de Jong-Gierveld et al., 1987; Jirka et al., 1996).

QoL is defined as the subjective perception of happiness or the current level of satisfaction with the life aspects which are important to oneself (Oleson, 1990). Since there are numerous types of tools for assessing this construct, the choice of the test must be done carefully, mainly in relation to the research question and study population. Furthermore, the existing QoL scales include pre-determined aspects or domains of life. Owing to the subjective nature and multidimensionality of this construct, the central problem in the assessment of QoL is the difficulty of incorporating the perspective of the individual (O'Boyle, 2001). There is a possibility that the domains which are of significance for the participants may not be included in the scale. There is an equal possibility that the pre-determined domains may be of little relevance to the participants, leading to the issue of low validity of these scales. The Schedule for Evaluation of Individual Quality of Life (SEIQoL; McGee, O'Boyle, Hickey, O'Malley, & Joyce, 1991) was chosen for this study as it addresses this issue by asking the participants to nominate five life domains or aspects that are crucial to their QoL.

Similarly, the measures of social support and loneliness were also chosen with caution. There are several measures of social support available. However, due to

the issues regarding the definition and conceptualisation of this construct as discussed in Chapter 2, it was essential for the measure to elicit information on social support in all important areas. Firstly, the measure should incorporate both of the important categories of social support i.e., structural and functional support. Secondly, it is important for the scale to cover perceived support and the support actually received over a specific time period in the recent past. For example, the Norbeck Social Support Questionnaire (NSSQ; Norbeck, Lindsey, & Carrieri, 1981) and the Social Support Questionnaire (SSQ; Sarason et al., 1983), although cover both structural and functional indices of perceived social support, do not include the level of support *actually* received. The Inventory of Socially Supportive Behaviours (ISSB; Barrera et al., 1981) only addresses the frequency of received supportive behaviours in the past month, and therefore does not seek sufficient information or the overall levels of perceived available support.

Taking the above-mentioned issues and limitations into consideration, a scale was needed which would not only include structural and functional indices of social support but also precisely enquire about the general support which may be available in case of the need. It was also important to include the support which has *actually* been utilised in the recent past.

5.2.2 Hypotheses

The following hypotheses were tested in the present study:

(1) Implicit loneliness will show a small positive correlation with explicit loneliness and a small inverse correlation with social support, determining the concurrent and construct validity of the implicit measure, respectively;

(2) Implicit loneliness will show a small inverse correlation with QoL, determining the criterion-related validity of the implicit measure; and

(3) Based on the previous literature, explicit loneliness will show a large inverse correlation with the self-reported index of QoL and social support will show a large positive correlation with QoL.

5.3 Method

5.3.1 Study Design

The present study uses a cross-sectional design with the administration of all the measures in a single session to healthy volunteers.

5.3.2 Participants

Participants were invited to take part in the study through the online recruitment system (Psycho Book). This system is accessible to the undergraduate and postgraduate students in the University of Southampton. However, since students in the School of Psychology were offered credits for taking part in this study, all the participants were psychology students. Fifty undergraduate and postgraduate students (15 males, 35 females) participated in this study.

5.3.3 Measures

5.3.3.1 Demographic Information.

This included gender and age (in years) (see Appendix A for demographic information sheet).

5.3.3.2 The Implicit Association Test-Loneliness (IAT-L).

A reaction-time IAT (Greenwald et al., 1998) was adapted to assess implicit loneliness. It is administered on a laptop computer. Similar to the standard IAT, it involves assigning words to a series of categories in five blocks. In general, this test measures the strength of association between target concepts and attributes. In each block, stimulus words, which are exemplars of either the target concepts or the attributes, appear randomly in the middle of the screen, and participants are asked to assign them to one of the categories of attributes or target concepts. In the first block, participants need to assign exemplars (e.g., *lonely*, *isolated*, *table*) to one of the two attribute categories (LONELINESS, FURNITURE), using one of the two assigned

keys (*e*, *i*) on the keyboard. In the second block, exemplar words (e.g., *me*, *mine*, *they*) are assigned to one of the two target concept categories (SELF, OTHERS), by pressing the relevant key *e* or *i*. In the third block, the two above-mentioned categories are combined, stimuli for both appear randomly, and a concept and attribute share the same response key (e.g., LONELINESS or SELF assigned to the *e* key). The fourth block is the reversal of response assignments in block 2 (i.e., key *e* for OTHERS instead of key *i*). In the fifth block, target concepts and attributes are combined again as in block 3, after reversing the keys (e.g., LONELINESS or OTHERS assigned to the *e* key). Each block comprises of 20 trials except critical blocks 3 and 5 having 40 trials each (a schematic description of the IAT is shown in Table 6) (see Appendix B for computer-based IAT-L).

Table 6. Schematic description of the IAT-L.

Blocks	1	2	3	4	5
Task description	Target Concepts	Attributes	Initial combined task	Reversed attributes	Reversed combined task
Task instructions	[e]Loneliness Furniture[i]	[e]Self Others[i]	[e]Loneliness [e]Self Furniture[i] Others[i]	[e]Others Self[i]	[e]Loneliness [e]Others Furniture[i] Self[i]

Each stimulus word remains on the screen until the participant responds and is replaced by a new word as soon as the response is made. If the response is correct, the next stimulus word appears on the screen. However, if the response is incorrect, an *X* appears for 200 ms followed by a new word (see Appendix C for list of stimulus words).

Scoring of the IAT-L was done according to the improved scoring algorithm (Greenwald et al., 2003). Initial data reduction was done as follows: (1) data from the critical blocks 3 and 5 were used; (2) trials with latencies > 10,000 ms were eliminated; (3) data of participants, for whom more than 10% of trials had latency less than 300 ms, were eliminated; (4) for standard treatment of the error latencies (incorrect responses), they were replaced by the respective block mean including

correct latencies + 600 ms. IAT-L score D^{13} was obtained by subtracting mean scores on block 3 from those on block 5 for each participant and dividing the resulting value by relevant pooled-trials' standard deviation.

Since this was the first loneliness-related IAT and no research had been done on assessing implicit loneliness, the study was designed with an exploratory approach to experiment with the categories on the IAT. There has been a debate in the literature on the selection and significance of these categories. Many of the previous studies used the bipolar or opposite reference categories such as *Shy* versus *Nonshy* or *Black* versus *White* (e.g., Asendorpf et al., 2002). However, a few studies, although followed this tradition in using one major coherent category consisting of exemplar words/images along one theme of interest, used the reference category which was not a unified one. For instance, in one of those studies, *condom* versus *noncondom* categories were used and the latter consisted of several varied objects e.g., different images of batteries and markers, etc. (Marsh et al., 2001).

In the present study, a neutral reference category (FURNITURE) was chosen to be used with LONELINESS category since loneliness as a category had no clear opposite. A nonword (nonsense) category was not used as there is evidence suggesting that a single coherent category against a category that does not have a coherent conceptual meaning (nonword) serves as *figure* in a figure/ground asymmetry (Rothermund & Wentura, 2001), and may tend to get more attention, likely to lead to longer reaction time and hence an erroneous IAT effect. Brendl, Markman, and Messner (2001) associated nonwords (nonsense syllables) with either *White names* (positive) or *insects* (negative) with *pleasant* and *unpleasant* categories in a series of IAT experiments. They found that in the case of the former, participants responded faster when the nonsense category was paired with the unpleasant category (versus *White names* and *pleasant* paired together). In the case of the latter, although it was hypothesised that the responses would be faster when the nonsense category was paired with the pleasant category, it did not happen. On the contrary, responses were faster when the nonsense category was paired with *unpleasant*, proving to be the *figure* on the figure/ground asymmetry. Thus, using a nonword

[13] Standard deviation in the denominator of *D* was computed from the scores on both critical blocks.

reference category may actually capture attention, fail to be a neutral category anymore and serve as a *figure*.

The neutral category has been used in a few studies. For instance, in a study on social anxiety and dysfunctional beliefs, an IAT was adapted to differentiate between high and low socially anxious individuals. This IAT used two sets of two-word categories. One set comprised of *neutral cues* (e.g., landing, sun lounge, sitting room) and *social cues* (e.g., date, presentation, blush, chat). The other set consisted of positive and negative outcome categories (stimulus words such as *joy*, *shame*) (de Jong, Pasman, Kindt, & van den Hout, 2001). In another study, Palfai and Ostafin (2003) used ELECTRICITY as a category with the ALCOHOL category in order to examine alcohol-related approach dispositions in hazardous drinkers. They reasoned using a neutral category (ELECTRICITY) on the following two grounds. One, the alcohol category did not have a clear opposite which made the choice of the contrast category difficult, as in the present study. Two, the goal of the task was not to assess whether individuals preferred alcohol over electricity but whether the strength of alcohol-approach tendency associations was related to individual differences on alcohol-related behaviour.

The internal consistency of the IAT-L in the present study was .57 which was computed by a correlation between the IAT measure based on trials 1-20 and the IAT measure based on trials 21-40 in blocks 3 and 5 (Greenwald et al., 2003).

5.3.3.3 The UCLA Loneliness Scale.

The University of California, Los Angeles (UCLA) Loneliness Scale (version 3; Russell, 1996) uses 20 items to gauge the subjective feelings of loneliness on a 1 (never) to 4 (always) frequency scale (see Appendix D). The following items are negatively scored: 1, 5, 6, 9, 10, 15, 16, 19 and 20. Higher scores indicated greater degrees of loneliness. Cronbach's alpha reliability of the scale in this sample was .91.

5.3.3.4 The Arizona Social Support Interview Schedule (ASSIS).

The ASSIS (Barrera, 1980) includes 24 questions for assessing social support

as: available network size (perceived network size), utilised network size (or actual network size), support satisfaction and support need. The first two indices representing structural support and the other two indicating the levels of functional support. These are determined by asking respondents to nominate providers in the areas of intimate interaction, material aid, advice, positive feedback, physical assistance and social participation. Overall support satisfaction is determined on a 1 (very dissatisfied) to 7 (very satisfied) scale and support need on a 1 (no need at all) to 5 (very great need) scale (see Appendix E for interview topic guide and scoring sheet). Assessment of the psychometric properties showed the ASSIS to be a promising social support measure (Barrera & Balls, 1983; Barrera & Garrison-Jones, 1992; Lorenzo, Bilge, Reinherz, & Frost, 1995).

5.3.3.5 The Schedule for Evaluation of Individual Quality of Life (SEIQoL).

The original SEIQoL (McGee et al., 1991) is a semi-structured interview on which participants identify the life aspects which are important to their QoL. In this study a computerised version of SEIQoL was developed which followed the steps of the original interview. The standard SEIQoL determines: (1) five life aspects that are crucial to one's QoL, (2) current satisfaction with those aspects, and (3) relative importance of each aspect. In the present study, these three steps were run on a computer, which then calculated the QoL score by multiplying each aspect's weight (importance) by the corresponding satisfaction score (determined on a 1-100 scale) and summing the products across the five aspects (see Appendix F for computer-based SEIQoL).

The SEIQoL has shown good reliability and validity in studies on healthy adults (Browne et al., 1994) and physically ill populations (McGee et al., 1991; O'Boyle, McGee, Hickey, O'Malley, & Joyce, 1992).

5.3.4 Procedure

Participants were asked to give their informed consent before the participation (see Appendix G for consent form). All the measures were conducted in

a lab and took maximum 25 minutes. This study was approved by the School of Psychology, University of Southampton ethics committee.

5.3.5 Statistical Analyses

Before the data analyses, demographic variables were tested for a possible association with the outcome of the study. This was done so that any significant demographic variable(s) were controlled for in the subsequent analyses. Pearson's correlation was conducted to test the correlation between age and QoL. Independent samples t-test was done to test whether male participants differed from female participants on QoL.

The following statistical analyses were conducted to test the hypotheses of the present study:

Pearson's correlations were used to measure the relationships between:
(1) Implicit, and explicit loneliness and social support;
(2) Implicit loneliness and QoL; and
(3) Explicit loneliness and social support, and QoL.

Finally a multiple regression analysis was done to predict the variance in QoL accounted for by all the social support and loneliness measures.

5.4 Results

5.4.1 Initial Data Screening and Preliminary Analyses

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) (Version 13). All tests were two-tailed. Prior to the analyses, variables were initially screened for normality.

The mean age of the participants was 24.1 years (SD = 4.8 years) (N = 50). Male participants had a mean age of 24.60 years (SD = 4.29 years) (n = 15) and female participants' mean age was 23.94 years (SD = 4.98 years) (n = 35).

The association of age and gender with QoL was analysed by conducting Pearson's correlation and an independent samples t-test, respectively. Results were nonsignificant for both age, r = -.05, p = .76 and gender, $t(48)$ = .67, p = .50. Therefore, these variables were not controlled for in the subsequent analyses.

5.4.2 Concurrent and Construct Validity of the IAT-L

To test the hypothesis that implicit loneliness will show a small positive correlation with explicit loneliness and a small inverse correlation with social support, Pearson's correlations were conducted. Table 7 shows the correlations of implicit loneliness with explicit loneliness and social support. Implicit loneliness significantly and positively correlated with explicit loneliness, r = .28, $p < .05$. Support satisfaction, an index of social support, inversely correlated with implicit loneliness but the correlation did not reach the conventional level of significance (p = .10). All other correlations, although not statistically significant, were in the expected directions.

Table 7. Pearson correlation coefficients between implicit loneliness, and explicit loneliness and social support.

	Implicit loneliness
	(N = 50)
Available network size	-.13
Utilised network size	-.18
Support satisfaction	-.22†
Support need	.18
Explicit loneliness	.28*

$^{*}p < .05$, $^{\dagger}p = .10$.

5.4.3 *Criterion-Related Validity of the IAT-L*

In order to establish the criterion-related validity of the IAT-L, it was hypothesised that implicit loneliness would show a small inverse correlation with QoL. Table 8 depicts the nonsignificant correlation between implicit loneliness and QoL, $r = -.20$, $p = .16$.

5.4.4 *Correlations between Loneliness, Social Support, and QoL*

A significant inverse correlation was found between explicit loneliness and QoL, $r = -.36$, $p < .01$. Support satisfaction was positively correlated with QoL. Support need was inversely correlated with QoL, showing that the higher the need for social support, the lower is the QoL. One of the structural support indices, utilised network size was positively correlated with QoL, while the correlation with available network size was nonsignificant.

Table 8. Pearson correlation coefficients between loneliness, social support, and QoL.

	QoL
	($N = 50$)
Available network size	.16
Utilised network size	.28*
Support satisfaction	.48**
Support need	-.26*
Explicit loneliness	-.36**
Implicit loneliness	-.20

*$p < .05$, **$p < .01$.

5.4.5 Multiple Regression Analysis

A standard multiple regression analysis was done to examine the percentage of the variance in QoL, accounted for by the social support and loneliness indices, which were significantly correlated with QoL in the bivariate analyses. Since age and gender were not significantly correlated with the QoL, they were not entered in the equation but IAT-L was included as it showed a nonsignificant trend. In the multiple regression analysis, the social support and loneliness indices accounted for 39 per cent of the variance in QoL, $F(5, 44) = 5.55$, $p = .001$, adjusted $R^2 = .32$. Support satisfaction made the strongest contribution to explaining QoL, $\beta = .36$, $p < .01$, followed by support need, $\beta = -.30$, $p < .05$ and explicit loneliness, $\beta = -.25$, $p < .05$.

5.5 Discussion

The results of the present study have shown a modest but significant correlation between implicit and explicit loneliness. The implicit loneliness did not significantly correlate with any of the social support indices with an exception of the index of support satisfaction which showed a nonsignificant trend.

According to the explicit-implicit ambivalence hypothesis, the correlation between implicit and explicit measures enhances their capability to predict the criterion measure. This effect however is more pronounced for the explicit measures (Poehlman et al., 2005). This hypothesis is proposed on the grounds that although self-reported or explicit measures may be biased and hence do not ideally predict the outcomes, a higher magnitude of correlation between the implicit and the explicit measures indicates the possibility that the explicit measure is comparatively free from the influence of presentational biases. This could be due to lower social (or personal) sensitivity of the construct being assessed, which makes it less socially or emotionally charged to respond to on the explicit measures and hence mimimises the likelihood of faking. This enhances the efficacy of the explicit measures to tap into the construct enabling them to predict the outcome more efficiently than in the case where they did not correlate with the implicit measure. The results of this study support this hypothesis as the two explicit measures which correlated or tended to

correlate with the implicit measure i.e., explicit loneliness and support satisfaction, were the ones showing the highest correlations with the criterion measure i.e., QoL. These measures have also accounted for the highest proportion of variance in QoL. However on the other hand, there is a small possibility that the explicit measure of loneliness was a better correlate of QoL than implicit loneliness because both were self-reported measures, and part of the correlations between such measures may have stemmed from shared-method variance (e.g., Salzer, 1998). Shared-method variance is defined as an association between variables at least partially due to similar methods of measurement.

Another point proposed by Greenwald and his colleagues (2003) suggests that higher implicit-explicit correlations may be indicative of greater construct validity of an IAT measure if association strengths are a component of both the implicit and explicit measures. They described the implicit factor as a shared latent component. The explicit factor can be understood as being influenced by the implicit factor alongside the other factors which may be correlates of the explicit factor, and hence may become an important part of this implicit-explicit correlation. The other factors, mainly the social sensitivity of the construct, vary and may also be responsible for the differences in the magnitude of the implicit-explicit correlations.

The internal consistency of the IAT-L measured the homogeneity of this tool by calculating the correlations between the two IAT scores: one based on trials 1-20 and the other based on trials 21-40 of the critical blocks. This method of measuring the internal consistency has been recommended by Greenwald et al. (2003) for IATs which do not include a practice block before each of the critical blocks. The resulting internal consistency of .57 is low which may suggest a low homogeneity and coherence between the two halves of the IAT. This may be due to using the neutral reference category (FURNITURE) which might have failed to engage the responses when associated with a conceptually different category (LONELINESS). Previous studies which used neutral reference category (e.g., de Jong, et al., 2001) did not state the internal consistency of their IATs. However, studies with bipolar categories yielded internal consistency coefficients of various variants of the IAT showing values in the range of .80 (e.g., Banse et al., 2001; Egloff & Schmukle, 2002). These findings may prompt the use of a bipolar category not only to elicit small to medium

correlations with the explicit measures but also to obtain satisfactory internal consistency. Moreover, low internal consistency may also have reduced the criterion-related validity of the IAT-L in relation to QoL. Based on previous studies (e.g., Egloff, Wilhelm, Neubauer, Mauss, & Gross, 2002), it is possible that the implicit measure of loneliness may be a better correlate of a physiological (or objective) criterion than of a self-reported one. Study 2 examines this issue.

Comparing structural and functional indices of social support, the latter showed stronger correlations with QoL, supporting the previous findings (Arkar et al., 2004). Both support satisfaction and support need showed significant correlations with QoL. The structural support index of utilised network size also significantly positively correlated with QoL. However, no significant correlation was found between available network size and QoL, undermining the significance of quantity of social support as compared to its quality with reference one's QoL.

As for the possible mechanisms which may be responsible for the association of loneliness or lack of social support with QoL, low self-esteem could be a mediator as it has been associated with both loneliness and low perceived QoL (Hornquist & Akerlind, 1987). Future studies need to test such an explanation.

5.6 Conclusion

This study showed a small but significant correlation between implicit and explicit loneliness, establishing the concurrent validity of the IAT-Loneliness. However, no significant correlations between this IAT-L and explicit social support measures were found, thus not supporting the IAT-L's construct validity. The IAT-L score did not significantly correlate with QoL, hence there is also no support for the criterion-related validity of this tool. Low internal consistency of the IAT-L found in this study is its weak point and an issue to be addressed in Study 2.

Chapter Six: Study Two - Social support, Loneliness and Cardiovascular Reactivity to Stress

6.1 Aims of the Study

This study aims to develop a modified IAT of loneliness, and establish its predictive validity by demonstrating the relationship between implicit loneliness and cardiovascular reactivity to laboratory stress. This study also aims to explore if the modified IAT-Loneliness exhibits satisfactory internal consistency, and correlations with explicit loneliness and social support measures.

6.2 Introduction

Loneliness has been described as a product of social isolation and can be defined as a subjective experience resulting from an unpleasant or inadmissible lack of (the quality of) certain social relationships (de Jong-Gierveld, 1987). A related construct, namely, social support can be categorised into two broad types: structural support and functional support. The former constitutes the quantity of support and includes properties such as the size, range and density of the social network. The latter refers to the quality of social support, and includes instrumental (tangible), emotional and informational support (Berkman et al., 2000). Loneliness has been inversely correlated with quantity (Cutrona & Peplau, 1979) and quality of social relationships (Borys et al., 1985). Lonely people also report higher levels of stress, and exaggerated frequency and intensity of daily hassles than their nonlonely counterparts (Cacioppo et al., 2000).

Several structural support indices have been bidirectionally associated with cardiovascular indices for example, lower social support resources were associated with higher resting blood pressure in older adults (Dressler, 1983) and larger social network size was associated with lower blood pressure in both males and females aged between 20 and 70 (Bland, Krogh, Winkelstein, & Trevisan, 1991). Functional support indices such as poor quality of relationships with family and friends were

associated with higher resting systolic blood pressure (SBP)[14] in women (Cottington, Brock, House, & Hawthorne, 1985), and appraisal support predicted age-related differences in SBP and diastolic blood pressure (DBP)[15] (Uchino, Cacioppo, Malarkey, Glaser, & Kiecolt-Glaser, 1995).

Lack of secure social relationships (Antonucci & Ernest, 1994) and loneliness (Rozanski, Blumenthal, & Kaplan, 1999; Sorkin, Rook, & Lu, 2002) have been reviewed to be associated with greater risk of developing CVD[16] and coronary artery disease (CAD)[17] (Strike & Steptoe, 2004). Dickens et al. (2004) found that not having a close confidant in life, with whom the patient had regular contact (at least once a month) and with whom he or she could share sensitive personal information and gain support, predicted cardiac events and cardiac-related mortality in the year after a myocardial infarction (MI) episode, after controlling for demographic factors and severity of MI.

Marital status or change in marital status has been shown to be an independent predictor of incidence of CVD (e.g., Ebrahim, Wannamethee, McCallum, Walker, & Sharper, 1995; Rosengren, Wedel, Wilhelmsen, 1989). In a study on marital status, low-grade inflammation and cardiovascular risk factors, Engstrom, Hedblad, Rosvall, Janzon, and Lindgarde (2006) found an increased risk of coronary events in healthy divorced men, after adjusting for several life style and biological risk factors.

A related concept of social conflict, marital distress has been associated with CVD morbidity and mortality in female coronary patients aged between 30 and 62 over a 4-year follow-up, after controlling for demographic, behavioural and disease variables (Orth-Gomer et al., 2000).

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[14] SBP is the pressure against the walls of the heart during the period of contraction or systole.
[15] DBP is the pressure against the walls of the heart during the period of dilation or diastole.
[16] CVD is a broad term used for a number of diseases that affect the heart and/or the blood vessel system, particularly the veins and arteries leading to and from the heart.
[17] CAD (also called CHD or ischaemic heart disease) is caused by the accumulation of atheromatous plaques within the walls of the arteries. Clinical manifestations of CAD are myocardial infarction (MI) and angina pectoris.

The view that an exaggerated cardiovascular reactivity (CVR)[18] to stress in daily life may accumulate possibly leading to cardiovascular disorders including hypertension and CHD, which was put forward more than 5 decades ago by Hans Selye (1956) has now been discussed in the literature (Christenfeld & Gerin, 2000; Krantz & Manuck, 1984; Manuck, 1994; Steptoe et al., 2004). Models in health psychology consider this heightened CVR as one route by which psychological factors may lead to CVD. In a systematic review of prospective studies on CVR and the development of CVD, Treiber et al. (2003) found reasonable evidence suggesting that CVR can predict the development of some preclinical states (e.g., increased left ventricular mass (LVM) and blood pressure). They also found some evidence for new clinical events in some patients with essential hypertension or CHD. Both LVM and CVR have also been postulated to be risk factors for the development of hypertension and CVD (Pickering, 1996).

Social support may buffer the effect of stress on CVR by acting as a moderator (Cohen & Wills, 1985). For example, Christenfeld et al. (1997) found in an experimental design that presence of a supportive friend yielded lower CVR to stress than of a supportive stranger, which yielded lower CVR than a neutral stranger, demonstrating the importance of social presence and quality of relationship in reducing CVR to stress. Another similar study found that *presence of friend* condition ameliorated the effects of two laboratory stressors compared to *alone* condition. Participants in the former condition showed reduced heart rate (HR) and blood pressure (BP) reactivity in response to these stressors than the ones in the latter condition (Kamarck, Manuck, & Jennings, 1990).

Fontana, Diegnan, Villeneuve, and Lepore (1999) asked undergraduate women to perform stressful tasks in one of the three conditions: alone, with a same-sex stranger, or with a same-sex best friend. They found that alone women had the greatest increases in SBP and HR while women in the stranger and friend conditions did not differ in their responses. They also found that CVR responses were smallest in women who were highly satisfied with the level of general support in the friend condition, highlighting the fact that laboratory conditions could be generalised to

[18] CVR reflects the physiological changes from a resting or baseline state to some type of psychological or physical challenge or stressor.

everyday life. Another study found that participants exhibited the greatest levels of SBP reactivity when discussing a negative event with an ambivalent friend compared to a supportive friend (Holt-Lunstad, Uchino, Smith, & Hicks, 2007). These findings suggest the significance of the quality of social relationships.

Similar findings were reported by another group of researchers (Craig, Lynch, & Quartner, 2000) where they found a significant association between reduced mean arterial pressure (MAP)[19] and DBP, and higher social support in a clinical sample of cardiac rehabilitation patients when they were exposed to two identical affective stress interviews in the presence and absence of a small friendly dog. In the same sample, perceived levels of social support in life were significantly associated with CVR, suggesting that social support has an ameliorative effect on CVR independent of situational support and a buffering effect of social support. Uchino and Garvey (1997) found similar results for SBP, DBP and HR in response to a speech stressor administered in laboratory either in support availability or no support availability condition.

Another set of studies considered social support a stable variable (Sarason, Sarason, & Shearin, 1986), and assessed its naturalistic levels and correlation with CVR to stress in the laboratory. Social support was assessed as structural support (Roy, Steptoe, & Kirschbaum, 1998), number of ambivalent ties (Uchino, Holt-Lunstad, Uno, & Flinders, 2001) and perceived instrumental and emotional support (Knox, 1993). Naturalistic levels of social support were found to be inversely related to ambulatory measures of CVR, particularly during high-stress periods. Linden, Chambers, Maurice, and Lenz (1993) found that the quality of social support was an independent predictor of ambulatory SBP in women. This finding was not confounded with subjective daily-life stress in the sample, suggesting a main effect model rather than the buffering effect model of social support. Another study examined the associations of social support from coworkers and supervisors with workday ambulatory BP and HR, and found that for women, immediate supervisor support was inversely associated with workday SBP and DBP. For men, these results were significant for coworker support and SBP only. However, immediate supervisor

[19] MAP is the pressure in the large arteries, averaged over time. Systolic and diastolic arterial pressures are then considered as the upper and lower limits of periodic oscillations about this mean pressure (Berne & Levy, 2001). MAP = [SBP + (2DBP)] / 3.

support was inversely associated with SBP reactivity during high-stress conditions, which is in line with buffering effect of social support (Karlin, Brondolo, & Schwartz, 2003). Smith, Ruiz, and Uchino (2004) employed a novel methodology in this area, and asked undergraduate students to write about supportive ties or casual acquaintances followed by the assessment of HR and BP after a speech stressor. Compared with the acquaintance condition, the supportive tie condition resulted in reduced CVR. These effects were found in low, but not in high, hostile participants. This finding suggests that mental activation of supportive ties can alter the effects of stress.

Despite that a significant portion of evidence in the literature does hint towards social support having a medium to large attenuating effect on CVR (Thorsteinsson & James, 1999), the findings in this area are fairly inconsistent. Lepore (1998) in his review article also identified inconsistent and inclusive findings across studies in this area a major problem as some studies did not find significant associations between social support and CVR. For example, a study investigating the effect of three same-sex conditions: alone, with a friend and with a stranger on CVR to laboratory stressors, reported no significant associations. Friends yielded higher ratings of support than strangers (Sheffield & Carroll, 1994). In another study, the number of close friends was not associated with CVR to a mental arithmetic stress task. However, social network size moderated the relationship between stressful personal life events and HR reactivity. These stressful events were identified as those appropriate to young adults and covered three broad domains: work, education and money; family life; and personal life (Phillips, Carroll, Ring, Sweeting, & West, 2005). Uchino et al. (2001) also did not find any significant correlation between supportive ties and CVR reactivity to laboratory stressors. In another study, structural support index including the existence and number of socially supportive relationships, aspects of network structure such as proximity, and quality of primary relationships were unrelated to CVR to stressors in male adolescents (Boyce & Chesterman, 1990). Uchino, Kiecolt-Glaser, and Cacioppo (1992) found a similar pattern of results in a sample of family caregivers of Alzheimer's disease victims, where none of the structural or functional indices of social support were significantly associated with CVR.

Some findings have also been counter-intuitive, where higher CVR was positively correlated with the size of social network. Roy et al. (1998) found mean number of people listed as potential sources of support was positively correlated with the higher CVR to an arithmetic stress task. It is important to note that initially both structural and functional indices of social support were assessed in this sample however the satisfaction with social support score was skewed and hence was not included in the final analyses. Although men showed higher CVR to stress than women in some studies (e.g., Polefrone & Manuck, 1987), gender has not been found to be a moderator in this link. Lepore, Allen, and Evans (1993) found that the mean values of SBP and DBP reactivity in response to a speech task were higher in men than in women but the results for interaction analyses were nonsignificant. However, some studies showed the contrary (e.g., Linden et al., 1993).

Unlike social support, only a few studies have investigated the association between levels of loneliness and CVR to stress induced in the laboratory. Steptoe et al. (2004) found a positive correlation between naturalistic levels of loneliness and DBP reactivity to acute mental stress in a sample of 240 middle-aged women but not in men, after controlling for the effects of age, marital status, socioeconomic status, smoking status and body mass. No such effects were found for SBP or HR. By contrast to the findings of this study, no such effects were found by Cacioppo et al. (2002) in their two studies involving undergraduate students and an elderly community sample, in which the levels of loneliness were not found to be associated with BP reactivity measures.

There are a few limitations of research in this area due to which the question of the buffering (or main) effect of social support in CVR to stress is unresolved. First, despite some evidence in its favour, the stressors induced in the laboratory may not provide a perfect substitute for real-life stressors. However, there is evidence that the sympathetic activation which is responsible for elevated levels of BP and HR in response to psychosocial laboratory challenges has a greater potential than physiological challenges e.g., cold presser task, to generalise to real-life stress. With reference to sympathetic activation, it is important that in the case of psychosocial tasks, the stimulation is suprapituitary with the stressor being processed in the brain before it activates the HPA axis. While in the case of physiological challenges, the

stimulation of the HPA axis is at pituitary level. Moreover, the nature of the stressor determines the pathways of HPA activation. Psychosocial stressors activate the HPA axis by stimulating the paraventricular nucleus (PVN) through the limbic system (prefrontal cortex, hippocampus, amygdala), whereas, physiological stressors have a more direct pathway to the PVN (Herman & Cullinan, 1997).

Second, an important limitation of the research in this area is the reliance on self-reported measures of social support and loneliness. It is an established fact that explicit measures are contaminated by social desirability and prone to presentational biases (Holtgraves, 2004). These biases could be interpersonal (evaluation apprehension or intention to impress) or intrapersonal (self-deception) in nature (Nosek, 2005). It is tempting to speculate that in instances where self-report measures did not correlate with CVR, one of the plausible explanations could be the possibility of these presentational biases influencing the self-reported responses. The use of implicit tools may prove to be a solution to these limitations. A few studies demonstrated that implicit measures superseded explicit measures in predicting physiological outcomes (Egloff et al., 2002; Gidron, Danzinger, Gurski, Heldman, & Gurman, 2005; Phelps et al., 2000). It can be argued that in contrast to the consciously-controlled responses on the explicit measures, implicit measures elicit more automatic responses and hence are more likely to correlate with physiological responses which also occur automatically. Moreover, since explicit and implicit measures of psychosocial constructs are not typically strongly correlated (Greenwald et al., 1998), they may differentially predict various health outcomes.

6.2.1 Modified Measurement of Implicit Loneliness

Due to poor internal consistency of the IAT-L in Study 1, a modified version of the IAT was adapted to measure loneliness. This IAT-Loneliness (IAT-L (M)) included opposite or bipolar categories on the speculation that it would have a higher internal consistency and predict the criterion measure in this study better than in Study 1 as the criterion measure comprised a physiological outcome.

The IAT-L (M) is a computerised reaction-time test which assesses the relative strength of associations by comparing the performance on two bipolar pairs

of concepts. Although respondents do not lack awareness that the IAT is being administered, it assesses psychosocial constructs indirectly without any verbal self-report. Moreover, responses on the IAT are difficult to fake (Egloff & Schmukle, 2002). Due to the fact that the implicit-explicit correlation may vary across different social constructs, and many factors moderate this relationship (Nosek, 2005), it is important to demonstrate the predictive validity of this tool, which was the aim of the present study. Both explicit measures of social support and loneliness and IAT-L (M) were administered to investigate their correlation with CVR to psychosocial stress.

6.2.2 Hypotheses

The following hypotheses were tested in the present study:

(1) Loneliness and support need will show a positive correlation with CVR to stress;
(2) Available and utilised network sizes, and support satisfaction will show inverse correlations with CVR to stress;
(3) Implicit loneliness will correlate more strongly with CVR to stress than explicit loneliness.

6.3 Method

6.3.1 Participants

Fifty[20] female non-smoking psychology students from the University of Southampton were randomly assigned to either Experimental (stressor) or Control Group. This study focused mainly on the Experimental Group i.e., those exposed to the stressor. Given the gender differences in the relations between loneliness and CVR i.e., quality of social support was inversely correlated with ambulatory blood pressure index in young women and not in men (Linden et al., 1993) and loneliness was positively associated with DBP reactivity to acute mental stress induced in the laboratory in middle-aged women (Steptoe et al., 2004), and since most of the

[20] The present study was conducted as part of another study entitled "the effects of stress on DNA damage" due to the logistics of the TSST protocol. Therefore, the TSST was jointly administered by myself and another PhD student in the school who was also studying the effects of stress.

current students in the school were women, men were not included in the present study. The data of two participants were excluded due to high baseline BP (> 140/90 mmHg). The remaining normotensive sample's mean age was 22.09 (SD = 6.1) years (n = 23).

This study was approved by the school ethics committee and the participants gave informed consent to take part in the study (see Appendix H for consent form and debriefing statement).

6.3.2 Procedure

6.3.2.1 The Trier Social Stress Test (TSST).

The TSST (Kirschbaum, Pirke, & Hellhammer, 1993) was used to induce psychosocial stress in the laboratory. The original protocol was followed, which consisted of a speech task and a mental arithmetic task. In the speech task, participants were asked to imagine that they had applied for a research-assistant job in the school of psychology, and were there to present themselves to a committee which would evaluate them on the basis of their personal characteristics. The task was to convince the committee in a free speech that they were the best candidate for the vacant position.

Ten minutes were given to prepare the speech (anticipation period) followed by a 5-minute speech in front of a committee sitting behind a one-way mirror (protocol was modified according to Lupien et al., 1997; committee included only one member behind a one-way mirror). Some standard but relevant questions were also asked by the committee member. In the subsequent arithmetic task, participants' task was to count backwards from 1687 to 0 in 13-step sequences. In case of an error, the participant had to start again from 1687. This task lasted for 5 minutes and was carried out in the similar one-way mirror condition.

In the control condition, participants were asked to write a letter of application and a paper-and-pencil arithmetic task without any evaluation (Domes, Heinrichs, Reichwald, & Hautzinger, 2002) (see Appendix J for complete protocols).

6.3.3 Measures

6.3.3.1 Demographic information and confounders.

These included age and relationship status (see Appendix K for demographic information sheet). The latter was assessed by using the following categories: single, with a partner, married/living as married, separated, divorced or widowed. Due to low frequencies and contextual overlap between the relevant categories, the categories *single*, *separated*, and *divorced* or *widowed* were merged and given a score of 1, and the categories *with a partner* and *married/living as married* were merged and scored as 2. The Fear of Negative Evaluation (FNE) Scale-Brief Version (Leary, 1983) was used to control for the possible confounding effect of this construct. Previous research has shown higher levels of CVR in high social-fear participants than in low social-fear ones (Burns, 1995). This 12-item scale assesses the degree to which people experience apprehension at the prospect of being evaluated negatively, on a 5-point rating scale ranging from *not at all* to *extremely* (see Appendix L). Higher scores indicated higher level of FNE. The following items were negatively scored: 2, 4, 7 and 10. Cronbach's alpha reliability of the scale in this sample was .91 ($n = 23$).

6.3.3.2 Visual Analogue Scale (VAS).

It was used to assess the subjective pre- and post-TSST levels of stress. The participants were asked to mark on a 10-cm horizontal line, showing *no stress* and *the worst stress I have ever felt* on the two ends, the point which represented their level of stress: (1) before, and (2) after TSST (see Appendix M).

The evaluation of subjective stress is important as the physiological response to stressors may vary as a function of social threat associated with the stressors. Kamarck, Annunziato, and Amateau (1995) found that social support in their sample of young adult women was associated with attenuated CVR to the stressors only in the group which reported high perceived social threat.

6.3.3.3 Cardiovascular reactivity measures.

SBP, DBP (in mmHg) and HR (in beats per minute) were measured while seated at: (1) baseline (after a 10-minute rest period), (2) anticipation period, (3) after speech task, (4) after arithmetic task, and (5) follow-up (25 minutes later), using an Omron digital automatic blood pressure monitor (Omron Healthcare UK Ltd.).

6.3.3.4 The Arizona Social Support Interview Schedule (ASSIS).

The ASSIS (Barrera, 1980) was used to assess social support. It includes 24 questions for assessing four indices of social support: available network size (perceived network size), utilised network size (or actual network size), support satisfaction, and support need. These are determined by asking respondents to nominate providers in the areas of intimate interaction, material aid, advice, positive feedback, physical assistance and social participation, thus making the ASSIS reflect both structural and functional support. Overall support satisfaction is determined on a 1 (very dissatisfied) to 7 (very satisfied) and support need on a 1 (no need at all) to 5 (very great need) scales (see Appendix E).

6.3.3.5 The UCLA Loneliness Scale.

This scale (version 3; Russell, 1996) uses 20 items to gauge the subjective feelings of loneliness on a 1 (never) to 4 (always) frequency scale. Higher score indicated higher level of loneliness (see Appendix D). The following items were negatively scored: 1, 5, 6, 9, 10, 15, 16, 19 and 20. Cronbach's alpha reliability of the scale in this sample was .90.

6.3.3.6 The Implicit Association Test-Loneliness (Modified) (IAT-L (M)).

This is a modified version of the previously adapted IAT-L (Study 1) designed to measure implicit loneliness and runs on a laptop computer. It involves a series of seven blocks including two practice blocks before each of the two critical ones. In each block, stimulus words, which are exemplars of either two target concepts or two attributes, appear in the middle of the screen, and the participant

needs to assign them to one of the categories of attributes or target concepts. In the first block, the participant assigns exemplars of one of the two target concept categories (SELF, OTHERS), using one of the two assigned keys (*e* or *i*) on the keyboard. In the second block, the participant assigns the exemplar words to one of the two attribute categories (LONELY, NONLONELY), by pressing the relevant key (*e* for LONELY, *i* for NONLONELY). In the third block, the two above-mentioned categories are combined and stimuli for both appear randomly, and a target concept and attribute share the same response key (e.g., LONELY or SELF assigned to key *e*). The fourth block features the reversal of response assignments in Block 2 (i.e., key *e* for NONLONELY instead of key *i*). In the fifth block, target concepts and attributes are combined again as in Block 3, after reversing the keys (e.g., LONELY or OTHERS assigned to key *i*). Each block comprises 20 trials except critical Blocks 3 and 5 which include 40 trials each.

Each stimulus word remains on the screen until the participant responds. If the response is correct, the next stimulus word appears on the screen. However, if the response is incorrect, an *X* appears under the stimulus word and remains on the screen until the correct response is made. This process of the provision of the correct response is called the built-in penalty which includes the total time (in ms) until the correct response is made. This built-in penalty makes this IAT-L different from the IAT-L used in Study 1, where the *X* following an incorrect response was replaced by a new word after 200 ms. The inter-trial interval in the IAT-L (M) is 150 ms. Scoring of the IAT-L (M) is done according to the recommended scoring algorithm for the IAT (Greenwald et al., 2003). Initial data reduction is done as follows: (a) data from the critical and practice blocks are used; (b) trials with latencies > 10,000 ms are eliminated; (c) data from participants who, on more than 10% of trials, exhibit latencies less than 300 ms are eliminated. The IAT-L (M) score *D* is obtained by subtracting mean scores on Block 3 from those on Block 5 (and practice Block 3 from practice Block 5) for each participant, dividing the resulting value by relevant pooled-trials' standard deviation, and finally averaging the two resulting quotients (i.e., practice and critical).

The stimulus words for the modified IAT were generated by nominating 16 synonyms for each of the LONELY and NONLONELY categories. These words

were generated by an online thesaurus of the English language (Thesaurus.com) using the keywords *lonely, alone* for a list of synonyms and antonyms. A list of 16 finally selected words in each category was given to 10 postgraduate research students at the School of Psychology, University of Southampton, who acted as judges. They were asked to rate these words on their relevance to the LONELY and NONLONELY categories on a 1 (Not at all) to 5 (Extremely relevant) rating scale. Finally, 5 words were chosen for each category if they fell into the *extremely relevant* category by ≥ 70 % of the judges (see Appendix N for list of words for judges and final list of stimulus words).

6.3.4 Statistical Analyses

To analyse the effects of stress on BP and HR, a two-way mixed Analysis of Variance (ANOVA) was done with Time as the within-subjects factor (baseline, after speech task, after arithmetic task, follow-up) and Group as the between-subjects factor (Experimental, Control). The association between loneliness and social support, and CVR to each of the tasks[21] was analysed by partial correlations, after controlling for the respective CVR baseline and relationship status. Given that research has shown that increased CVR to stressful daily life may have a cumulative effect predictive of CVD (Krantz & Manuck, 1984), and since the rate of mortality from CVD has been correlated with marital status (Menotti & Giampaoli, 1998), one would assume higher CVR to stress in single people than in the ones with partners. We thus controlled for the effects of relationship status since people with partners may have a perception of availability of the partner's support which may buffer the effects of stress on CVR. A two-way mixed ANOVA was done to analyse the effects of TSST versus Control on the levels of subjective stress.

The relationships of FNE score and age with CVR indices were analysed by Pearson's correlation. Finally, the association between implicit and explicit loneliness was tested using Pearson's correlation. The correlations among social support indices were also tested using Pearson's correlations.

[21] There is a possibility that the correlation between social support and CVR indices may differ in response to different types of stressors (Kamarck et al., 1990), and some people might find public speaking more stressful than the arithmetic task or vice versa, even if both tasks involve performance in the face of evaluation. Therefore, we analysed CVR to each of the tasks separately.

6.4 Results

6.4.1 Initial Data Screening and Preliminary Analyses

All statistical analyses were performed using the SPSS (Version 14). All variables were initially tested for variation and significant deviation. The following positively skewed distributions were transformed, in order to produce the skewness and kurtosis values nearest zero: *IAT D* (square root), *age* (logarithm) and *DBP index* (logarithm).

The internal consistency of the IAT-L (M) in this sample was .78 which was computed by the correlation between the IAT measure based on practice blocks and another IAT measure based on critical blocks (Greenwald et al., 2003).

6.4.2 Effects of the Stress on CVR

The effects of Time, $F(3,138) = 11.70, p < .001$, Group, $F(1, 46) = 15.91, p < .001$ and the interaction Time x Group, $F(3,138) = 22.78, p < .001$ were significant for SBP. The effects of Time, $F(3,138) = 11.46, p < .001$, Group, $F(1, 46) = 16.53, p < .001$ and Time x Group, $F(3,138) = 18.36, p < .001$ were significant for DBP. Similarly, Time, $F(3,138) = 7.83, p < .001$, Group, $F(1,46) = 3.94, p = .05$ and Time x Group, $F(3,138) = 5.29, p < .01$ effects were significant for HR (see Figures 7 and 8). Further t-tests revealed that the Experimental Group had significantly higher levels of ΔSBP, ΔDBP and ΔHR after both speech, and arithmetic tasks (all $ps < .05$) than Controls.

Regarding the levels of stress, results showed that the effects of Time, $F(1,46) = 90.80, p < .001$, Group, $F(1,46) = 21.86, p < .001$ and Time x Group, $F(1,46) = 25.73, p < .001$ were significant, suggesting that the Experimental Group experienced significantly higher levels of stress after the TSST than the Control Group.

Having established that the TSST induced greater stress[22] and hence higher CVR than the Control tasks, we now focus on the TSST group alone in relation to prediction of CVR by loneliness and social support.

FNE scores were not correlated with any of the CVR indices (see Table 9). Age was also not significantly associated with any of the CVR indices except SBP after speech task (see Table 9). Therefore, both were not controlled for.

[22] Pearson's correlation coefficients between CVR indices and post-TSST subjective stress (and also the difference between pre- and post-TSST stress) were nonsignificant (two-tailed, results not shown).

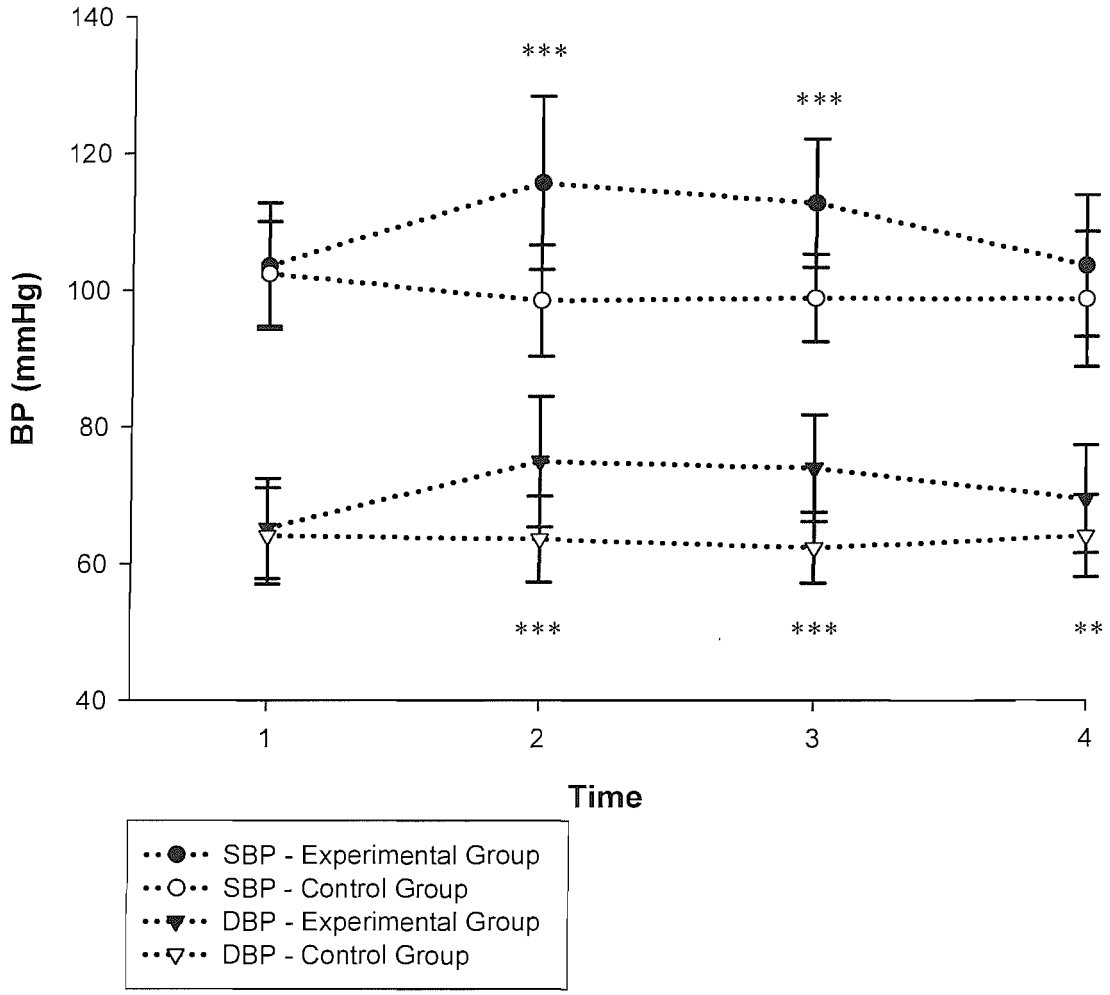


Figure 7. Effects of manipulation of stress on SBP and DBP at: (1) baseline, (2) after speech task, (3) after arithmetic task, and (4) follow-up (Experimental Group $n = 23$, Control Group $n = 25$). $^{**}p = .01$, $^{***}p < .001$, two-tailed.

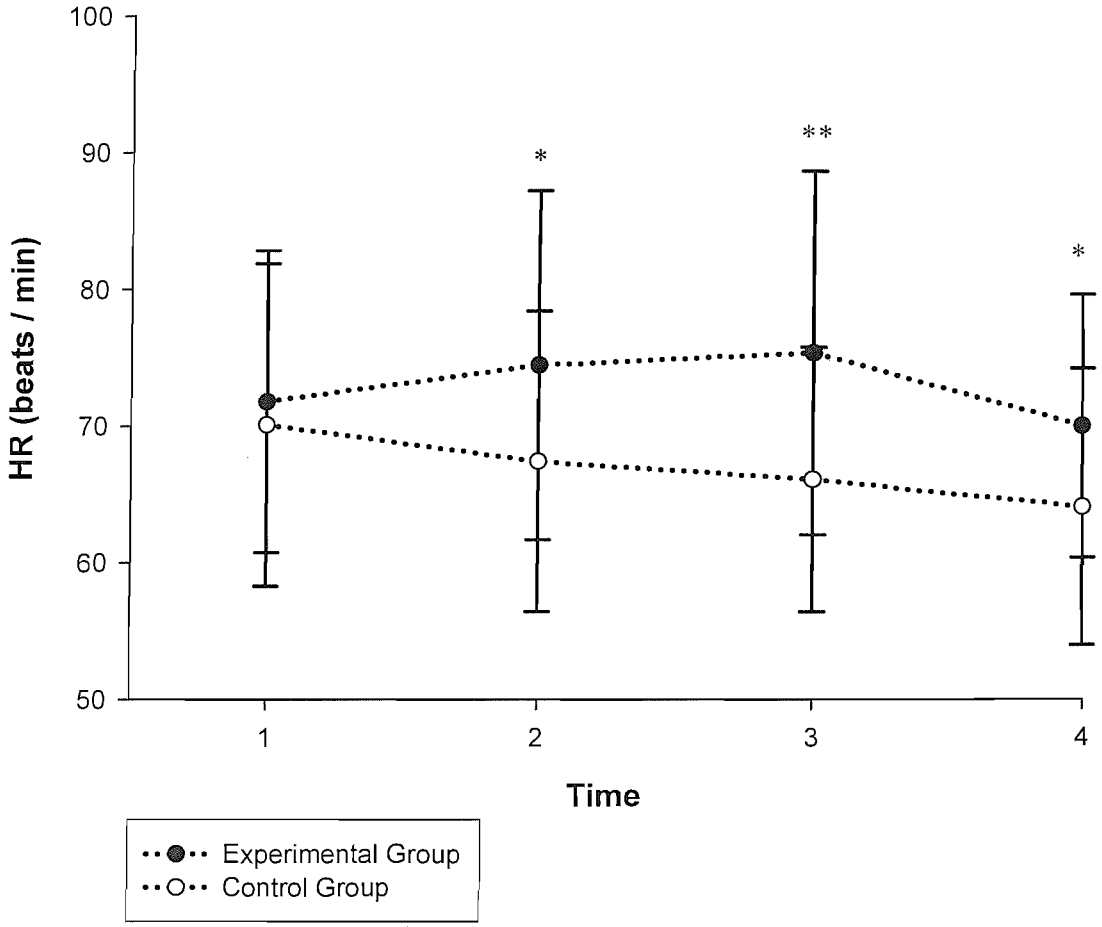


Figure 8. Effects of manipulation of stress on HR at: (1) baseline, (2) after speech task, (3) after arithmetic task, and (4) follow-up (Experimental Group $n = 23$, Control Group $n = 25$). $^{*}p < .05$, $^{**}p < .01$, two-tailed.

Table 9. Pearson's correlation coefficients between FNE score and age, and: (1) BP reactivity, (2) HR reactivity to stress.

	SBP(s)	SBP(a)	DBP(s)	DBP(a)	HR(s)	HR(a)
			(n = 23)			
FNE	.35†	.22	.31	.30	.11	-.09
Age	.46*	.41†	.30	.20	.06	.08

$^{*}p \leq .05$, $^{\dagger}p < .10$, two-tailed.

Note. (s) = After speech task, (a) = After arithmetic task.

6.4.3 Correlates of CVR

The relationship between the measures of loneliness and social support, and CVR indices is presented in Table 10. Support need was positively correlated with SBP reactivity after speech task, $r = .43, p < .05$ and DBP reactivity after both speech, $r = .37, p = .05$ and arithmetic, $r = .47, p < .05$ tasks. HR reactivity after arithmetic task was inversely associated with support satisfaction, $r = -.60, p < .01$, while the inverse correlation between HR reactivity after speech task and support satisfaction showed a trend toward statistical significance, $r = -.35, p = .06$. Although explicit loneliness failed to correlate significantly with CVR indices, implicit loneliness was positively correlated with DBP reactivity after the arithmetic task, $r = .51, p < .01$. No significant correlations were found between the structural indices of social support and CVR to stress. All correlations were found after controlling for the respective baseline and relationship status.

Table 10. Partial correlation coefficients between loneliness and social support, and: (1) BP reactivity, (2) HR reactivity to stress, after controlling for respective baseline and relationship status.

	SBP(s)	SBP(a)	DBP(s)	DBP(a)	HR(s)	HR(a)
			(n = 23)			
Explicit loneliness	.29	.13	.17	.32†	-.00	-.05
Implicit loneliness	-.15	-.01	.08	.51**	-.10	-.06
Available network size	.24	-.01	.25	-.11	.08	.12
Utilised network size	.04	-.15	.18	-.11	-.15	-.13
Support satisfaction	.08	.34†	-.12	-.17	-.35†	-.60**
Support need	.43*	.17	.37*	.47*	-.14	-.17

$^{*}p \leq .05$, $^{**}p < .01$, $^{\dagger}p < .10$, one-tailed.

Note. (s) = After speech task; (a) = After arithmetic task.

6.4.4 Correlations between Implicit and Explicit Measures

Implicit loneliness as measured by the IAT-L (M) did not significantly correlate with explicit loneliness, $r = .16$, $p = .29$. The correlations between implicit loneliness and social support indices were also nonsignificant ($N = 48$) (see Table 11). However, there was a trend toward a significant correlation between implicit loneliness and support need, $r = .26$, $p = .07$, suggesting that the higher the implicit loneliness, the higher is the need for social support. Correlations among the indices of social support are shown in Table 12.

Table 11. Pearson's correlation coefficients between implicit and explicit measures.

	Explicit Loneliness	Available Network Size	Utilised Network Size	Support Satisfaction	Support Need
			($N = 48$)		
Implicit Loneliness	.16	-.22	-.07	-.18	.26†

†$p < .10$, two-tailed.

Table 12. Pearson's correlation coefficients among indices of social support.

	Available network size	Utilised network size	Support satisfaction	Support need
		($n = 23$)		
Available network size	-	.90**	.19	.18
Utilised network size	-	-	.18	.20
Support satisfaction	-	-	-	.08

**$p < .01$, two-tailed.

6.4.5 Incremental Validity of the IAT-L (M)

Incremental validity of this test was determined by calculating partial correlation between implicit loneliness and DBP reactivity after arithmetic task, controlling for explicit loneliness, baseline DBP and relationship status. The results were significant, $r = .50$, $p = .01$, establishing the incremental validity of the IAT-L (M).

6.5 Discussion

This study adapted a modified IAT to measure loneliness, and used it alongside the explicit loneliness and social support measures to investigate whether the IAT correlates with CVR to stress induced in the laboratory. The purpose of adapting a modified version of IAT-Loneliness was to improve its internal consistency by using bipolar categories. The internal consistency of a measure

imposes a theoretical standard for the degree to which it can be related to other measures of the same construct. This IAT-L (M) showed higher internal consistency than the IAT-L which was used in Study 1, indicating theoretical soundness of this tool. It is however important to note that the strength of the internal consistency does not guarantee that the magnitude of correlations between the IAT-L and other explicit measures of the same construct will be stronger as it depends on a number of variables including the level of presentational biases affecting the explicit measures.

Results of this study showed that SBP reactivity after speech task, and DBP reactivity after both speech and arithmetic tasks were positively correlated with support need, suggesting that the greater the need for social support, the higher is the participants' BP reactivity to stress. Also, lower satisfaction with social support was associated with higher HR reactivity after the arithmetic task. More importantly, implicit, but not explicit, loneliness was significantly correlated with DBP reactivity after the arithmetic task. Given that implicit loneliness correlated with DBP reactivity and not with any other reactivity index, this finding warrants caution and replication. However, it is interesting to note that although the correlations between the implicit and any of the explicit measures did not reach the conventional level of statistical significance in this sample, there was a strong trend in the case of support need. The fact that support need, which is a subscale of social support, was consistently and significantly associated with the CVR indices in this study, suggested that support need and implicit loneliness may be related concepts predictive of greater CVR. The greater DBP reactivity suggests greater sympathetic arousal or alternatively, greater parasympathetic withdrawal. This pattern of correlation between support need and implicit loneliness may thus hint at the construct validity of the IAT-L (M). The results of this study are in line with and extend the findings of previous studies. Whilst some of those studies found significant associations between social support (or the lack of) and both SBP and DBP (Allen, Blascovich, Mendes, 2002), others found them for only one CVR index such as Gerin et al. (1995) found lower DBP reactivity to a laboratory stressor in *roommate present* condition than in *alone* condition. Lepore et al. (1993) found that participants who were supported by a confederate exhibited smaller increases in the SBP than their alone counterparts in response to a speech task. Steptoe and his colleagues (2004) found significant correlations between explicit loneliness and DBP

reactivity in women, unlike in the present study. No such associations were found for SBP and HR in this sample. Similarly, Knox (1993) found significant correlation between perceived instrumental and emotional support, and DBP reactivity to laboratory stress, while SBP and HR did not differ between the high and low social support groups during stress. There is a possibility that the smaller size and age of our sample magnified the presentational biases, which might have accounted for the disparity between the former and the present study. Nevertheless, our findings extend those of Steptoe et al. to an implicit measure of loneliness. It is difficult to say as to why these differences in BP reactivity indices were found in the studies. There is evidence which suggests that "although HR and BP vary together, BP changes relatively less than the HR because of reflex compensatory mechanisms" (Opie, 2004, p. 443). Considering the nonsignificant trend in the case of explicit loneliness and DBP reactivity after arithmetic task in the present study, there is a possibility that this association would become statistically significant with a larger sample size.

The CVR was associated with the functional, but not structural, indices of social support in the present study, which replicates previous findings. It has also been shown that the effectiveness of different indices of functional support varies and may depend on the need of a particular situation e.g., in a study on functional support and exaggerated CVR to a math stressor, Craig and Deichert (2002) found that men receiving instrumental support with the stressor from a close friend exhibited reduced DBP and better recovery from stress than men in emotional support or no support conditions, supporting the buffering effect model of social support. Structural indices have been found to be poor correlates of CVR to stress (Roy et al., 1998) merely due to the limited, and sometimes misleading, information these measures provide. It could be the reason behind the counter-intuitive direction of their correlations in the present sample. Moreover, the evidence that relationship quality moderates the effect of social support on CVR validates our findings e.g., Uno, Uchino, and Smith (2002) found that the quality of friendship with the friend present during a series of speech stressors moderated the effects of support on DBP in a group of young women. In another study of similar design, perceived closeness to the friend and length of friendship were positively correlated with the size of the SBP reduction (Kors, Linden, & Gerin, 1997).

Although all the correlations between the implicit and explicit measures were in the expected direction, none reached the conventional level of significance in our sample. As mentioned above, a strong trend was found between support need and implicit loneliness, suggesting a link between these concepts. Since this IAT showed satisfactory internal consistency, a plausible explanation for these nonsignificant findings could be that the implicit-explicit correlations may vary across different social constructs (Nosek, Banaji, & Greenwald, 2002) and can be moderated by several factors (Nosek, 2005) as discussed in Chapter 2. According to the MODE model, the motivation and opportunity to deliberate alters the responses on the explicit measures, resulting in low correlations between the explicit and implicit measures (Fazio & Olson, 2003). The fact that increasing the spontaneity of explicit measures (hence reducing the opportunity to deliberate) increased the correlations between the implicit and explicit measures (Hofmann, Gawronski, Gschwendner, & Schmitt, 2005), supports this model. Given that the participants were undergraduate students and younger people may associate loneliness with low popularity more than older adults do, our sample's explicit responses may have been more biased by social desirability. A similar pattern of weak implicit-explicit correlations was found in previous studies on implicit anxiety and self-esteem (Egloff & Schmukle, 2002; Greenwald & Farnham, 2000) yet, as in the present study, the IATs showed higher predictive validity than the explicit measures.

A relevant issue with reference to the use of different stressors in the laboratory to assess CVR is their subjective level of difficulty. There is evidence which suggests that the response-attenuating effects of affiliation sought from the presence of social relations in the laboratory or the ameliorating effects of available social support in life are limited to conditions that involve high social threat. Kamarck et al. (1995) found that the presence of a close friend in the laboratory during a stressor was associated with CVR only under conditions of high social threat which varied in high and low social threat groups by having experimenter formally attired and providing harsh feedback, and informally dressed and no feedback, respectively.

The CVR response to a threatening situation may also vary as a function of certain personality characteristics such as social fear or social anxiety (Burns, 1995).

However, no significant association was found between the score on FNE Scale and CVR in the present sample.

With reference to the studies on social support and CVR in laboratory setting, an important issue which may influence the responses of the participants is of gender of the provider or the recipient of social support. Glynn et al. (1999) examined these gender-related issues in a study involving a speech task, and found that social support provided by women reduced cardiovascular changes for both male and female speakers compared with presence of nonsupportive women, while social support from men did not. This supports findings from past research indicating that friendships in which one or both partners are female (female-female and male-female dyads) are often described as more intimate (Winstead, 1986). Many studies on friendship suggest that female friends are perceived by females and males as more emotionally supportive than male friends and that time spent with a female friend may be a buffer against loneliness (Wheeler, Reis, & Nezlek, 1983).

While most of the studies which assessed the CVR in response to stress induced in the laboratory and its association with the presence or absence of friends, roommates, pets, etc. aimed at investigating if social support had a direct effect of the levels of stress and physiological functioning, Gerin et al. (1995) examined the possibility that social support operates as a moderator of CVR. They tested main effect and buffering effect models of social support in 26 young women, and found the evidence for both. The results indicated that the support manipulation (alone, with a roommate) produced significant main effects for DBP and stress ratings, with lower DBP and ratings observed in *with roommate* condition. Also, the interaction between support and stress produced lower CVR in the high stress but, not the low stress, condition supporting the buffering effect hypothesis. The buffering effect of social support was also found in a study where the effects of size of social network were accentuated when event frequency was high, suggesting that life events and support interacted to sensitise future CV responses to stress (Roy et al., 1998).

The use of multiple statistical analyses with a small sample size was a limitation of this study. However, significant correlations suggested that the effect size of these associations is strong.

Pathways of the relationship between social support and cardiovascular functioning.

One may speculate on the pathways leading to the observed relations. Lack of social support may alter the perception of one's capability to deal with the stressor by having an adverse effect on self-esteem or self-efficacy. There is evidence that the cognitive-emotional responses to stressors encompass perceptions, evaluations and affective responses which in turn contribute to physiological responses (Lovallo & Gerin, 2003). Such perceived incapacity may possibly enhance the effects of stress, leading to peripheral responses involving the hypothalamus and brain stem which are responsible for increased CVR in response to the stressors. Hypothalamus is able to regulate endocrine functions and brain stem to regulate the ANS. Persistent increased CVR to daily-life stressors may translate into higher CVD risk (Everson-Rose & Lewis, 2005; Knox & Uvnas-Moberg, 1998).

Therefore, the two major mechanisms through which lack of social support may play a role in cardiovascular health are behavioural and neuroendocrine pathways. There are a number of behaviours which are associated with inefficiency of the cardiovascular system such as irregular exercise, high alcohol consumption, a diet high in saturated fats and irregular medical check-ups. Also, there is evidence that these behaviours may be associated with a lack of social support or loneliness. In the Edgecombe County Blood Pressure Study, it was reported that women who dropped out of the treatment had less social support on the job, less perceived spousal approval (if married) and a lower level of perceived access to supportive resources (Williams et al., 1985). In a set of two studies on social support for exercise and physical activity in middle-class males and females and middle-class male and female teachers, social support for exercise from friends and family was positively correlated with physical activity (Treiber et al., 1991). Another study found that low social anchorage (a composite measure of social network characteristics, social support, marital status and social class) was an independent risk factor along with physical activity and high BMI in men aged 68 years with inadequate diet (Hanson, Mattisson, & Steen, 1987). Hanson, Isacsson, Janzon, and Lindell (1990) found that perceived emotional support had a significant correlation with successful smoking cessation, after adjusting for social class, marital status,

alcohol consumption, physical activity, smoking status of spouse and medical conditions.

Lack of social support or loneliness may negatively influence cardiovascular function and promote atherosclerosis through the HPA axis and/or the ANS, which are activated in response to emotional stimulation and stress. Psychosocial stress and negative emotional states which may result from a lack of social support can bidirectionally influence the action of proinflammatory cytokines (Ritchie & Nemeroff, 1991) (see Figure 9). The primary cause of CHD or its first precursors, myocardial infarction and stroke, is atherosclerosis or endothelial injury which is caused in response to either some kind of mechanical injury (i.e., sheer stress) or immunological factors and toxins. Immune cells dominate early atherosclerotic lesions, accelerate their progression, and activation of inflammation can elicit acute coronary syndromes (Hansson, 2005). The risk of the incidence and progression of CVD could be a function of either acute or chronic psychosocial stress (Everson-Rose & Lewis, 2005). There is evidence indicating that the CNS is involved in the development of arterial lesions. The available data strongly suggest that sympathetic activation is associated with platelet aggregation (a prothrombotic process), and lesion formation and endothelial dysfunction, both of which can be caused by chronic stress (Markovitz & Matthews, 1991). It has also been suggested that a neuropeptide oxytocin is a possible mediator with regards to the buffering effects of social support, a reduction of which in socially isolated people can lead to enhanced sympathetic activation and endothelial dysfunction (Knox & Uvnas-Moberg, 1998).

The findings suggesting that people with low social support have an increased level of urinary noradrenaline, independent of their stress levels (Fleming, Baum, Gisriel, & Gatchel, 1982), and resting plasma adrenaline explains significant variance in resting SBP, DBP and HR in young men (Knox, Theorell, Svensson, & Waller, 1985) support the above-mentioned pathways. Moreover, healthy divorced men showed elevated levels of inflammation-sensitive proteins (ISPs) which are precursors of atherosclerosis (Engstrom et al., 2006).

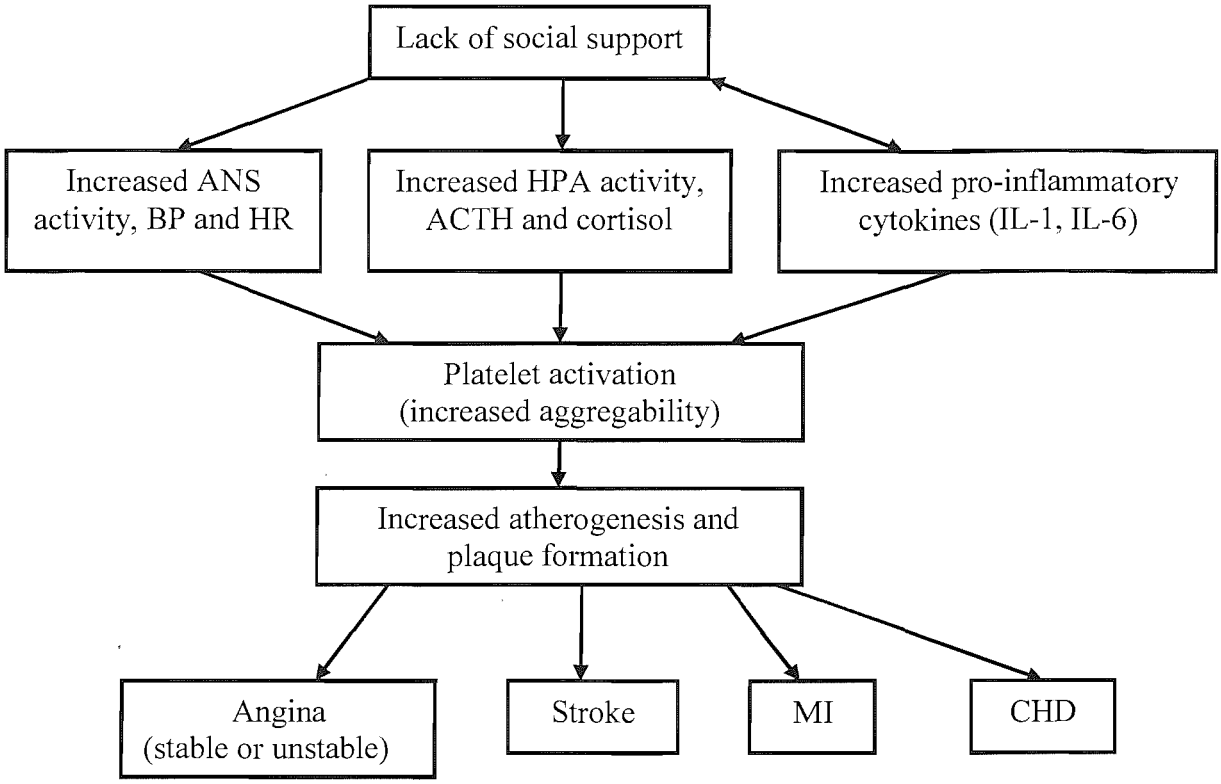


Figure 9. Proposed physiological mechanisms, and pathways linking lack of social support or social isolation and atherogenesis (and related outcomes). (Markovitz & Matthews, 1991).

Based on the findings of this study, the IAT-L (M) was found to be an effective tool in predicting cardiovascular stress responses and may also be useful in predicting other physiological outcomes.

6.6 Conclusion

The present study adapted a modified implicit measure of loneliness, and used it alongside the measures of explicit loneliness and social support, to investigate their correlations with CVR to laboratory psychosocial stress. In the literature, self-reported or explicit loneliness and social support have been inconsistently associated with CVR to stress. Functional support indices of social support were significantly correlated with CVR reactivity to stress in the present sample. As speculated implicit, but not explicit, loneliness was significantly correlated with CVR after one of the stressors. No associations were found between structural support and CVR indices. The IAT-L (M) showed more satisfactory internal consistency than the IAT-

L which was discussed in Study 1, and satisfactory incremental validity. The next study will include this modified tool to investigate the main research question of this thesis, along with other explicit measures of social support and loneliness.

Chapter Seven: Study Three - Social Support, Loneliness and Disease Markers in Colorectal Cancer

7.1 Aims of the Chapter

This chapter includes an account of the physiological aspects of colorectal cancer, and a study which aims to investigate whether social support and loneliness are associated with several markers of disease severity in colorectal cancer. The present study also aims to improve past methodologies in psychosocial oncology by using both explicit and implicit measures of loneliness, and biological markers measured at tumour site (in situ).

7.2 Introduction

7.2.1 Colorectal Cancer

Colorectal cancer is the cancer of the large bowel (also collectively known as colon and rectum). The anatomic distribution of the large bowel can be divided into the caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon and the rectum. The parts of the colon upto the mid-transversum are considered the right-sided or proximal colon, whereas the parts of the colon after the mid-transversum are included in the left-sided or distal colon (see Figure 10).

7.2.2 Epidemiology

In terms of incidence, cancers of the colon and rectum comprise the third most frequent type of malignancy worldwide in both sexes, with two-thirds occurring in developed countries, where colorectal cancer incidence ranks second only to lung cancer. The five-year survival ranges from 45 per cent to 60 per cent, and the variation between developed and developing countries is not particularly large (Parkin & Bray, 2006).

In the UK, colorectal cancer is the third most common cancer after breast and lung cancers. In 2003, 35,006 new cases were registered in the UK, two-thirds (21,617) of which were in the colon and one-third (13,389) in the rectum. The distribution of cases throughout the large bowel varies. The left side of the bowel is affected by cancer more often than the right: tumours in the sigmoid colon, rectosigmoid junction and the rectum together account for over half of all cases (see Figure 10). The five-year relative survival rates for both male and female colon and rectal cancer have doubled between the early 1970s and the late 1990s (Cancer Research UK, 2007b).

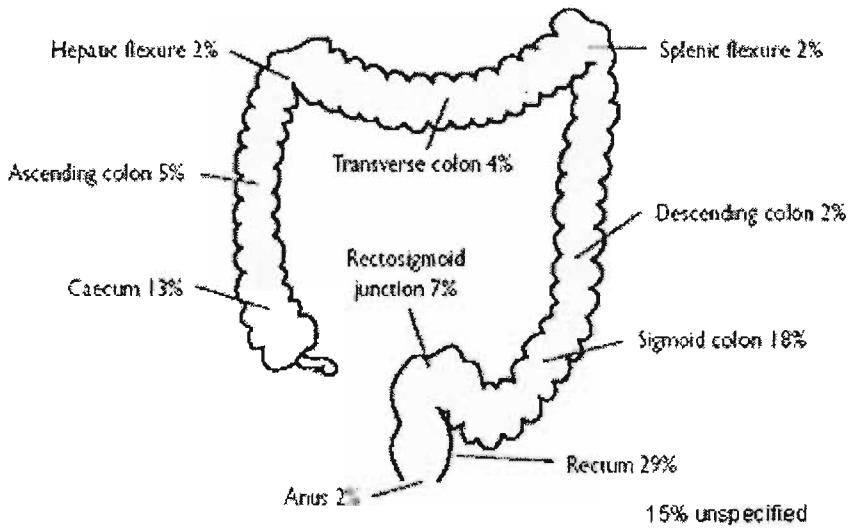


Figure 10. Percentage distribution of cases of colorectal cancer by site (1997 - 2000) (Cancer Research UK, 2007b).

7.2.3 Aetiology of Colorectal Cancer and Risk Factors

Colorectal cancer is believed to be more of an environmental disease with a wide range of factors involved in its aetiology. These environmental factors include cultural and lifestyle practices. Studies on ethnic and racial differences in colorectal cancer suggest that environmental factors such as urbanisation play a major role in the aetiology of this disease (Neagoe, Molnar, Acalovschi, Seicean, & Serban, 2004). Studies on migrants support these findings. For instance, Israeli males born in Europe or the USA are at higher risk of colon cancer than those born in Africa or

Asia. Similarly, risk in the younger generations of Japanese populations who have migrated to the USA has changed: the rate of incidence of colorectal cancer now approaches or surpasses that in white people in the same population and is 3-4 times higher than among the Japanese in Japan (Boyle & Langman, 2000).

A brief account of the major risk factors for developing colorectal cancer is given below:

7.2.3.1 Diet.

Westernised diets containing high proportions of meat and animal fat but little fibre have been associated with an increased risk of colorectal cancer (Willett, Stampfer, Colditz, Rosner, & Speizer, 1990), which explains the high incidence of this disease in North America, Western Europe and Australia. This implies the significance of dietary and environmental risk factors. Research indicates that a high intake of preserved meat particularly red meat increases the risk for colorectal cancer. The intake of fruits and vegetables reduces the risk for several cancers including colorectal cancer, and it is recommended that diets include at least 400 gm/day of total fruits and vegetables (Key et al., 2004).

7.2.3.2 Physical activity, cigarette smoking and alcohol consumption.

Studies show that people who regularly undertake vigorous physical activities have a lower incidence of colorectal cancer. It has been estimated that 12-14 per cent of colon cancer could be attributed to lack of frequent involvement in physical activities (Slattery, 2004). This is due to the fact that physical activity shortens the transit time of excrement in the intestine and reduces the contact between intestinal mucosa and carcinogens which may be present in the food. Some evidence from longitudinal studies also showed an inverse relationship between social support from family and physical activity (Dowda, Dishman, Pfeiffer, & Pate, 2007), suggesting that social support may play a role in way people initiate and maintain the patterns of physical activity.

There is some evidence that high alcohol consumption increases the risk for colorectal cancer (Souhami & Tobias, 1998). However, some studies failed to find supporting evidence for it (e.g., Chen, Qiu, Zhang, & Zhao, 2003). A recent meta-analysis suggested that the evidence for cigarette smoking as a risk factor is not significantly strong (Chen et al.).

7.2.3.3 Family history.

Approximately 80 per cent of colorectal cancers are sporadic or occur in individuals with no known predisposition to the disease. The rest arise in patients with a family history of colorectal cancer or polyps, previous colorectal cancer, or a predisposing condition such as inflammatory bowel disease. First-degree relatives (parent, sibling or off-spring) of colorectal cancer patients are the largest group of individuals at increased risk of colorectal cancer (Gili, Roca, Ferrer, Obrador, & Cabeza, 2006). However, patients with a family history of colorectal cancer in one or more first-degree relatives, but with no defined genetic syndrome, may account for 10-15 per cent of incidence (Dorudi & Williams, 2000).

7.2.4 Symptoms and Screening of Colorectal Cancer

Despite some common symptoms, in most cases the symptoms of colorectal cancer vary according to site. An account of the symptoms and percentage of their prevalence according to site is shown in Table 13.

Table 13. Symptoms and percentage of their prevalence according to site in colorectal cancer.

Right-sided lesions of colon	Left-sided lesions of colon	Lesions of rectum
Pain 80%	Pain 60%	Pain 5%
Mass 70%	Mass 40%	Mass 0%
Rectal bleeding 20%	Bleeding 20%	Bleeding 60%
Diarrhoea + change in bowel habit 40%	Change in bowel habit 60%	Change in bowel habit 80%
Weight loss 50%	Weight loss 15%	Weight loss 25%
Vomiting 30%	Vomiting 10%	Vomiting 0%
Obstruction 5%	Obstruction 20%	Obstruction 5%

Note. From Souhami and Tobias (1998).

Colorectal examination is the most important procedure for diagnosing these tumours and can be performed by the following procedures:

7.2.4.1 Faecal occult blood test.

The faecal occult blood test is a cheap test which aims to detect early asymptomatic cancers. It is based on the premise that such cancers will bleed and the blood will be detectable chemically or immunologically in the stool. Since some tumours tend to bleed later in their formation, some early cancers may be missed, which warrants frequent tests and/or other methods of testing. Also, since tumour bleeding may not occur and/or may be intermittent, 40 per cent of cancers may be missed by relying on this test only (Hobbs, 2000).

7.2.4.2 Barium enema.

A barium enema is carried out using a special type of X-ray to examine the large bowel. This procedure has a role in confirming suspected lesions. However, it requires bowel preparation and is uncomfortable (Burgess, 2005).

7.2.4.3 Flexible sigmoidoscopy.

Flexible sigmoidoscopy is the visual examination of the inside of the rectum and sigmoid colon, using a lighted, flexible tube connected to an eyepiece or video

screen for viewing. It allows examination of upto the distal 25 cm of the large bowel, and the majority of rectal tumours can be diagnosed by this procedure as three-quarters of all rectal lesions are within its reach. However, due to the difficulties with access, only about 65 per cent of pre-malignant early tumours can be detected by this procedure (Nicum, Midgley, & Kerr, 2003).

7.2.4.4 Colonoscopy.

Colonoscopy allows increased sensitivity in direct visualisation of the entire colon as far as the caecum and is used for accurate preoperative diagnosis of the majority of large bowel cancers. Its use can be substituted by barium enema examinations which are easier and less expensive. However, on the right side of the colon, particularly in the caecum, the tumour may not be easily detected by barium enema therefore colonoscopy is usually recommended (Souhami & Tobias, 1998).

7.2.5 Staging of Colorectal Cancer

The biological behaviour of and prognosis in colorectal cancer depends on the degree of penetration of the cancer through the bowel wall, the presence or absence of lymphatic dissemination, and the presence or absence of systemic metastases. Staging systems are also based on these above-mentioned characteristics of cancer. Dukes staging system which is commonly used in the UK is shown in Table 14.

Table 14. Dukes staging system.

Stage	Description
A	Carcinoma limited to the bowel wall
B	Local spread of cancer beyond the bowel wall, but no involvement of lymph nodes
C1	Lymph node involvement - local nodes only
C2	Lymph node involvement - apical nodes
D	Distant metastases present

Note. From Balfe and Semin (1998).

7.2.6 Treatment of Colorectal Cancer

7.2.6.1 Surgical procedures.

Surgical removal of the tumour is the main form of treatment and approximately 80 per cent of patients undergo one of the following surgical procedures (Biddles, 2005):

Colon cancer.

(1) Right hemicolectomy. Carcinoma of the caecum or right side of the colon is usually managed by this procedure, which removes part of (or completely which is called extended right hemicolectomy) the transverse colon and the ascending colon.

(2) Left hemicolectomy. Carcinoma of the descending colon is usually managed by the removal of part of the transverse colon and the descending colon.

(3) Abdomino-perineal (AP) resection. Removal of ascending colon and caecum.

(4) Sigmoid colectomy. Carcinoma of the sigmoid colon is occasionally managed by sigmoid colectomy with the removal of sigmoid colon, although more frequently anterior resection or left hemicolectomy is the surgical option of choice.

Rectal cancer.

(1) Anterior resection. Excision of at least part of the rectum and the sigmoid colon.

(2) Low anterior resection. Excision of the sigmoid colon and whole rectum.

7.2.6.2 Chemotherapy and radiotherapy.

Post-surgery colon cancer patients are regularly given a six-month course of intravenous chemotherapy. Chemotherapy is made available to patients following surgery for Dukes C if they are well enough to tolerate it; patients with metastatic or locally inoperable primary cancer (Dukes D) require careful evaluation, and may be appropriate for palliative chemotherapy and/or radiotherapy. Whether to use

chemotherapy in Dukes B tumours is frequently discussed between patients and their oncologists.

The benefits for adjuvant chemotherapy for rectal cancer patients are less clear. Pre-surgery combined radiotherapy and chemotherapy (also called neoadjuvant therapy) reduce the chance of recurrence of rectal cancer, and improve the overall survival. For patients with advanced disease the median survival is around six months and chemotherapy can improve median survival by three to four months (Simmonds, 2000).

7.2.7 Social Support and Colorectal Cancer

This section summarises the findings of the studies on colorectal cancer and those which combined various cancers including the cancers of the colon and rectum. Despite the high prevalence of colorectal cancer, relatively few studies have examined psychosocial issues in this cancer compared to other types of cancer. In addition to disease onset, severity and progression, other outcomes in colorectal cancer such as screening attendance and QoL have been investigated in a few studies with reference to social support and/or loneliness. Social support has been found to be a significant factor which contributes to adherence to cancer screening programmes for colorectal cancer (Sewitch, Leffondre, & Dobkin, 2004). However, the literature on attendance to screening is divided on the significance of structural versus functional support indices of social support. For example, Honda and Kagawa-Singer (2006) found that emotional support from family and friends, but not the size of the network, was significantly associated with screening attendance. In a study on psychosocial determinants of adherence to a colorectal cancer screening programme, Gili et al. (2006) found that people who showed adherence perceived significantly higher levels of listening, affective and material support, and also reported greater satisfaction with the social support given. Analysis of the groups of adherers and nonadherers also revealed that the former group perceived a significantly greater level of social support particularly from friends, work colleagues and health professionals. In contrast, Kinney, Bloor, Martin, and Sandler (2005) found that, compared with those with the fewest social connections, those who were most socially connected were more likely to report recent use of colorectal cancer

screening in North Carolina, USA. Neither emotional (e.g., offering reassurance that one is cared for) nor instrumental (e.g., giving material assistance) support was associated with screening behaviour, suggesting that structural rather than functional aspects of social support may be important in influencing colorectal cancer screening behaviour.

Some studies on the psychosocial aspects of colorectal cancer revealed that social networks and social support may have an important relation with both QoL and health-related quality of life (HRQoL). Sapp et al. (2003) found that structural support indices including network size, number and frequency of social ties, and overall social connectedness was positively correlated with mental health status which was assessed as part of HRQoL, after controlling for age, extent of disease at diagnosis, comorbidities, body mass and education. In another study on structural and functional aspects of social support and HRQoL in patients with colorectal cancer, Sultan et al. (2004) found that functional support, but not social integration (assessed as in Sapp et al.), was significantly associated with HRQoL. Specifically, the availability of emotional and instrumental support was associated with a mental composite score, while only instrumental support was correlated with a physical composite score.

In a systematic review of the studies on QoL and colorectal cancer, Dunn and colleagues (2003) reviewed 41 studies and concluded that the literature was inconsistent in relation to the determinants of QoL experienced by colorectal cancer patients. They highlighted a need for large-scale, population-based studies in this area.

Two important studies have investigated the role of social relationships and survival in colorectal cancer. Villingshoj et al. (2006) studied marital status, and frequency of contact with the people in the social network before and after the surgery to measure their correlation with survival in 770 Danish colorectal cancer patients. In this 11-year follow-up study, they found a significantly higher mortality rate among those who had lost their partner before the operation compared to patients cohabiting with the same partner as before the operation. Contrary to expectations, they also found significantly higher mortality among patients reporting increased

frequency of contact with their children compared to patients reporting unchanged contact frequency, after adjusting for sex, age, stage, recurrence and comorbidity at diagnosis. A low physical functioning score and deteriorating physical health over the follow-up period might have confounded these findings. Ell et al. (1992) found no significant evidence for the relationship between social integration and perceived adequacy of emotional support, and survival in colorectal and lung cancers. These findings were adjusted for stage and functional status. It is important however to note that lung cancer is a more aggressive cancer having a poorer prognosis as compared to colorectal cancer, and any beneficial effect of social support in colorectal cancer survival could have been masked since the analyses combined both cancers.

Courtney, Longnecker, and Peters (1996) investigated psychosocial aspects of work and the risk of colon cancer in a large population-based case-control study in Los Angeles, USA. They concentrated on job stress (defined in terms of perceived job demand and job control), social support at work, and the risk of colon cancer. Results showed that participants with low job control had a slightly increased risk. However, this effect was independent of job demand. Lower levels of job social support were associated with a decreased risk. These findings suggest that some aspects of job stress may determine the onset of colon cancer. The possible role of social support at work as a moderator in this relationship between job stress and cancer risk was not explored in this study. Another study investigated the role of structural support in colorectal, breast and prostate cancers, and found no significant correlation with survival in a 10-year follow-up (Goodwin et al., 1996).

Little research has been done on social support and stage or severity of colorectal cancer at diagnosis. A study by Kinney and colleagues (2003) on the role of religious involvement and social support in the risk of colon cancer among blacks and whites, studied the stage at diagnosis as an outcome variable. They found that minimal emotional support was strongly associated with the odds ratio for having colon cancer, and with both local and advanced disease stage at diagnosis among blacks, compared to greater emotional support. These results were found after controlling for suspected colon cancer risk factors and other potential confounders (e.g., race, family history of colorectal cancer and physical activity). However, no such associations were found among whites.

Unmarried people (marital status as a proxy measure of network support) were more likely to be diagnosed at more advanced stages of the disease in cancers of breast, prostate and colorectum (Goodwin et al., 1987). Kinney et al. (2003) found modest associations of structural support indices such as not being married versus living as married and smallest network sizes with later stages of colon cancer in both black and white patients. They also found that low emotional support was strongly associated with both local and distant stages of the disease in blacks only. It is important to note however that patient delay i.e., the time interval between symptom onset and their presentation to doctors, has neither been considered nor controlled for in these studies. Patient delay may prove to be an important factor in the link between social support and severity of cancer as it has been associated with disease stage in different types of cancer including cancers of colon and rectum. Young et al. (2000) found that patients with delay were less likely to have a stage A tumour at diagnosis. Patient delay has also been associated with demographic factors such as gender. Young et al. found that male colorectal cancer patients are more likely to delay seeking medical help than females and hence are less likely to have an early-stage disease at diagnosis.

Andersen and Cacioppo (1995) presented the following components of delay for physical illnesses: appraisal delay (time between the first detection of an unexplained symptom and inference of illness), illness delay (time between appraisal and making a choice to seek medical help), behavioural delay (time between the decision to seek help and the act of making an appointment), scheduling delay (time between making of an appointment and the first medical consultation), and treatment delay (time between first medical consultation and the beginning of the treatment). Studies have identified determinants of seeking medical help for several health complaints. However, these studies did not distinguish between various stages of delay. It is believed that there are different sets of reasons behind each of these stages. Social factors including a lack of social support and being unmarried have been thought to be associated with the initial stages of delay in seeking medical help. However, a systematic review of the evidence on the factors predicting delayed presentation of breast cancer did not find sufficient evidence for the role of social support (Ramirez et al., 1999). They found strong evidence for older age and fewer

years of education playing a role in this delay. Also, strong evidence supported that being unmarried was unrelated to delays.

A Danish interventional study (Ross, Thomsen, Karlsen, Boesen, & Johansen, 2005) aimed to improve the well-being of colorectal cancer patients undergoing surgery and randomly assigned 249 patients to either a control or an interventional group. The interventional group was designed to provide support to the patients. The latter received 10 home visits carried out by a project nurse or medical doctor during the first two years after discharge. The patients in the intervention group were visited in their homes five times during the first 2-3 months and visits were repeated approximately 4, 7, 11, 16 and 24 months after discharge. Results showed no significant effect of intervention on the well-being of patients. However, the authors recommended testing the effect of shorter but intensive interventions carried out by trained therapists. Northouse, Mood, Templin, Mellon, and George (2000) recommended family-focused intervention for colon cancer patients during the first year following surgery, in order to identify couples at greater risk of poorer adjustment such as patients and spouses who have higher levels of stress and low social support. A qualitative study explored patient perspectives on the disease and found that important needs of patients include informational and overall social support, for which patients usually rely on cancer specialists, general practitioners, family and friends respectively (Sahay, Gray, & Fitch, 2000).

In conclusion, most of the studies on the psychosocial aspects of colorectal cancer included patients with more than one type of cancer. Only a few population-based studies on social support and disease severity in colorectal cancer have been conducted. Therefore, the scarcity of conclusive findings in this cancer warrants further research.

7.2.7.1 Social support and mood.

Research has shown that social support may be an important moderator in the relationship between mood and physical symptoms in cancers other than colorectal cancer (e.g., Lee, Yae Chung, Boog Park, & Hong Chun, 2004). Due to limited research on colorectal cancer, no evidence is available on these relations in this

cancer. However, negative mood and emotional distress have been correlated with low social support and conflictual social interactions among physically ill populations, in general. It has been suggested that conflictual social interactions and social isolation may aggravate each other, and result in psychological distress (Fleishman et al., 2000; Trunzo & Pinto, 2003). Loucks (1980) found that lonely people differed significantly from those who were not lonely on mood. In elderly population, Holmen, Ericsson, & Winblad (1999) reported loneliness having a negative influence on the state of mood. Therefore, mood will be assessed in the present study, in order to investigate its relationship with social support, loneliness and disease markers in colorectal cancer.

After summarising the evidence and issues related to the psychosocial aspects of colorectal cancer, the following section will provide supporting evidence for: (1) a number of disease markers which are important with reference to colorectal cancer, and (2) a potential link between social support and these disease markers in cancer. This evidence will explain how social support (or a lack of it) may be theoretically associated with the levels of several disease markers in colorectal cancer.

7.2.8 Social Support and Disease Markers in Colorectal Cancer

7.2.8.1 Disease stage, tumour size and carcinoembryonic antigen.

Carcinoembryonic antigen (CEA) refers to one of the families of glycoproteins produced by many epithelial tumours. It is produced by normal colonic epithelium but is not usually present in the blood unless there is inflammation or cancer involving the epithelium. CEA has been found to predict progression of colorectal cancer (Kama et al., 2003) and severity of tumour penetration. Indeed, its levels are higher in Dukes C and D than in patients with Dukes A and B (Walach, Guterman, Zaidman, Kaufman, & Scharf, 1991). Some clinical research shows that CEA sensitivity presents a statistically significant difference between stage IV (TNM classification; equivalent to Dukes D) and stages I, II and III (equivalent to Dukes A, B, C1, C2) colorectal tumour (Fernandes, Kim, & Matos, 2005), thus it may particularly serve to distinguish severe from less severe tumours. There is also a positive correlation of CEA with VEGF (proangiogenic cytokine), tumour size and

grading (peritumoral vascular invasion). Diagnostic sensitivity of VEGF for colorectal cancer is higher than CEA. However, sensitivity to predict colorectal cancer severity is higher when combining both CEA and VEGF (Celen, Kahraman, Yildirim, Berberoglu, 2004).

It has been previously cited in this chapter that some of the indices of social support may be associated with cancer stage at diagnosis, in certain populations. However, owing to limited research on this type of cancer which also includes studies which combined several types of cancer, the findings have been inconclusive. To the best of my knowledge, no previous research has been done on the relationship between psychosocial factors, and tumour size and CEA in colorectal cancer.

7.2.8.2 Cytokines.

VEGF.

VEGF is thought to be the most potent angiogenic factor in cancers (Paley et al., 1997) and its higher plasma levels have been associated with cancer severity in colorectal cancer (Nakayama et al., 2002). The immunohistochemical expression of VEGF in tumour tissues has been reported to be an independent prognostic factor (Hu et al., 2007). Minagawa et al. (2002) investigated the correlation between the plasma level and immunohistochemical expression of VEGF in 31 patients with colorectal cancer. They measured the preoperative plasma levels of VEGF and immunostained the resected specimens for VEGF. The plasma levels significantly correlated with the immunohistochemical expression of VEGF and liver metastasis. The immunohistochemical expression was significantly associated with lymph node metastasis and disease stage. These findings suggest that plasma level of VEGF is a good predictor of its immunohistochemical expression in patients with advanced colorectal cancer.

Plasma levels of VEGF have also been associated with psychosocial factors in cancer patients (e.g., Lutgendorf et al., 2002) as discussed in Chapter 4. These findings have also been replicated in colorectal cancer with reference to depression, anxiety and mood (Sharma et al., 2007).

IL-6.

IL-6 is another proinflammatory cytokine which is associated with poor prognosis and with psychosocial factors in cancer patients, in previous studies (e.g., Costanzo et al., 2005). In these studies the levels of IL-6 were determined in blood serum or plasma. However, there is evidence that high values of IL-6 in serum are associated with positive immunohistochemical staining in the cytoplasm of cancer cells in colorectal cancer (Ashizawa et al., 2006).

TNF-α.

TNF-α is a pleiotrophic inflammatory cytokine (Carswell et al., 1975) which has been associated with psychosocial factors in cancer (e.g., Marucha et al.; Wu et al., 2001). TNF-α has been found to be involved in causing apoptotic cell death, cellular proliferation, inflammation and tumorigenesis. On the contrary, some evidence suggests that TNF-α level is inversely correlated with tumour proliferation in colorectal cancer (Evans et al., 2006). Therefore, this cytokine can be cytotoxic to tumour cells and can also induce tumour regression, indicating its role as a *double-edged sword* (Aggarwal, 2003).

7.2.8.3 Oxytocin.

The expression of oxytocin and its receptors in the human gut has been recently detected by a Swedish group of researchers (Monstein, Grahn, Truedsson, & Ohlsson, 2004). Although there have been inconsistent findings in different species, these recent observations found mRNA for oxytocin receptors throughout the human gastrointestinal (GI) tract. Similar to its significant role in milk ejection reflex and parturition, oxytocin also contributes to the control of the GI motility, where it has been shown to be secreted in response to endogenous (after a fatty meal), and exogenous cholecystokinin (CCK) in women (Ohlsson, Rehfeld, & Forsling, 2004). Oxytocin acts as a relaxant for the ileum and caecum, while it has a contracting effect on the colon (Bisset & Lewis, 1962). Its intravenous infusion has shown to have increased colonic peristalsis and accelerated gastric emptying, whereas an

oxytocin receptor antagonist delays the gastric emptying (Ohlsson, Ringstrom, Abrahamsson, Simren, & Bjornsson, 2004).

The evidence discussed in Chapter 4 suggests that oxytocin is also associated with social bonding and plays an anti-proliferative role in cancer. This role in regulating cell proliferation, as well as the widespread expression of oxytocin receptors in neoplastic tissues of different origin, open new perspectives on the biological role of the oxytocin-oxytocin receptor system in cancer (Cassoni, Sapino, Marrocco, Chini, & Bussolati, 2004). Neoplastic oxytocin receptor expression has been found in cancers including endometrial and ovarian (Mechsner et al., 2005), small-cell lung, non small-cell lung (Pequeux, Breton, Hagelstein, Geenen, & Legros, 2005) and prostate cancers (Whittington et al., 2007). It has been shown that the oxytocin receptor is activated and acts as a mediator of the growth regulating effect of oxytocin in cancer cells (Kimura, Tanizawa, Mori, Brownstein, & Okayama, 1992). In in vitro studies where oxytocin inhibited the proliferation of neoplastic cells of either epithelial (mammary and endometrial), nervous or bone origin, all neoplastic cells expressed oxytocin receptors. This is in line with the hypothesis that the receptor mediates the growth regulatory effects of oxytocin in tumours (Cassoni et al., 2004).

Another study confirmed this hypothesis by showing an inhibiting, dose-dependent effect of oxytocin on the proliferation of a prostate cancer cell line (which does not synthesise oxytocin) in vitro exerted through specific oxytocin receptor (Cassoni et al., 2004). They observed a significant inhibition of cell proliferation when cancer cell lines were treated with oxytocin, while co-incubation with the oxytocin antagonist abolished such an effect. These findings showed the functionality of the oxytocin receptor, suggesting its biological effect on cell proliferation which became evident following oxytocin addition in the culture medium, inhibiting the neoplastic cell growth. Whittington, Assinder, Gould, and Nicholson (2004) conducted an immunohistochemical detection study of oxytocin and oxytocin receptors in tissues from patients undergoing prostectomy, and in normal human prostate epithelial and stromal cell lines. They found that oxytocin and oxytocin receptors were present both in normal and neoplastic cells. However, less immunoreactivity was found in the malignant cells as compared to benign

prostate hyperplasia, suggesting that expression of oxytocin and its receptors are reduced with tumour progression and may provide a marker for invasive disease.

A very limited amount of research has been carried out on oxytocin and disease severity in colorectal cancer. Considering the above evidence and its links with social bonding and its down-regulatory effect on HPA axis, it may be speculated that the levels of oxytocin, which may fluctuate as a function of social interactions (Turner et al., 1999), may mediate the possible relationship between social support and severity of colorectal cancer. Therefore, the present study will include the measurement of the expression of oxytocin receptors in tumour cells as an indictor of the anti-proliferative function of oxytocin in colorectal cancer and as a correlate of social support. Due to the fact that the pattern of oxytocin receptor staining by immunohistochemical procedures[23] (assessing protein level) has been found to be identical to that observed by in situ hybridisation analysis[24] (assessing mRNA level) (Cassoni et al., 2004), the former procedure will be adopted in the present study.

7.3 Aims and Significance of this Study

A high prevalence of colorectal cancer has been reported in the UK, where cancers of the colon and rectum are the third most common cancers after those of breast and lung (Cancer Research UK, 2007b). Despite its high prevalence, fewer studies have been done on the psychosocial aspects of colorectal cancer as compared to other types of cancer. The studies reviewed in Chapter 3 included only three studies on colorectal cancer (Ell et al., 1992; Goodwin et al., 1996; Villingshoj et al., 2006), one of which recruited colorectal cancer patients (Villingshoj et al., 2006) while the other two had patients with mixed cancers.

The role of the biological markers (VEGF, IL-6, TNF-α and oxytocin receptors) in the possible link between (lack of) social support and colorectal cancer severity has not been examined, nor has the specific role of oxytocin in this link been

[23] A set of procedures for identifying cellular or tissue constituents (antigens) by means of antigen-antibody interactions (a detailed account is given in the Method Section).
[24] This technique allows the demonstration of specific nucleic acid sequences (genes) in their cellular environment.

investigated in any cancer. Identifying these biological markers in this study may contribute to the scientific basis for planning targeted immunotherapeutic interventions in socially-isolated cancer patients. To the best of my knowledge, the immunohistochemical staining for these biological markers has not been studied with reference to psychosocial factors in humans.

The important factors of patient delay (time interval between symptom onset and their presentation to a doctor) and doctor-related delay (time interval between initial presentation and beginning of the treatment) will also be determined and analysed with reference to psychosocial, and disease severity variables in this study.

Finally, all research in psycho-oncology has been based on explicit self-report measures of social support and loneliness. In contrast to explicit measures, implicit measures provide indirect assessment of constructs, which is less affected by presentational biases (Fazio & Olson, 2003). As discussed in Chapters 2 and shown in Chapter 6, implicit measures are more strongly correlated with physiological parameters than the explicit self-reported measures of the same construct (also supported by Egloff et al., 2002; Phelps et al., 2000). Since different aspects of social support may predict different disease outcomes such as incidence or onset, severity, progression, recurrence, etc., future research in psycho-oncology may also wish to use explicit and implicit measures of psychosocial factors in order to increase the ability to predict such outcomes. The present study therefore will include an implicit measure of loneliness alongside the explicit measures of loneliness and social support.

To summarise, the present study will address the relationship between social support and loneliness, using explicit and implicit measures, and severity of colorectal cancer, as assessed by disease markers including the following: cancer stage, tumour size, lymph node status, CEA, and four important biological markers previously related to social support (VEGF, IL-6, TNF-α and oxytocin receptors[25]).

[25] Oxytocin receptors will be referred to as oxytocin in this thesis.

7.3.1 Hypotheses

The following hypotheses will be tested in this study, and include the main research questions of this study which are on the relationship between social support and disease markers (see Set 3 below). Set 2 of the hypotheses aim at validating the implicit test of loneliness (IAT-L (M)). The rest of the hypotheses aim to confirm previous findings on the relationships between variables (Sets 1, 4 and 5).

Set 1: Relationships among disease markers.

Based on the literature discussed earlier, higher plasma levels of CEA, VEGF and IL-6 may be found in Dukes C and D patients than in patients with Dukes A and B. It has also been suggested in Chapter 4 and earlier in the current chapter that oxytocin plays an anti-proliferative role in cancer, while TNF-α acts towards both tissue destructive reactions and recovery. However, since relations regarding the expression of oxytocin receptors and TNF-α, and stage have not been previously assessed in colorectal tumour tissues, this study will attempt to test the validity of the immunohistochemical analyses to measure their in situ levels and their relationship with disease stage in colorectal cancer. Specifically, I hypothesise that:

(1) CEA, and the levels of VEGF, IL-6, TNF-α and oxytocin will explain a significant percentage of the variance in Dukes stage (A and B versus C and D). Oxytocin will be inversely related to disease severity, while CEA, VEGF and IL-6 will have positive relations with disease severity. Due to the dual properties of TNF-α, the direction of its relationship with disease severity is not predicted.

Set 2: Relationships among the measures of social support, marital status and mood.

Based on previous studies, it is expected that married patients will show higher levels of structural and functional support than single and divorced/widowed patients. The concurrent and construct validity of the IAT-L (M) in this study will be

established by testing its correlations with explicit loneliness, and social support and mood respectively. Therefore, it is hypothesised that:

(1) Implicit loneliness will have a small to moderate inverse correlation with positive affect and a positive correlation with negative affect.
(2) Implicit loneliness will have a small positive correlation with explicit loneliness, and a small inverse correlation with structural and functional indices of social support. The correlations will be expected to be small due to social desirability and presentational biases associated with explicit measurement.

Set 3: Relationships between social support and disease markers.

This set represents the key research questions and hypotheses for this study. On the basis of the findings of the systematic review on cancer progression reported in Chapter 3, it may be concluded that both structural and functional support indices of social support are prospectively associated with slower disease progression and increased survival in cancer, and possibly with a less severe illness. Therefore, the following hypothesis will be tested to explore if this relationship exists cross-sectionally in the current sample of colorectal cancer patients:

(1) Patients with more advanced disease and positive lymph node status will have lower structural and functional support than patients with lower disease stage and negative lymph node status.

Previous studies have investigated the relationship between serum or plasma levels of biological markers and social support indices (as discussed in Chapter 4). The present study aims to extend these findings by exploring this relationship in tumour tissues in colorectal cancer. The following relevant hypotheses will be tested:

(2) Patients with higher structural and functional support will have lower levels of VEGF and IL-6 than patients with lower support.
(3) Patients with higher structural and functional support will differ from patients with lower support on the levels of TNF-α.

(4) The indices of social support will positively explain significant variance in the levels of oxytocin.

It has also been discussed in Chapter 2 and shown in Chapter 6 that implicit loneliness may be a better correlate of physiological outcomes than explicit loneliness. Therefore:

(5) Implicit loneliness will explain a greater percentage of the variance in disease stage, lymph node status, and levels of VEGF, IL-6 and TNF-α than explicit loneliness.

Set 4: Relationship between doctor-related delay and disease severity.

(1) Patients with longer doctor-related delay will have more advanced disease and positive lymph node status than patients with shorter doctor-related delay.

Set 5: Relationship between patient delay and social support.

The evidence for the role of social support in patient delay is insufficient. Despite its seemingly important role, social support was not found to be associated with patient delay in some of the important studies. Also, little is known about the sociodemographic factors which may moderate the relationship between social support and patient delay. This study will therefore explore if measuring loneliness (or lack of social support) by the IAT-L (M) predicts the differences in patient delay in colorectal cancer patients, as a function of loneliness. Also, whether sociodemographic factors (age, gender and education) moderate this relationship.

7.4 Method

7.4.1 Patients and Procedure

Patients with a confirmed diagnosis of colorectal cancer were initially approached by the researcher[26] on their visit to Southampton General Hospital (Southampton University Hospitals Trust) where they were attending the pre-assessment clinic for the pre-surgery tests. This visit was routinely made once 1-2 weeks prior to the surgical treatment for colorectal cancer.

The inclusion criteria for this study were as follows: patients diagnosed with colorectal cancer, undergoing surgery for colorectal cancer, who have not received chemotherapy and/or radiotherapy and who had no known psychiatric conditions (confirmed by their medical notes). Patients who met these criteria were identified from the list at the clinic with the help of the colorectal nurse specialist and were given the information about the study (see Appendix P for patient information sheet). This information included the contact details of the researcher. Patients were encouraged to contact the researcher if they wished to ask any questions regarding the study.

They were finally approached by the researcher to consent to take part in the study after 1-2 weeks in the ward where they were admitted 1-2 days before the surgery. They were given an opportunity to ask questions and were eligible for taking part in the study only if they provided informed consent (see Appendix Q for consent form).

Eighty-eight of 91 eligible patients were approached. The surgery for two patients was cancelled due to comorbid conditions (chest pains) and one was directly taken into surgery without the routine 1-2 days stay on the ward. Fifty-one (58 per cent) of the 88 eligible patients agreed to participate. The reasons for refusal included tiredness, stress, or preoccupation with their imminent surgery. These patients were undergoing any one of the surgical procedures mentioned in the section on Treatment of Colorectal Cancer earlier in this chapter.

[26] Myself.

This study was approved by Southampton and South West Hampshire Research Ethics Committee (reference number: 05/Q1702/31), and was carried out between 01.11.2005 and 30.04.2007.

7.4.2 Measures

The following measures were conducted in a private cubicle/room on the ward and took a maximum time of 35-40 minutes:

7.4.2.1 Information on sociodemographic factors and life-style habits.

Information was sought on the following (see Appendix R for sociodemographic information and life-style habits sheet):

Age.

Measured in years.

Gender.

Male scored as 1, female scored as 2.

Marital status.

Divorced/widowed, single and married/living as married scored as 1, 2 and 3, respectively.

Education.

Below GCSE, GCSE/O level and A level scored as 1, and vocational qualification or degree and higher degree scored as 2.

Socioeconomic status.

Subjective social status was assessed using the MacArthur Scale of Subjective Social Status (Adler, Epel, Castellazzo, & Ickovics, 2000) which asks participants to place themselves on a ladder in reference to their community on money, education and jobs. The score ranges between worst off (1) to best off (10) and people place an *X* where see themselves on the ladder. This ladder has been used in several diverse studies with adults, and has been shown to be an extremely powerful determinant of health-related outcomes, even when traditional measures of socioeconomic status are included (e.g., Hu, Adler, Goldman, Weinstein, & Seeman, 2005).

Ethnicity.

Categories included *white*, *black*, *asian*, *other* and *do not wish to answer*.

Dietary habits.

The following questions were included to assess the dietary habits of the patients: (1) are you a vegetarian? *yes* scored as 3 and *no* scored as 1. The following two questions were answered only if the answer to this question was *no*, in order to determine their intake of meat, particularly red meat. (2) do you eat more fruits and vegetables than meat? *yes* scored as 1 and *no* scored as 0. (3) do you eat more white meat than red meat? *yes* scored as 1 and *no* scored as 0. A total score of 3 was scored either by vegetarians or by non-vegetarians with a balanced vegetable/fruit and meat intake. Therefore, a total score of 3 indicates healthier dietary habits than a score of 1 or 2.

Physical exercise.

Physical activity was assessed by the Physical Activity Index (Paffenbarger, Wing, & Hyde, 1978) which is a four-item self-report measure. This measure asks participants to indicate the number of flights climbed, meters/yards walked (the original scale included *blocks* which was replaced by meters/yards in order to make it

easier to comprehend for the participants in the UK), and amount of light and strenuous sports engaged in, during a typical week. The items are weighed to calculate a total score of energy expenditure, such that number of flights is mutiplied by 28, meters by 56, light sports by 300 and strenuous sports by 600.

Smoking.

Yes or *no*.

Family history of colorectal cancer.

Yes or *no* to history of colorectal cancer in first-degree relatives.

Patient delay and doctor-related delay.

Patient delay, computed by the interval between symptom onset and their presentation to a doctor, was assessed by asking the time when they first noticed symptoms and signs related to colorectal cancer e.g., rectal bleeding, change in bowel habits especially without abdominal pain, and the time when they sought medical help i.e., consulted their general practitioner. A score was calculated in months between these two time points.

Doctor-related delay was calculated by adding the delay (in months) due to the medical system i.e., the time between the first consultation with their general practitioner and beginning of the treatment at the hospital.

7.4.2.2 The Arizona Social Support Interview Schedule (ASSIS).

The ASSIS (Barrera, 1980) is a 24-item interview guide for assessing at least four separate indices of social support: available network size, utilised network size, support satisfaction, and support need, as described in Chapters 5 and 6 (see Appendix E).

7.4.2.3 The UCLA Loneliness Scale.

The UCLA Loneliness Scale is a 20-item questionnaire designed to gauge subjective feelings of loneliness (version 3; Russell, 1996). Items are arranged on a 4-point rating scale ranging from *never* to *always* (see Appendix D). The following items are negatively scored: 1, 5, 6, 9, 10, 15, 16, 19 and 20. Higher scores indicated greater degrees of loneliness. Cronbach's alpha reliability of the scale in this sample was .85.

7.4.2.4 The Implicit Association Test-Loneliness (Modified) (IAT-L (M).

IAT-L (M) (Nausheen, Gidron, Gregg, Tissarchondou, & Peveler, 2007) was administered to measure implicit loneliness (see Chapter 6 for a detailed description of this test).

This test showed satisfactory internal consistency and predicted a physiological outcome more strongly than an explicit measure of the same construct (Nausheen et al., 2007). The internal consistency of the IAT-L (M) in this sample was .79.

7.4.2.5 The Positive and Negative Affect Schedule (PANAS) Scales.

The PANAS (Watson, Clark, & Tellegen, 1988) consists of two scales having 20 items in total, assessing two primary dimensions of mood: positive and negative affect (PA and NA). Items are rated according to the way people felt in the *past month* on a 5-point rating scale ranging from *very slightly or not at all* to *extremely* (see Appendix S). Scores for PA and NA items are calculated separately. NA and PA have been correlated with different classes of variables among which health complaints, and social activity and satisfaction respectively, are the most relevant ones in the context of this study.

Cronbach's alpha reliability of PA and NA scales in this sample were .78 and .82, respectively.

7.4.2.6 Cancer stage, tumour size and CEA.

The stage and size (in mm) of cancer were routinely determined (post-surgery) from surgical specimens, and were obtained from patients' medical records. Cancer stage was determined by the commonly used Dukes staging system, using standard dissection procedures in accordance with the minimum dataset for colorectal cancer histopathology reports (The Royal College of Pathologists, 2000).

The pre-surgery levels of CEA were also obtained from patients' medical records.

7.4.2.7 Immunohistochemical analyses of biological markers.

The affinity between antigens and antibodies serves as the basis for the immunohistochemical analyses. Immunohistochemistry is an in situ method allowing antigen detection in tissues through a labelled antibody attachment followed by light microscopy. The antibody-antigen reaction is specific and therefore results in the positive identification of tissue constituents.

(Strept) avidin-biotin method.[27]

It is the most widely used immunohistochemical method which can provide good signal amplification (staining) due to the possible binding of four molecules of biotin to one molecule of (strept) avidin (see Figure 11).

Tumour tissues were initially embedded in paraffin wax. Sections were cut using the microtome and left on the slides in the oven overnight.

A cytomation pen was first used on the bottom and top of the slides to limit the amount of area that the reagents were treating by localising the area of treatment. The following steps were carried out on the slides: treatment with avidin for 15 minutes followed by washing three times for three minutes each with Tris phosphate

[27] These immunohistochemical analyses were done by a trainee cellular pathologist, under the supervision of a consultant pathologist at the department of cellular pathology (Southampton University Hospitals Trust).

buffer (TBS) to remove any excessive avidin, treatment with biotin for 15 minutes followed by washing three times for three minutes each with TBS, treatment for 30 minutes with anti-horse serum to block any endogenous protein, addition of the antibody onto the tissue sections, dilution of antibodies with TBS buffer, overnight incubation of the slides in the fridge. The following day the slides were washed in TBS three times for three minutes each, followed by addition of secondary biotinylated antibody onto the tissue sections, then addition of the avidin-biotin complex (ABC) containing horseradish peroxidase.

Finally, the strength of staining was independently scored by two pathologists according to the following criteria and any discrepancies were adjudicated.

VEGF.

The VEGF staining intensity was scored on cytoplasmic[28] positivity in tumour cells on a 0-3 scale, where 0 = negative, 3 = most positive.

IL-6.

IL-6 was graded positive if more than 30 per cent of the cells[29] in the tumour tissue were positive. Previous studies have used this method to score the intensity of the expression of IL-6 (Kinoshita, Ito, & Miki, 1999).

TNF-α.

TNF-α stains were scored on cytoplasmic[30] positivity in tumour cells on a 0-3 scale, where 0 = negative, 3 = most positive.

[28] VEGF is secreted from, and stains the cytoplasm of epithelial and stromal cells (VEGF product datasheet, 2005).
[29] IL-6 is produced by fibroblasts, activated T cells, activated monocytes, macrophages and endothelial cells (IL-6 product datasheet, 2005).
[30] TNF-α labels the cytoplasm of the macrophages from where it is secreted (TNF-α product datasheet, 2005).

Oxytocin receptor.

Oxytocin receptor staining was scored on cytoplasmic intensity in tumour cells on a 0-3 scale, where 0 = negative, 3 = most positive (Ohlsson, Truedsson, Djerf, & Sundler, 2006).

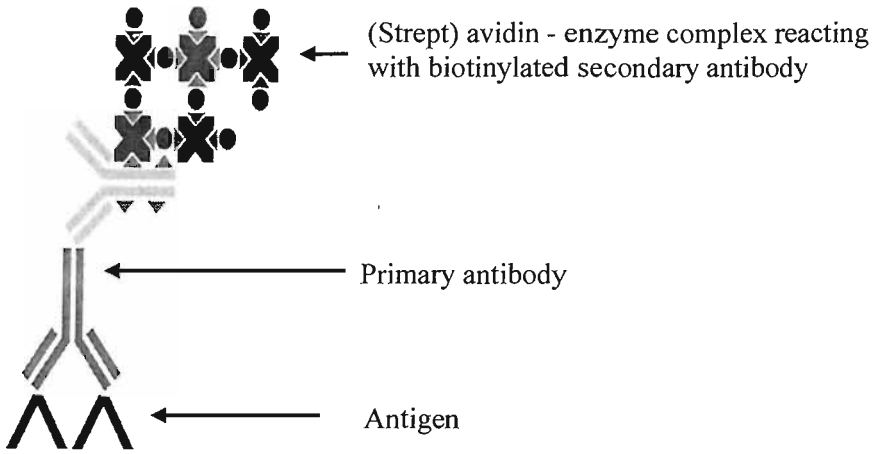


Figure 11. (Strept) avidin-biotin method.

7.4.3 Sample Size Calculations

Since this was the first study which investigated the relationship between social support and in situ levels of four important biological markers, it was difficult to calculate the precise effect size of this relationship. However, a study by Lutgendorf and colleagues (2002) looked at the relationship between social support and plasma levels of one of the biological markers of this study, VEGF. They found that social well-being, as assessed by closeness to and satisfaction with utilisation of emotional support from family/friends/partner, explained 56 per cent of the variance in the levels of VEGF in ovarian cancer patients. This suggested a large effect size of this relationship ($f^2 = .54$) with a sample of 24, including 5 patients with Dukes stages A and B and 19 with stage C or D. Although the statistical analyses included dichotomised outcomes in the present study, on the basis of this finding it may be speculated that this relationship is possibly replicable to the in situ levels of VEGF in the present study with a sample size as small as 24.

Based on the results of Study 2, healthy volunteers had a mean score of 35.14 (SD = 8.21) on the UCLA Loneliness Scale. According to a rough estimate, it may be assumed that cancer patients will have 15 per cent higher levels of loneliness. Therefore, using this effect size, a sample size of 39 patients per group (78 patients in total) should be sufficient to detect a significant association between loneliness and severity or stage of cancer with 80 per cent power and an α level of .05 (two-tailed).

On the basis of the above estimation, a sample size between 24 and 78 should be sufficient for the present study.

7.4.4 Statistical Analyses

Before data analyses began, it was important to test whether the background sociodemographic and biomedical variables were associated with the major outcome variables. This was done so that the significant background variable(s) were controlled for in the subsequent analyses. The background variables were initially selected on the basis of strong supportive evidence in the literature with reference to colorectal cancer. Dietary habits, physical exercise and family history of colorectal cancer were found to be more strongly associated with colorectal cancer incidence than other sociodemographic and biomedical variables (Gili et al., 2006; Slattery, 2004; Willett et al., 1990). The following statistical analyses were conducted to test whether these sociodemographic or biomedical variables were correlated with disease stage, CEA, VEGF, IL-6, TNF-α and oxytocin:

Dietary habits: chi-square tests to test the relationship of dietary habits with disease stage, VEGF, IL-6, TNF-α and oxytocin. One-way between-groups ANOVA to test whether there were significant differences among the groups of dietary habits on CEA.

Physical exercise: independent samples t-tests to test whether there were a significant differences between the groups of localised and advanced disease stage, and the groups of low and high levels of VEGF, IL-6, TNF-α and oxytocin on physical exercise. Pearson's correlation to test the relationship between physical exercise and CEA levels.

Family history: chi-square tests for the relationship of family history with disease stage, VEGF, IL-6, TNF-α and oxytocin. Independent samples t-test to test whether there was a significant difference between the groups of patients with and without family history of colorectal cancer on CEA.

The following statistical analyses were conducted to test the hypotheses of the present study:

Set 1.

Logistic regression analyses were conducted to explore whether immunohistochemical staining scores of the biological markers (VEGF, IL-6, TNF-α and oxytocin) in tumour tissues, predicted a significant percentage of variance in disease stage. Disease stage was dichotomised into Dukes Tis, A and B (scoring 1) versus Dukes C and D (scoring 2) due to a small number of cases in some categories ($n = 1$ for Dukes C1 and $n = 0$ for Dukes D) and as reflecting a clinically significant cut-off. There were several missing values for the biological markers (see Table 15 for n for each marker). To reduce the number of missing values in the analyses, logistic regressions in relation to disease stage were conducted in two groups. The first group included VEGF and IL-6 to confirm the previous findings regarding the relationship of disease stage with the serum levels of these biological markers. The second group included TNF-α and oxytocin, given the unclear role of the former and the novelty of testing the role of the latter, in cancer. CEA was not included in the analyses due to a large number of missing values ($n = 9$) (see Table 15 for frequency and percentage distributions of the biological markers).

Table 15. Frequency and percentage distributions of the four biological markers.

Marker	*N*	%
VEGF		
1	6	13.3
2	19	42.2
3	20	44.4
IL-6		
0	17	37.8
1	28	62.2
TNF-α		
0	1	2.3
1	9	20.5
2	26	59.1
3	8	18.2
Oxytocin		
0	18	48.6
1	13	35.1
2	6	16.2
3	-	-

Set 2.

One-way between-groups ANOVAs were used to test if married patients had higher levels of social support than single and divorced/widowed patients. Patients were divided into three groups according to their marital status (Group 1: divorced/widowed; Group 2: single; Group 3: married/living as married).

To explore whether implicit loneliness was correlated with the explicit indices of social support, loneliness and mood, Pearson's correlations were conducted.

Set 3.

The main research question of this study i.e., whether a lack of social support is associated with disease markers in colorectal cancer, was tested in two groups. For

the first group of disease-severity markers, independent samples t-tests were used for the dichotomised disease stage and lymph node status variables, in relation to social support. In the second group, the relationship between social support and the cytokines was tested using one-way between-groups ANOVA for VEGF, and independent samples t-tests for IL-6 and TNF-α. Participants were divided into 2 groups on TNF-α scores (*0* and *1* versus *2* and *3*) as the number of cases in the *0* category was small ($n = 1$). IL-6 was dichotomised as stated in Measures Section.

Due to the previously shown associations of oxytocin with social bonding and social support, a logistic regression analysis was conducted to test which social support indices explained higher significant variance in the levels of oxytocin in tumour tissues. Oxytocin was dichotomised due to missing values ($n = 37$) and no cases in *3* catgeory. The score was dichotomised as *0* versus *1* and *2*.

In order to test whether implicit loneliness predicts more variance in disease severity than explicit loneliness, logistic regression analyses were done for disease stage, lymph node status, VEGF, IL-6 and TNF-α. Due to the small number of cases in some of the categories of biological markers (VEGF and TNF-α), dichotomised categories were used, hence the logistic regression.

Set 4.

To analyse whether disease-severity markers differed as a function of doctor-related delay, independent samples t-tests were conducted for disease stage and lymph node status, as a function of delay.

Set 5.

Pearson's correlation was conducted to test the relationship between patient-delay and implicit loneliness.

7.5 Results

7.5.1 Data Screening and Preliminary Analyses

All statistical analyses were performed using the SPSS (Version 14). All tests were two-tailed. Prior to the analyses, all variables were initially screened for normality. The following positively skewed distributions were transformed, in order to produce the skewness and kurtosis values nearest zero: *physical exercise* (square root), *doctor-related delay* (square root), *patient delay* (logarithm) and *CEA* (logarithm).

7.5.2 Comparison between Participants and Non-Participants

Participants (n = 51) and non-participants (patients who declined to take part in the present study, n = 37) did not differ on gender. However, non-participants were significantly older than the participants (mean age of 74 versus 68), $t = 2.46$, $p < .05$ (a flow chart of the recruitment procedure is shown in Figure 12).

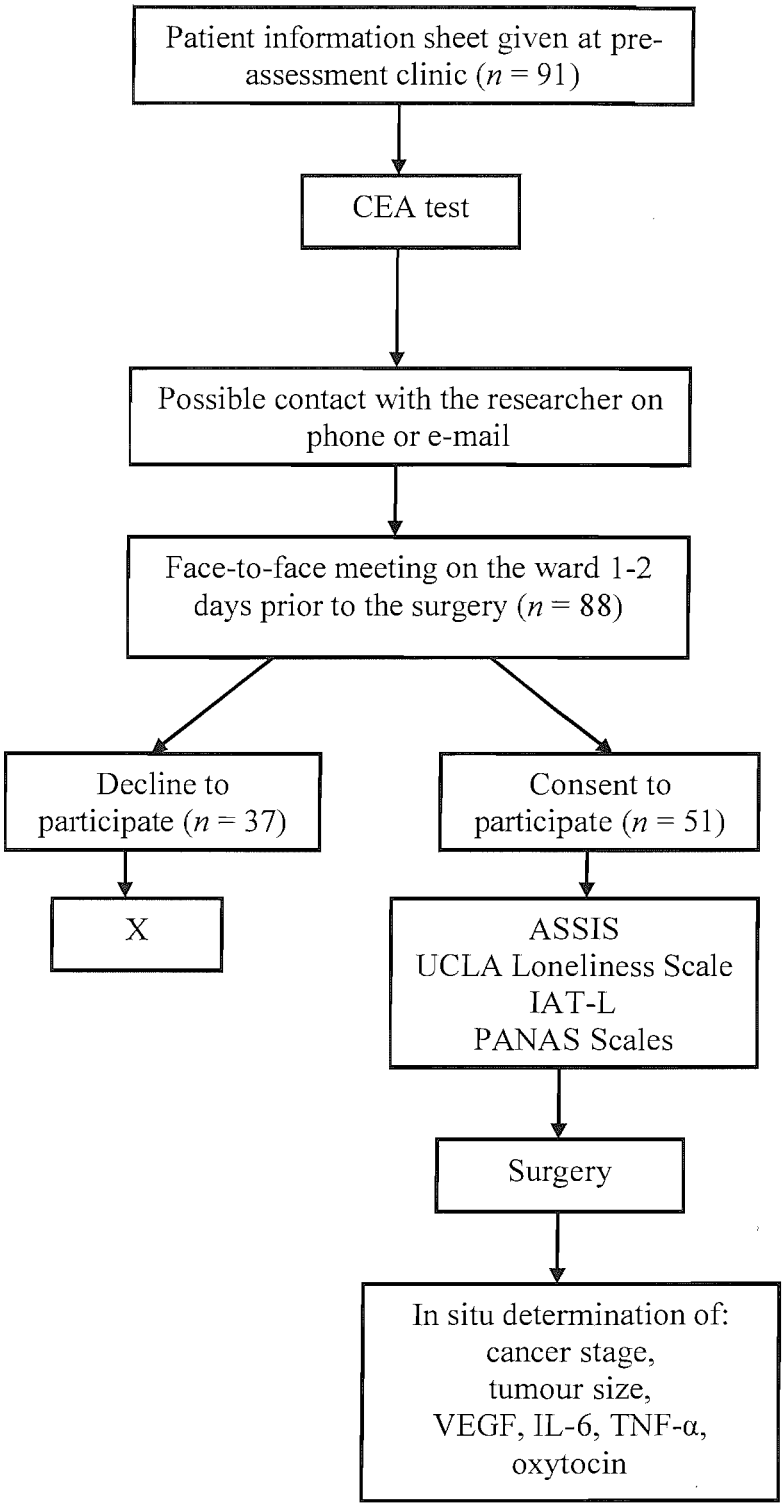


Figure 12. Flow chart of the recruitment procedure.

7.5.3 Sociodemographic and Biomedical Variables

Table 16 provides a summary of the sociodemographic and biomedical variables. The mean age of the patients was 68.27 years (*SD* = 10.12 years). Male patients constituted 57 per cent of the sample. Most of the patients were white and non-smokers. A large number of them were married or living as married and had education below or upto A-level. The mean patient delay and doctor-related delay were 1.43 months (*SD* = 3.26 months) and 4.38 months (*SD* = 5.04 months), respectively.

Table 16. Sociodemographic and biomedical characteristics of the patients.

Variables	No. of patients ($N = 51$)	%
Gender		
Male	29	57
Ethnicity		
White	50	98
Chose not to answer	1	2
Marital status		
Married/living as married	35	69
Single	2	4
Divorced/widowed/separated	14	27
Socioeconomic status (1-10)		
High (≥ 6)	33	65
Education		
≤ A-levels	40	78
Vocational/higher degree	11	22
Smoking		
No	46	90
Family history of colorectal cancer		
No	44	86
Dukes stage		
Tis	5	10
A	7	14
B	22	43
C1	16	31
C2	1	2
D	0	
Tumour size		
< 40 mm	23	45
≥ 40 mm	28	55
CEA ($N = 42$)		
< 13 ug/L	35	83
≥ 13 ug/L	7	17
Positive lymph nodes		
Yes	17	33
No	34	67

A chi-square analysis was conducted to evaluate whether poor dietary habits were more prevailing in patients with localised or advanced disease stage. The two variables were dietary habits with three levels (scores 1, 2 or 3) and prevalence of disease stage with two levels (Dukes Tis, A and B versus Dukes C and D). Dietary habits and disease stage were not found to be significantly related, $\chi^2(8, N = 51) = 3.6, p = .89$. Separate chi-square analyses which were conducted to test whether poor dietary habits prevailed more in patients with low or high levels of VEGF, $\chi^2(2, N = 45) = .36, p = .84$, IL-6, $\chi^2(2, N = 45) = 3.0, p = .22$, TNF-α, $\chi^2(2, N = 44) = .55, p = .76$, and oxytocin, $\chi^2(2, N = 37) = 1.9, p = .39$ were nonsignificant. VEGF, TNF-α and oxytocin were used as dichotomised variables. Results were also nonsignificant for Brown-Forsythe test (between-groups ANOVA) which was done to test if there were significant differences among the groups of dietary habits on CEA, without assuming homogeneity of variance, $F(2,22) = 1.3, p = .30$.

Separate independent samples- t-tests were conducted to test the groups of disease stage, VEGF, IL-6, TNF-α and oxytocin for significant differences on physical exercise. No significant differences were found between the groups of localised and advanced disease stage, $t(49) = -.03, p = .97$, VEGF, $t(43) = -.18, p = .86$, IL-6, $t(43) = -.42, p = .68$, TNF-α, $t(42) = .38, p = .71$, and oxytocin, $t(35) = -.32, p = .75$. Pearson's correlation coefficient between physical exercise and CEA was also nonsignificant, $r = -.21, p = .18, n = 42$.

Another set of chi-square analyses was conducted for family history, and disease stage, VEGF, IL-6, TNF-α and oxytocin. The variable of family history had two levels (scores 1 and 2). Family history was not found to be significantly correlated with disease stage, $\chi^2(1, N = 51) = .52, p = .47$, VEGF, $\chi^2(1, N = 45) = .10, p = .75$, IL-6, $\chi^2(1, N = 45) = .00, p = 1.0$, TNF-α, $\chi^2(1, N = 44) = .80, p = .37$, and oxytocin, $\chi^2(1, N = 37) = .81, p = .37$. An independent samples t-test revealed that there was no significant difference between the groups of patients with or without family history of colorectal cancer on CEA, $t(40) = -.83, p = .41$.

On the basis of these results, the variables of dietary habits, physical exercise and family history were not controlled for in the subsequent analyses.

7.5.4 Set 1: Relationships among Disease Markers

Logistic regression analyses which were conducted to explore whether immunohistochemical staining scores of the biological markers explained a significant percentage of variance in disease stage revealed that the results for the tested cytokines and oxytocin were nonsignificant. Adjusted odds ratios from the analyses are shown in Table 17.

Table 17. Adjusted odds ratios of biological markers on disease stage.

Disease marker	OR	95% CI	*p*
VEGF	.59	.16-2.11	.41
IL-6	1.02	.27-3.80	.98
TNF-α	3.11	.66-14.66	.15
Oxytocin	.89	.22-3.60	.87

Celen et al. (2004) suggested that combining CEA and VEGF may enhance their effectiveness to predict colorectal cancer severity. On the basis of this, it may be speculated that CEA and VEGF will also show a positive correlation. In order to confirm this, a one-way between groups ANOVA was conducted to further explore whether the levels of CEA significantly vary across the groups of VEGF scores. VEGF scores were divided into three groups (1, 2 and 3). Although the mean CEA scores increased linearly with the strength of VEGF staining, there was no statistically significant difference in CEA levels for the three groups of VEGF, $F(2,35) = .31, p = .73$.

7.5.5 Set 2: Relationships among the Measures of Social Support, Marital Status and Mood

One-way between-groups ANOVAs used to test if married patients had higher levels of social support than single and divorced/widowed patients revealed that married patients were not significantly different from single and divorced/widowed patients on available network support, $F(2,48) = .40, p = .68$, utilised network size, $F(2, 48) = 1.47, p = .24$, support satisfaction, $F(2, 48) = .24$, p = .79 and support need, $F(2, 48) = .29, p = .75$ (see Table 18 for means and standard deviations of social support scores in marital status groups).

Table 18. Means (and standard deviations) of social support scores in marital status groups.

Social support	Divorced/widowed (n = 14)	Single (n = 2)	Married/living as married (n = 35)
Available network size	7.79(4.02)	10.0(7.07)	8.70(3.90)
Utilised network size	6.57(3.08)	10.0(7.07)	8.33(3.75)
Support satisfaction	36.21(2.91)	34.50(10.60)	36.18(3.11)
Support need	16.14(3.39)	18.0(4.24)	17.06(4.72)

A two-way between-groups ANOVA was conducted to explore if age and mood moderated the relationship between marital status and social support. Due to a small number of participants in the *single* group, only the other two groups were included in the interaction analyses (1 = divorced/widowed, 3 = married/living as married). Positive and negative affect were dichotomised for these analyses on the basis of a median split. There was a statistically significant main effect of negative affect on available network size, $F(1, 47) = 4.10$, $p < .05$ with a moderate effect size (partial eta squared = .09). Counter-intuitively, the mean scores for available network size were higher in the high negative affect group as compared to the low negative affect one. However, the difference between these mean scores for high and low negative affect groups did not reach the conventional level of statistical significance, $t(47) = 1.90$, $p = .06$. All other main and interaction effects were nonsignificant (results not reported).

Another moderation analysis was conducted for age. Participants were divided into two groups according to their age (Group 1: ≤ 70 years; Group 2: > 70 years). These groups were based on a median split. No interaction effect, $F(1, 43) = .00$, $p = .95$ or main effects, $F(1, 43) = 1.18$, $p = .28$ were statistically significant.

Pearson's correlations between implicit loneliness, and explicit loneliness, social support and mood were all nonsignificant (see Table 19). The direction of results was as anticipated for support need, and positive and negative affect i.e.,

loneliness as measured by the IAT-L (M) was positively correlated with support need and negative affect, and inversely correlated with positive affect. However, other results were in the direction opposite to what was hypothesised.

Table 19. Pearson's correlation coefficients between implicit and explicit measures.

	Explicit Loneliness	Available Network Size	Utilised Network Size	Support Satisfaction	Support Need	Positive Affect	Negative Affect
			($N = 48$)				
Implicit Loneliness	-.16	.01	.02	.14	.53	-.08	.13

7.5.6 Set 3: Relationships between Social Support and Disease Markers

Independent samples t-tests revealed that there were no significant differences between the patients with localised and advanced disease, and with positive and negative lymph node status, on available network size, utilised network size, support satisfaction and support need. Also, no statistically significant differences were found in the levels of the four indices of structural and functional support for the groups based on VEGF, IL-6 and TNF-α staining. However, the results for disease stage, lymph node status and IL-6 showed a nonsignificant trend on support satisfaction in a counter-intuitive direction, where support satisfaction was higher in the patients with more advanced disease, positive lymph node status and higher levels of IL-6. Results of one-way between-groups ANOVAs and independent samples t-tests are given in Table 20.

Table 20. Differences between groups of disease stage, lymph node status, IL-6, VEGF and TNF-α on indices of social support.

		Available network size		Utilised network size		Support satisfaction		Support need	
		M(*SD*)	*t*(*p*)	M(*SD*)	*t*(*p*)	M(*SD*)	*t*(*p*)	M(*SD*)	*t*(*p*)
Disease stage ($n = 49$)	Local (Tis, A, B)	7.94(3.13)	-1.40(.17)	7.67(2.78)	-.62(.54)	35.58(3.52)	-1.67(.10)†	16.21(4.39)	-1.47(.15)
	Advanced (C, D)	9.63(5.28)		8.38(5.23)		37.25(2.72)		18.13(3.98)	
Lymph node status ($n = 49$)	Negative	7.94(3.13)	-1.40(.17)	7.67(2.78)	-.62(.54)	35.58(3.52)	-1.67(.10)†	16.21(4.39)	-1.47(.15)
	Positive	9.63(5.28)		8.38(5.23)		37.25(2.72)		18.13(3.98)	
IL-6 ($n = 44$)	0	8.53(5.08)	-.14(.89)	7.71(4.87)	-.24(.81)	35.12(3.76)	-1.67(.10)†	16.18(3.21)	-.72(.48)
	1	8.70(3.48)		8.0(3.15)		36.78(2.83)		17.07(4.50)	
TNF-α ($n = 43$)	0 (0, 1)	9.00(4.03)	.28(.78)	8.00(3.43)	.09(.93)	35.80(3.39)	-.32(.75)	17.10(5.50)	.42(.68)
	1 (2,3)	8.58(4.25)		7.89(4.08)		36.18(3.33)		16.48(3.55)	

(Cont.)

		Available network size		Utilised network size		Support satisfaction		Support need	
		M(*SD*)	*F*(*p*)	M(*SD*)	*F*(*p*)	M(*SD*)	*F*(*p*)	M(*SD*)	*F*(*p*)
VEGF	1	10.80(4.38)		9.40(4.28)		34.60(2.88)		15.80(5.22)	
(*n* = 44)									
	2	8.05(3.41)	.88(.42)	7.79(3.10)	.44(.65)	36.16(3.24)	.66(.52)	16.63(4.21)	.19(.82)
	3	8.65(4.66)		7.60(4.67)		36.50(3.46)		17.05(3.73)	

$^{\dagger}p \leq .10$, two-tailed.

Logistic regression was conducted to explore if social support indices will positively explain significant variance in the levels of oxytocin expression in tumour tissues. Results were nonsignificant for all the indices (see Table 21). There was a trend in the case of utilised network size, suggesting that higher utilised network support was associated with lower odds of having higher in situ levels of oxytocin. However, this result did not reach statistical significance ($p = .06$).

Table 21. Adjusted odds ratios from logistic regressions explaining the levels of oxytocin.

Social support	OR	95% CI	*p*
Available network size	1.47	.84-2.59	.18
Utilised network size	.54	.28-1.03	.06†
Support satisfaction	.92	.72-1.18	.50
Support need	1.00	.83-1.22	.98

†$p < .10$.

Logistic regression was also conducted to test if implicit loneliness explained a higher percentage of variance in disease-severity markers than explicit loneliness. Results were nonsignificant for disease stage, lymph node status, IL-6 and TNF-α (see Table 22). Implicit loneliness explained 38 per cent variance in the levels of VEGF, also contributing towards the incremental validity of the IAT-L (M). The whole model including implicit and explicit loneliness explained 11 to 15 per cent variability in VEGF.

Table 22. Adjusted odds ratios from logistic regressions explaining disease stage, lymph node status, and levels of VEGF, IL-6 and TNF-α by implicit versus explicit loneliness.

Variable	OR	95% CI	*p*
Disease stage			
Implicit loneliness	.90	.26-3.15	.87
Explicit loneliness	1.01	.93-1.09	.88
Lymph node status			
Implicit loneliness	.90	.26-3.15	.87
Explicit loneliness	1.01	.93-1.09	.88
VEGF			
Implicit loneliness	4.56	.99-20.96	.05*
Explicit loneliness	.99	.92-1.08	.88
IL-6			
Implicit loneliness	2.44	.60-9.87	.21
Explicit loneliness	1.01	.93-1.10	.79
TNF-α			
Implicit loneliness	1.60	0.35-7.27	.55
Explicit loneliness	1.02	0.94-1.12	.61

*$p \leq .05$.

7.5.7 Set 4: Relationship between Doctor-Related Delay and Disease Severity

Independent samples t-tests were conducted for disease stage and lymph node status, to analyse whether they differed as a function of delay. Results revealed that there was no significant difference in the scores for localised ($M = 1.88$, $SD = 1.24$) and advanced ($M = 1.39$, $SD = 1.12$) disease stages on delay, $t(48) = 1.36$, $p = .18$. The magnitude of the differences in the means was small (eta squared = .04). Similarly, the difference in scores for negative lymph node status ($M = 1.88$, $SD = 1.24$) and positive lymph node status ($M = 1.39$, $SD = 1.12$) was nonsignificant for delay, $t(48) = 1.36$, $p = .18$ and the magnitude of the differences was also small (eta squared = .04).

7.5.8 Set 5: Relationship between Patient Delay and Social Support

The correlation between implicit loneliness and patient delay was nonsignificant, $r = -.11$, $p = .64$. Two-way ANOVAs were used to test whether demographic factors (age, gender and education) moderate this relationship. Participants were divided into two groups according to their age (Group 1: ≤ 70 years; Group 2: > 70 years), two groups on implicit loneliness (high and low based on median split), and two groups on education as stated in the Measures Section.

There were no significant Age main, $F(1, 16) = .26$, $p = .62$ or Age x Implicit Loneliness interaction, $F(1, 16) = .68$, $p = .42$ effects. The Education main, $F(1, 44) = .00$, $p = .96$ and Education x Implicit Loneliness interaction, $F(1, 44) = .01$, $p = .93$ effects, and Gender main, $F(1, 44) = .10$, $p = .76$ and Gender x Implicit Loneliness interaction, $F(1, 44) = .01$, $p = .93$ effects were also nonsignificant.

All of the above analyses were also repeated for explicit loneliness. None of the results were significant (results not reported).

An independent samples t-test was conducted to explore further if gender played a role in patient delay, as suggested by Young et al. (2000). Results showed that male patients did not differ from female patients on seeking medical help, $t(49) = .04$, $p = .97$.

7.5.9 Sample Size Calculation for Future Studies

Owing to the categorical nature of the outcome variables and the risks associated with their assessment (as discussed in the Discussion Section below), the assumptions of normal distribution could not be adequately met in the present study. Also, the logistic problems with patient recruitment led to a smaller sample size than anticipated. Therefore, on the basis of the results of this study, an estimate of the sample size for the future studies is given below:

Based on two means which were used in the independent samples t-test to investigate whether a lack of social support is associated with disease stage in

colorectal cancer, a sample size of 110 patients in total (55 in each group) would be required to achieve 80 per cent power with a significance level of .05, two-tailed (estimated for the index of support satisfaction) to detect a significant difference between the groups of localised and advanced disease stage. A similar estimate was done from the results of the present study for social support and groups of low and high levels of IL-6. A sample size of 126 (63 in each group) would be required with 80 per cent power and a significance level of .05, two-tailed, in order to detect a significant difference between the groups of low and high in situ levels of IL-6 on support satisfaction.

7.6 Discussion

The aim of this study was to investigate the relationship of social support and loneliness with severity of colorectal cancer at time of diagnosis. The severity of cancer was assessed by disease markers including cancer stage, tumour size, lymph node status, CEA, and four important biological markers (VEGF, IL-6, TNF-α and oxytocin).

Prior to investigating the major research question of the study regarding social support, it was important to validate the immunohistochemical analyses for measuring the biological markers in this sample. This was done by analysing the relationship between the immunohistochemical staining scores for the biological markers and stage of cancer. Since some previous studies found a positive correlation between the levels of VEGF, IL-6 and TNF-α in tumour tissues and the severity of colorectal cancer (e.g., Hsu & Chung, 2006; Hu et al., 2007; Wu et al., 2001), it was crucial to look for their association with the index of disease stage. This was the case particularly for oxytocin because only a few previous studies have assessed the levels of oxytocin and its receptors in tumour tissues by rating the strength of its immunohistochemical expression. The adjusted odds ratios for the biological markers in relation to disease stage did not show any significant results in this study.

There could be a few reasons for these nonsignificant findings. It may be speculated that this lack of association resulted because the sample comprised of patients who were newly diagnosed and were going through surgical treatment for

the very first time. As there were no cases of Dukes D (n = 0), it was not possible to test whether the tumour levels of VEGF were significant correlates of metastasis in colorectal cancer. The reason for the lack of cases for Dukes D is that surgery is not a recommended treatment for advanced stage and usually patients with Dukes D diagnosis go through other treatment regimens (e.g., chemotherapy and radiotherapy) before they are surgically treated, if at all. Studies which did include patients with more severe disease found significant correlations between certain biological markers such as VEGF and disease severity (i.e., recurrence and worsening of disease; Nakayama et al., 2002).

The role of TNF-α has been dual and uncertain as it is reported both to cause necrosis to cancer cells and to promote the growth of tumour cells (Aggarwal, 2003). Although in the latter instances its high levels correlated with an increase in risk of mortality (Rink & Kirchner, 1996), no association between TNF-α and disease severity was found in the present study. It is possible that this cytokine may have predicted the prognosis of the patients in this study, but no follow-up was conducted.

Since research has shown the effectiveness of the combination of CEA and VEGF in distinguishing severe from less severe tumours (Fernandes et al., 2005), it was explored if the levels of CEA significantly differed in the three groups of VEGF in this study. Results were nonsignificant. However, due to logistic problems the target sample size could not be recruited which might have been responsible for the nonsignificant findings and which is why the combined effects of these markers on disease severity could not be tested.

Disease stage did not significantly correlate with social support indices in the present study. Although the literature findings on social support and progression of cancer have been encouraging, previous studies using cancer severity at diagnosis as an outcome found no significant correlation (Giraldi et al., 1997; Weihs et al., 2005), supporting the nonsignificant findings of the present study. A large-scale population-based study found a significant correlation between emotional support and severity of colorectal cancer in black but not in white patients (Kinney et al., 2003), suggesting that factors such as ethnicity may moderate the relationship between social support and severity of cancer. Due to the fact that the sample of the present

study comprised of white patients, testing this aspect was not possible, and needs to be done in future studies.

The role of social support in cancer-related outcomes has been thoroughly investigated in recent decades. The outcomes or findings of those studies included cancer onset, severity, progression and survival, as discussed in Chapter 3. However, research on social support and proinflammatory cytokines as markers of cancer severity is in its infancy. Previous studies have investigated the relationship between psychosocial variables including social support and the blood levels of VEGF, IL-6 and TNF-α. Those studies found significant results (Lutgendorf et al., 2000; Lutgendorf et al., 2002) in which lower levels of social support predicted higher serum levels of VEGF in ovarian cancer patients. However, no study had investigated whether the in situ levels of VEGF and other proangiogenic cytokines were also correlated with psychosocial factors including social support. The present study aimed to answer this question by measuring the immunohistochemical expression of these cytokines in tumour tissues. To the best of my knowledge, this is the first study of its kind and the levels of these cytokines in tumour tissues have not been previously investigated with reference to social support. The present study also measured the levels of oxytocin in tumour tissues, to investigate their relations with social support and loneliness.

In the present study, there were no significant relations between levels of structural and functional support, and the immunohoistochemical staining of VEGF, IL-6 and TNF-α. There could be a few explanations for these findings. First, there was the limitation of a small sample size. It is possible that some significant effects could be found with a larger sample size. Previous studies found significant relations between social support and serum levels of these cytokines (e.g., VEGF) with samples as small as 24, half the sample size of the present study (Lutgendorf et al., 2002). It is possible that serum levels of these markers correspond more closely to psychosocial factors than do tissue levels that were used in the present study. There is also a possibility that psychosocial factors induce greater increases in systemic levels of cytokines as compared to local levels at the tumour site, a pattern observed for the systemic and local production of IL-6 in a study on marital conflict and wound healing (Kiecolt-Glaser et al., 2005). However, considering the evidence

showing positive relationship between the levels of VEGF in serum and in tumour tissues (Minagawa et al., 2002), it is difficult to speculate on it. As far as IL-6 is concerned, previous studies showed that its higher values in serum are associated with positive immunohistochemical staining in colorectal cancer cells (Ashizawa et al., 2006). On the basis of this, it can be suggested that the correlations between psychosocial factors and levels of IL-6 in tumour tissues may be stronger in more advanced disease. Second, a restricted range of scores (0-3 rating scale) for the strength of staining of the biological markers in the present study may have led to reduced associations, warranting the use of more sensitive methods for measuring these markers. Third, error due to manual handling and treatment of the data may have been responsible for problems in staining and subsequent incorrect or unreliable rating. Future studies need to incorporate computerised quantification and measurements of these parameters (e.g., Hu et al., 2007). Fourth, due to a small number of cases in some scoring categories for the biological markers, VEGF and TNF-α scores were dichotomised in order to include sufficient number of cases in each scoring category. This may have masked important differences between levels of these biological markers, potentially linked with social support. Finally, presentational biases may have resulted in altered responses on the explicit measure of social support. It is likely that presentational biases may have contaminated the results, particularly in light of the significant VEGF-implicit loneliness relationship observed in the present study, which will be discussed later in this Section.

Due to accumulating evidence linking oxytocin with social support and social bonding (Carter, 1998), all structural and functional support indices assessed in this study were tested in relation to oxytocin. Although results were nonsignificant for available network size, utilised network size, support satisfaction and support need, the index of utilised network size tended to explain some of the variance in the levels of oxytocin. However, the results did not reach the conventional level of statistical significance ($p = .06$). Although it must be interpreted with caution as this finding, contrary to the speculations, suggested that the utilisation of support from people in the social network in the month prior to the surgery may be associated with reduced chances of high levels of oxytocin in colorectal cancer tissues (in comparison, implicit loneliness did not explain significant variance in the levels of oxytocin; results not reported). This counter-intuitive finding could be attributed to an altered

perception regarding the levels of social support in the context of the critical phase of cancer diagnosis and treatment, as discussed in detail in the following paragraph. Future studies need to test this in larger samples and identify any possible health consequences this relation may have.

7.6.1 Why did social support correlate with cancer progression in previous studies but fail to correlate with cancer severity in the present study?

It may be speculated that additional factors such as patient delay may also be important with reference to this relationship. Therefore, this study included patient and doctor-related delay as variables. Another factor which may be important in this regard is the timing at which patients were invited to take part in the present study. One to two days before their surgical treatment may have been a particularly stressful time for the patients and this may have been responsible for an altered perception of social support since people in their social networks were more supportive during this critical period than possibly at any other time. This may have been the case where patients with more advanced disease, positive lymph node status and higher levels of IL-6 reported higher support satisfaction than the patients who had localised disease in the present study. It is also possible that higher expectations of social support from their loved ones in this critical time resulted in disappointment and hence lower reported social support. In both cases, this altered perception could be attributed to the time at which patients were approached and tested for this study, and could have affected their reported levels of support and satisfaction with it. A direct evidence for this view comes from the study by Villingshoj and colleagues (2006) who found that increased contact with children was associated with a higher mortality rate compared to unchanged contact with the children, before and after cancer surgery for colorectal cancer. This provides support for the finding that the levels of social support reported at the critical time of surgery may not be indicative of a routine life situation and changes in support may have prognostic significance. This possible distorted perception of social support in this critical time may also have affected the levels of biological markers. Nevertheless, since tumour tissues obtained surgically were used to assess the levels of the biological markers, pre-surgery recruitment was unavoidable and testing patients 1-2 days before surgery was appropriate.

Regarding the relationship among the social support and marital status, there were no significant differences among widowed/divorced, single and married/living as married patients on the indices of social support. However, the mean values suggested that single patients had the largest available and utilised network sizes, followed by married and divorced patients. Interestingly, single patients also had the lowest support satisfaction and the highest support need. These scores, even though nonsignificant, may suggest that single people have large support networks but the quality of support may not necessarily be satisfactory. These results also suggested a degree of superficiality in their social connections. It could be due to the fact that single people do not have offspring and other kin-based contacts which are available for people in the other two categories.

7.6.2 Patient Delay and Doctor-Related Delay

An important part of this study was the effect of delay in treatment on disease stage. Contrary to the hypothesis that patients with longer doctor-related delay will have more advanced disease, there was no significant difference in the severity of the disease as a function of delay in treatment. According to a recent system, general practitioners in the UK are now able to request urgent investigation of patients with a possible malignancy in *2-week* clinics since April 2000 (Department of Health, 2000). This system, if followed properly, minimises the potential to get a delayed cancer screening and treatment. The average doctor-related delay in this study was 4.4 months. In these instances where the doctor-related delay was long, patients may also have had comorbidities such as diverticular disease and haemorrhoids, which have similar symptoms as colorectal cancer. Therefore, the initial symptoms may well have been related or attributed by the patient and doctor to those comorbidities.

Results for another aspect of delay i.e., the correlation between patient delay and social support were also nonsignificant, replicating the findings of a systematic review on the topic of patient delay in breast cancer (Ramirez et al., 1999). This review did not find any evidence for the role of social support in patient delay. There could be mixed reasons for this finding. There are individual differences in the way people react and live with loneliness or minimal social support. Some studies found evidence for the fact that lack of social support is associated with delay in seeking

medical help for physical symptoms (Kristofferzon, Lofmark, & Carlsson, 2003). Tromp, Brouha, de Leeuw, Hordijk, and Winnubst (2004) found that seeking less support as a coping style was one of the psychosocial factors along with less optimism, health hardiness and active coping, which determined patient delay in patients with head and neck cancer. Seeking less support from the social network was also found to be a determining factor in longer patient delay by patients with acute myocardial infarction (Bleeker et al., 1995). On the other hand, some lonely people may look after themselves better than their *nonlonely* counterparts knowing that there are not many close relations who would do it for them. There is also a possibility that the degree of autonomy moderates the relationship between social support and delay. There is evidence which suggests that the availability of social support determines health care attendance i.e., people who are lonely and have fewer social resources for coping with stress tend to use the medical system more frequently than people who are not lonely (Robinson & Granfield, 1986). Moreover, people with families, particularly young children, may be too busy to take time out for their medical appointments and other health-related concerns or commitments. Thus, the possible relationship between social support and delay is potentially complex and may require assessment of other moderating variables such as social context or attachment style.

7.6.3 Implicit Measurement of Loneliness

A novelty of the present study was the use of a combination of both implicit and the conventional explicit measures of loneliness and social support with a sample of cancer patients. Despite the growing popularity of implicit measures of psychosocial constructs, these tests have not been used with cancer patients. As far as the validity of the IAT-L (M) in this clinical sample is concerned, predictive validity was supported by significant variance in the levels of VEGF accounted for by implicit but not explicit loneliness. Implicit loneliness alone explained 38 per cent of variance in the levels of VEGF. This finding replicated the findings of previous studies which found that the IAT predicted physiological outcomes more strongly than the explicit measures of the same constructs (Egloff & Schmukle, 2002; Nausheen et al., 2007). Also, this finding replicated an important previous finding, where lower levels of social well-being (assessed by an explicit self-report

questionnaire as closeness to and utilistion of emotional support from family/friends/partner, and satisfaction with support) were found to be significantly associated with higher serum VEGF levels in patients with ovarian cancer (Lutgendorf et al., 2002). The finding in the present study extended this to a sample of colorectal cancer patients, using an implicit measure of loneliness. However, given the multiple statistical tests conducted in this study, the possibility of type I error can not be ruled out. Nevertheless, this effect was detected in a specific test comparing the predictive validity of the implicit and explicit measures of loneliness.

There were no significant results to establish the construct and concurrent validity of this tool. However, the direction of the correlations with support need, and positive and negative affect was as anticipated, while it was contrary to what was hypothesised for explicit loneliness, available network size, utilised network size and support satisfaction. It is important to note that functional support indices of support satisfaction and support need have been found to be important regarding the validity of the IAT-L in Study 1 and 2, respectively. Although not reported, it is possible that the performance (on the IAT) of the older sample of the present study suffered due to age-related factors such as age-related slowing and/or spurious responses (e.g., Ratcliff, Spieler, & McKoon, 2000) or unfamiliarity with computers. Although some of the previous theoretical and methodological analyses have provided methods of dealing with speed-accuracy problems, these issues may be more relevant to studies which include both young and older participants (Greenwald et al., 2003).

7.6.4 Potential Pathways

It is important to speculate on the underlying pathways in this relationship between implicit loneliness and higher VEGF levels. Stress is an important factor which has been found to be a moderator in social support-physical health relationship (Cohen & Wills, 1985). Moreover, the role of stress has also been studied as a mediator in this link. With reference to social support and VEGF, Lutgendorf et al. (2003) experimentally investigated the effects of stress-related mediators including noradrenaline, adrenaline, isoproterenol and cortisol on the production of VEGF by two ovarian cancer cell lines. They found that noradrenaline and isoproterenol (a nonspecific β-adrenergic agonist) significantly enhanced VEGF production by

SKOV3 cells, and these effects were blocked by a β antagonist, supporting a role for β-adrenergic receptors in these cells. This pathway by which psychosocial stress mediators experimentally contributed to tumour progression is depicted in Figure 13.

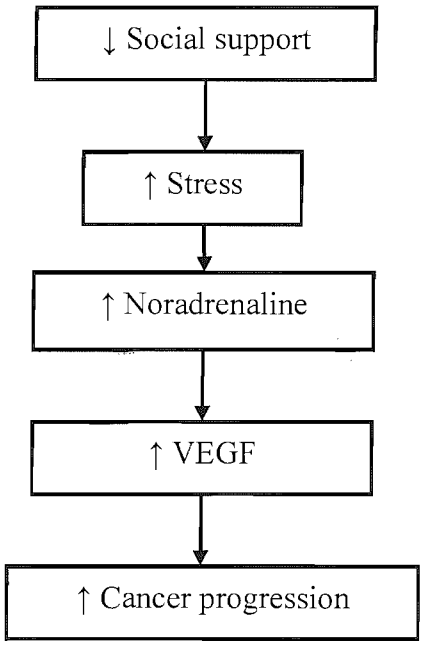


Figure 13. Pathway between social support, psychosocial stress and tumour progression.

However, the present study did not test the model depicted in Figure 13 since none of the biological markers, including VEGF, correlated with cancer severity, and since the adrenergic activity was not measured in the present study. Thus, this model needs to be viewed as theoretical which may be more relevant to indices of cancer progression, not tested here. Furthermore, since results for all other biological markers in relation to implicit loneliness were nonsignificant, this significant finding should be interpreted with caution.

7.6.5 Limitations

The findings of the present study must be interpreted in the context of its limitations. Despite arduous efforts, the rate of recruitment could not be increased. The total number of patients recruited in the present study was 51 over a period of 18

months, given the exclusion criteria and participants' consent to take part in the study. Fewer number of cases for the biological markers was attributed to the following reasons: (1) exclusion of cases from the immunohistochemical analyses where the pre-surgery diagnosis of cancer turned out to be incorrect (Dukes Tis; n = 5), (2) since surplus tumour tissues were used for this study, tissues were not available in some cases (n = 1-2), (3) scarcity of oxytocin antibody due to unavailability of funds, limiting its sample size to 37.

The significant findings of this study should be interpreted with caution. This applies particularly in the light of a small sample size. However, keeping this limitation in consideration, a systematic approach to hypotheses was adopted where sets of statistical analyses were conducted for only those a priori hypotheses which were derived from clearly rationalised theoretical and/or empirical evidence. Another limitation of the present study was its cross-sectional design and that it focused on cancer severity at diagnosis rather than progression. This was due to feasibility issues. Future studies need to retest these findings in relation to prospective outcomes in colorectal cancer.

Another reason for the nonsignificant findings in this study could be that the immunohistochemical staining for biological markers and the rating of their expression were carried out manually. Factors ranging from human error in diluting the antibodies to the variation in the temperature in the laboratory on the days the batches of staining were done might have influenced the results.

7.6.6 Implications and Recommendations for Future Research

The findings of this study warrant more pilot work on the use of the Implicit Association Test of loneliness with cancer patients. Despite few exceptions, the findings of this study do not support the role of social relationships in cancer-related outcomes. Further prospective research is warranted not only to establish a causal link between (lack of) social support, and indices of cancer severity and progression but also to replicate the present findings.

Future studies can also mimimise the element of human error in immunohistochemical staining by using more rigorous and sophisticated methods such as counting the immunostained tumour cells in more than one section from every patient to improve the reliability of rating (Ohlsson et al., 2006). The immunohistochemical staining intensity could be quantified by using more advanced technology such as semi-automated computerised image analysis (Zafirellis et al., 2007). In this procedure, microscopic images of immunostained histopathology sections are usually obtained by a special CCD-type camera that is connected to a computer-controlled image acquisition device. Quantitative analysis of such images aims at partitioning an image into homogenous groups or regions. The pixel intensity (colour)-based approach is an example of this analysis which aims at finding a discrimination point or threshold. The criterion to classify an image is to assign pixels to the same class whose intensity values are above (or below) the threshold (Wu, Zhao, Lin, & Ginsberg, 2005).

The clinical significance of this type of research lies in proposing additional treatment regimens for the target vulnerable population. These treatment regimens may include family-focused interventions for colorectal cancer patients, in order to identify couples at increased risk of poor adjustment i.e., high stress and low levels of social support.

Over the past decade, new treatment approaches have been introduced for colorectal cancer and the number of treatment options for patients with this type of cancer has increased with many more therapeutic agents in clinical development. New targeted therapies have been designed whose action is directed against proangiogenic cytokines e.g., VEGF (Vanhoefer, 2005). These include biological therapies that are being tested in new combinations with chemotherapy for both early stage and advanced disease. Given the findings of Lutgendorf et al. (2002) and, should those be observed in the present study, future studies may test the effects of blocking VEGF on the prognosis of lonely cancer patients.

7.7 Conclusion

Although colorectal cancer is highly prevalent, relatively few studies on the psychosocial aspects of this cancer have been done. The present study attempted to contribute to the field of psycho-oncology by beginning to fill this gap, while introducing new methods of research that include measuring biological markers in situ and the use of implicit measurement of an important psychosocial construct. Despite using a systematic approach in formulating hypotheses for this study, a large number of the findings were nonsignificant. However, those findings have been discussed with reference to the limitations of the study. The implicit test of loneliness superseded its explicit counterpart in predicting the levels of VEGF in tumour tissues. This finding replicated the previous finding which used blood levels of the same biological marker in a different type of cancer and used an explicit measure of social support. Another novel aspect of the present study included oxytocin which was studied for the first time with reference to social support and cancer severity. Although the results regarding oxytocin were statistically nonsignificant, this study explored new issues which warrant further research in order to reach conclusions in this area.

Chapter Eight: Discussion

8.1 Introduction

This research thesis reviewed definition and measurement of social support, and investigated the relationship of social support and loneliness with indices of well-being and disease. These indices included QoL (Chapter 5), CVR to stress (Chapter 6) in healthy volunteers and disease markers in patients with colorectal cancer (Chapter 7). While the two initial studies aimed to test the validity of a new implicit measure of loneliness (IAT-L) along with other measures of social support and loneliness, the main study tested the relations of implicit and explicit loneliness and social support with disease markers in colorectal cancer. These markers included severity markers (disease stage, tumour size and CEA) and biological markers (three cytokines and oxytocin). Studies have been conducted on the role of psychosocial factors in cancer-related outcomes for the past four decades. Despite a fairly large number of research studies in psycho-oncology, inconsistent findings have emerged regarding the role of social support in cancer progression. Also, little is known about the exact pathways which may link social support with progression of cancer. Another cancer-related outcome is the severity or stage of cancer at diagnosis, which has been used in the studies with cross-sectional or semi-prospective designs. Similar to cancer progression, this index has also yielded mixed and hence inconclusive findings in relation to social support. This gap in knowledge due to inconsistent findings may be attributed to: (1) variable ways of conceptualising, defining and categorising social support, (2) use of different measures of social support and problems with standardisation of these measures, (3) issues such as response biases which are inherently associated with self-report (or explicit) measurement of social support, a socially sensitive construct, (4) fewer studies on cancers other than breast cancer, (5) inclusion and simultaneous analysis of data on more than one type of cancer, possibly leading to masked effects of social support on any one type of cancer and hence misleading findings, and (6) difficulties in measurement of progression and the use of severity at diagnosis as its proxy measure.

Therefore, the precise aims of the present thesis were to: (1) systematically review and summarise the evidence regarding the role of social support in cancer

progression, (2) address and overcome the problems with conventional self-report measures of social support and loneliness by developing an implicit measure of loneliness, and using it in addition to self-report measures, (3) investigate the relationship of different indices of social support and loneliness with cancer severity in colorectal cancer, a prevalent but under-researched cancer, using a cross-sectional design, and (4) attempt to assess the possible pathways of the link between (lack of) social support and cancer severity by looking at the relationship between social support, loneliness, and four important biological markers.

This final chapter summarises the findings of each of the previous chapters, provides an overview of the empirical findings of this thesis, and integrates these findings with reference to one another and the previous literature. This chapter also discusses the strengths and weaknesses of the work included in this thesis, lists the implications to the fields of health psychology and psycho-oncology, and makes recommendations for future research.

8.2 Overview of the thesis

8.2.1 Background

The theoretical aspects of the construct of social support were discussed in Chapter 2 which provided an overview of the conceptualisation, categorisation and measurement of this construct over the past four decades. Although several categories of social support have been used by different researchers, the categories of structural and functional support have been the most popular and comprehensive approach to defining and assessing social support. Due to the fact that functional support is more indicative of the *actual* levels of social support as it takes into account the quality of support one has in relation to important aspects of daily living, it may be more relevant to health-related outcomes than structural support. Marital status is one of the most commonly used structural support indices, which has been used because married people may have higher levels of support than their unmarried counterparts. However, due to similar limitations with other structural support indices, marital status has been inconsistently associated with physical health and psychological well-being. With reference to cancer, marital status has shown

associations with its progression and other indices. However, disease variables have been found to play a more decisive role in progression and have superseded the ameliorating effects of being married.

Chapter 2 also discussed a related concept, namely loneliness, and shed light on the fact that although a lack of social support does not necessarily imply loneliness, social support and loneliness have been inversely correlated in the literature. Finally, like any other socially sensitive construct, self-reported assessment of social support and loneliness is not free from response biases such as social desirability and presentational bias. Therefore, an important aim of this thesis was to include an implicit measure of loneliness, in order to attempt to overcome these biases. Although no implicit measure of loneliness or social support has been previously used, implicit tests have repeatedly and successfully measured constructs such as self-esteem, racial attitudes and personality, and in some studies predicted physiological outcomes better than explicit tests of similar constructs. Chapter 2 presented the existing literature to provide the necessary background for the adaptation of an IAT of loneliness, in order to surmount the limitations of conventional self-report measures of social support and loneliness.

Chapter 3 set out the background for the main research question of this thesis. It gave a brief account of the biological aspects and prevalence of cancer. It also provided a summary of the evidence for the role of social support in cancer-related findings including cancer onset, severity at diagnosis and progression. The evidence for the role of (lack of) social support in cancer onset was weak. However, the findings were mixed for cancer severity, particularly suggesting that the relationship between social support and severity of cancer at diagnosis may be more convincing for specific populations.

8.2.2 Findings of the Systematic Review of the Literature on Social Support and Cancer Progression

Prior to testing the main hypotheses in the respective studies of this thesis, a systematic review was conducted to summarise the findings regarding the role of different indices of social support in cancer progression – the most important

outcome in longitudinal studies. This systematic review provided the necessary and much-needed conclusions on the role of social support in cancer progression which was lacking due to inconsistent findings on this topic. This review also uniquely attempted to discriminate the contribution of two important indices of social support (namely, structural and functional support) towards cancer progression. This distinction was useful due to a lack of uniformity in the conceptualisation and measurement of social support in the literature on cancer. The findings of the review suggested that the evidence for the role of social support was strong for breast cancer progression. Contrary to the evidence reviewed in Chapter 2, structural support indices were found to predict cancer progression more often than the indices of functional support. This review also pointed towards the significant prognostic role of disease-related factors such as severity, treatment, site of metastasis, etc. in cancer progression, suggesting that these variables must be considered in the analyses when evaluating the role of psychosocial variables such as social support in cancer-related outcomes.

This systematic review made a significant contribution to the field of psychosocial oncology by summarising the findings and limitations of the previous methodologically sound studies, in order to make future researchers more aware of how they may define and categorise social support and take into account the important disease-related variables. So far, the findings of this review suggested that the beneficial role of social relationships may not work in cancers of advanced stages and poor prognosis, which highlighted the importance of biomedical variables. More research is needed to conclude on the role of social support in cancers other than breast cancer and future studies need to concentrate on one type of cancer rather than including mixed cancers.

The findings of this review may also have important implications for future interventional studies in psychosocial oncology. More interventions are needed which are tailored around the specific social needs of the patients. Despite the fact that this review established the superiority of structural support indices over the ones measuring functional support, it may be implied that in the samples where this evidence was not found it may be interesting to study the causes of this nonsignificant relationship between structural support and disease progression: for

instance, the possibility that people have relationships in their social network but lack the skills to elicit support from them. Targeted interventions towards improving the skills of eliciting and seeking social support for the patients who have higher structural but lower functional support, may improve the beneficial effects of social support on their disease.

Results of this review warranted more research on cancers other than breast cancer. One such prevalent cancer is colorectal cancer which was chosen for testing the research questions of the present thesis.

Chapter 4 discussed the findings on the relationship of the four important biological markers i.e., three proangiogenic cytokines and oxytocin with psychosocial factors, particularly social support. These biological markers are considered to be important with reference to cancer as they have been established to play a role in its progression (or in slowing down the progression). Therefore, these markers may indicate the possible pathways linking social support with cancer progression. In conclusion, this chapter provided evidence for the possible bidirectional psychoneuroimmunological pathways of the link between social support and cancer progression, focusing on VEGF, IL-6, TNF-α and oxytocin.

8.2.3 Empirical Findings

8.2.3.1 Study 1 – Adaptation & validation of an implicit association test of loneliness.

Due to the limitations associated with the conventional self-report measures, one of the aims of this thesis was to use an implicit measure of loneliness alongside the conventional self-report measures, to investigate the main research questions. Therefore, Study 1 was designed to adapt and preliminarily validate an IAT of loneliness. Since implicit measures of social support or loneliness have not been previously used, this study set out with an exploratory approach and employed the neutral category (FURNITURE) with the LONELINESS category to be used in this test. Despite establishing the concurrent validity by having a small significant correlation with explicit loneliness, this IAT-L failed to have satisfactory internal

consistency. Due to nonsignificant correlations with social support indices and the index of QoL, the construct and criterion-related validity, respectively could not be established. As anticipated, functional support indices and explicit loneliness made the strongest contribution to explaining variance in QoL, in multivariate analysis.

Although previous research suggested a strong association between explicit social support and QoL, the possibility that the significant correlation between these two variables in this study were due to shared-method variance could not be ruled out. Also, the context of some recent findings suggesting that implicit measures might predict physiological outcomes more successfully as compared to self-reported outcomes (e.g., QoL), Study 2 was planned to explore this possibility in addition to improving the internal consistency of the IAT-L.

A possible limitation of this study was its convenience sampling owing to the online recruitment website and smaller number of male participants as compared to females.

8.2.3.2 Study 2 - Modified IAT of loneliness and cardiovascular reactivity to stress.

Study 2 was planned to overcome the limitations of the IAT-L, particularly its low internal consistency. It aimed to achieve this by replacing the neutral category with the bipolar (opposite) categories as these categories have been used more frequently in the literature, and may increase the internal consistency of this instrument. Since the findings of the previous studies on the relationship between social support and CVR to stress were mixed, this study selected CVR as an outcome to test the predictive validity of the implicit measure (modified IAT) of loneliness. More precisely, this study investigated whether implicit loneliness measured by the IAT-L (M) correlated with the CVR to laboratory stress more strongly than the explicit measures of social support and loneliness. As speculated, implicit loneliness positively correlated with CVR to stress, whereas explicit loneliness did not. Functional, but not structural, support indices correlated with CVR indices, supporting the previous literature. Also, the IAT-L (M) showed satisfactory internal consistency which made it superior to the IAT-L used in Study 1.

The results of this study were in line with the literature on the role lack of social support or loneliness played in increased CVR to stress. The findings of this study suggested that in the instances where CVR to stress was not significantly associated with social support in previous studies, the results could be partly attributed to response biases in the measurement of social support. Moreover, functional but not structural support was found to be relevant with reference to CVR to stress in this study. A small sample size was a weakness of this study. However, the magnitude of the associations came out to be significantly large. There is a possibility that the relationship of explicit loneliness with CVR could reach statistical significance with a larger sample. Future studies should replicate these findings in larger and diverse samples.

This study has wider implications for the field of psychometrics in health psychology. Although more research is needed to replicate these findings, the use of an implicit test to measure loneliness was a novel idea which seemed promising and extendable to other socially sensitive constructs in health psychology. Future researchers may also wish to use implicit measures of psychosocial constructs in addition to the conventional self-report measures, in order to predict health-related outcomes.

8.2.3.3 Study 3 - Social support, loneliness and disease markers in colorectal cancer.

This study attempted to contribute towards revealing the relationship of social support with disease markers in colorectal cancer, introducing several novel methodological strategies not previously used in health psychology. First, it included implicit and explicit measures of loneliness and social support. Second, this study measured the in situ levels of three important proangiogenic cytokines, and tested oxytocin for the first time with reference to social support and cancer. On the basis of the findings of Study 2, Study 3 included the IAT-L (M) and investigated the major research question of this thesis. The internal consistency of the IAT-L (M) was found to be satisfactory in this clinical sample, and the main results showed that social support was not significantly different in the groups of high and low levels of VEGF, IL-6, TNF-α and oxytocin. Also, patients with localised and advanced disease did not

have significantly different levels of social support. However, implicit, but not explicit, loneliness explained significant variance in the in situ levels of VEGF, replicating the previous finding of low social support and high serum levels of VEGF in ovarian cancer patients (Lutgendorf et al., 2002). Although implicit loneliness did not significantly relate with other biological markers, this finding contributed to the predictive validity of the IAT-L (M) and suggested that implicit levels of loneliness could be more relevant with reference to clinical outcomes. Since no other results for any of the biological markers were significant, this finding should be interpreted with caution and replicated in future studies. Since higher values of these cytokines (e.g., IL-6) in serum are associated with positive immunohistochemical staining in colorectal cancer cells (Ashizawa et al., 2006) and psychosocial factors may induce greater increases in systemic levels of cytokines as compared to local levels at the tumour site (Kiecolt-Glaser et al., 2005), the correlations between psychosocial factors and levels of cytokines at tumour site may be stronger in more advanced disease. These relations were not tested in the present study.

The relationship of social support with cancer severity at diagnosis was nonsignificant, replicating the previous findings (e.g., Giraldi et al., 1997). There is a possibility that patient recruitment for this study at the critical time of surgery may have resulted in biased reported levels of social support. The counter-intuitive results of a previous study on colorectal cancer support this notion where increased contact with children was associated with a higher mortality rate compared to unchanged contact before and after cancer surgery (Villingshoj et al., 2006), suggesting that the reported levels of social support may have been misleading. This may also be a potential factor behind the differences in the findings on severity at diagnosis and progression of cancer.

Although nonsignificant, the mean differences among the groups of single, married/living as married and divorced/widowed patients on social support suggested that single people had the highest levels of structural support but the quality of that support was the poorest as compared to the other two groups. This finding may suggest the superficiality of relationships of single patients which could be because of a lack of kin-based relationships.

A lack of significant relationship between doctor-related delay and disease stage, and between patient delay and social support supported the conclusions drawn by a previous systematic review (Ramirez et al., 1999), suggesting that this complex relationship may be influenced by possible moderators such as lack of cancer awareness/knowledge and attachment styles, respectively.

8.3 Integrating the Findings of this Thesis

8.3.1 Social Support and Loneliness

The means and standard deviations of social support and loneliness indices across the three studies are shown in Table 23. Negligible differences were found in the means on support satisfaction and explicit loneliness. Although the three samples differed significantly on available network, utilised network, support need and implicit loneliness, the healthy volunteers (Studies 1 and 2) did not show any consistent differentiating patterns on these indices in comparison with cancer patients (Study 3) (results not reported).

Table 23. Means (and standard deviations) of social support and loneliness indices across studies.

Index	Study 1 ($N = 50$)	Study 2 ($N = 48$)	Study 3 ($N = 51$)
Available Network	12.48(5.04)	9.0(3.08)	8.49(3.98)
Utilised Network	10.98(3.26)	8.42(3.19)	7.90(3.72)
Support Satisfaction	36.32(4.31)	36.75(3.19)	36.12(3.35)
Support Need	18.96(3.91)	17.79(3.07)	16.84(4.31)
Explicit Loneliness	37.86(8.81)	35.15(8.22)	35.02(8.03)
Implicit Loneliness	.37(.39)	-.32(.45)	-.47(.48)

8.3.2 Social support, Loneliness and Outcomes

The studies included in this thesis used standardised measures of social support and loneliness. The choice of these measures was carefully made in the light of the evidence reviewed in the introductory chapters. Most of the findings of this thesis supported the literature on the significance of functional support indices with reference to physical and psychological health. First two studies with healthy volunteers confirmed that higher satisfaction with social support and lower need for support were associated with better QoL (Study 1) and lower CVR to stress (Study 2). None of the structural support indices significantly correlated with these outcomes. However, results of the third study were different, showing that none of the indices of social support significantly correlated with disease markers in colorectal cancer. These discrepant findings may be attributed to the higher average age of the participants in Study 3 and their health condition. In Study 3, participants were recruited 1-2 days prior to surgery which may not be indicative of a regular life situation. Therefore, their responses at this time may have been biased by social pressure, social desirability or stressful context. This seems particularly convincing in the light of the significant result regarding implicit loneliness explaining the variance in the levels of VEGF in this study.

8.3.3 Implicit Measurement of Loneliness

The most important issues regarding the IAT of loneliness in this research have been concerning its reliability and validity. The reliability has been addressed by calculating and comparing its internal consistency across the studies of this thesis. None of the previous studies using the neutral category on the IATs reported their internal consistency. However, internal consistency of those with the bipolar categories has been promising i.e., in the range of .80. Therefore, low internal consistency of the IAT-L led to using the bipolar categories in Study 2. The resulting internal consistency of the modified IAT-L in Study 2 was satisfactory, supporting the reliability of this modified test. This internal consistency remained satisfactory in Study 3.

As far as the validity of the IAT-L is concerned, this thesis aimed to establish satisfactory concurrent, construct and predictive validity of this tool. The index of QoL was chosen in Study 1 as a criterion since previous studies had shown strong positive correlations of self-reported social support, and inverse correlations of self-reported loneliness with QoL. Since no significant associations were found between implicit loneliness and QoL in Study 1, the aim of Study 2 was to include a criterion which was *physiological*, as previous research had indicated that implicit tests were better correlates of physiological or more *objective* outcomes (e.g., Egloff et al., 2002). This was speculated as in contrast to the consciously-controlled responses on the conventional explicit measures, implicit measures elicit more automatic responses and hence are more likely to correlate with physiological outcomes which are also out of one's conscious control. Therefore, CVR to stress was used as an outcome in order to establish the predictive validity of the modified IAT of loneliness. Implicit loneliness as measured by the IAT-L (M) significantly correlated with one of the indices of CVR, while explicit loneliness did not correlate with this criterion. This finding supported the predictive validity of the IAT-L (M) in relation to an objective health-related outcome. Also, further analyses in Studies 2 and 3 confirmed the incremental validity of the IAT-L (M).

Although implicit loneliness significantly correlated with explicit loneliness only in Study 1, the fact that it tended to correlate with functional support indices (in Studies 1 and 2) provided evidence for the shared latent component theory which was proposed by Greenwald et al. (2003) to explain the implicit-explicit correlations. They used an analogy of height-weight to illustrate these correlations by asserting that just as a superior measure of height can change the height-weight correlation, the latent component in implicit-explicit is *implicit* which contributes to the explicit processes along with other factors such as presentational bias. Similar to *explicit*, weight can be understood as having contributions due to height, girth and density. Just as with height-weight correlations, the correlation between implicit and explicit can vary considerably for different samples. Implicit loneliness did not significantly correlate with social support indices in Studies 1 and 2. However, since components like support need and support satisfaction tended to be correlates of implicit loneliness, these components may be more relevant to implicit loneliness, whereas more *straightforward* indices of structural support (e.g., number of friends), possibly

more influenced by response biases, did not correlate with implicit loneliness. Further evidence for this came from the findings of Study 2 where support need significantly correlated with CVR along with implicit loneliness, suggesting that support need shared some common conceptual element with implicit loneliness.

8.4 Limitations, Implications and Recommendations for Future Research

The findings of this thesis should be viewed in the context of its limitations. Despite the large magnitude of the significant associations observed in this thesis, the cross-sectional design of the studies suggested that the findings should be interpreted with caution and causal inferences may not be drawn. Furthermore, in none of the studies, except Study 2, may we infer any conclusions about the direction of relations between social support, loneliness, and well-being. Due to time constraint, a prospective study on cancer progression was beyond the scope of this thesis. Therefore, the outcome of Study 3 included severity of cancer at diagnosis and four markers of biological importance in cancer, using a cross-sectional design. Methodologically sound prospective studies are needed in the future to investigate these questions and to find more conclusive answers.

The contamination by different factors such as human error in staining the tumour tissues and subjectivity in rating the strength of the staining to evaluate the levels of the biological markers could be minimised by employing more reliable procedures. More advanced and sophisticated methods are now available which can increase the reliability of the rating procedure such as the use of semi-automated computerised image analysis systems (Zafirellis et al., 2007) which could either replace or aid the rating done by pathologists, in order to make it more objective and reliable. Another limitation of Study 3 was its small sample size as the rate of recruitment was slower than anticipated and recruiting more patients was not possible due to time constraint. A bigger sample size would be an advantage for detecting the small effects.

There are ways in which more conclusive findings may be achieved by following this line of research in the future. For instance, taking into account that few studies have found a large magnitude of associations between the blood levels of

these proangiogenic cytokines and social support (Lutgendorf et al., 2002), future studies may also investigate the correspondence between the blood and in situ levels of these cytokines. However, in this context reliance on blood levels for Dukes D patients will be the only available option as they do not undergo surgical treatment and hence assessment of the in situ cytokine levels may not be possible.

Although the results for TNF-α and oxytocin were not significant in Study 3, due to accumulating research on their significance in cancer and their association with psychosocial factors, future research is needed to replicate the findings of this study on a larger sample. Larger samples may also enable the examination of moderating variables such as gender or family history, which have been found to moderate relations between psychosocial factors and disease severity in the literature (e.g., Vogt et al., 1992). Also, prospective research can measure post-surgery levels of disease severity markers such as CEA and cytokines, in order to explore their relationship with social support and to predict survival longitudinally.

Some of the proposed moderators were tested in this study including age and mood in the relationship between marital status and social support, and age, gender and education in the relationship between loneliness and patient delay. However, due to a small sample size, only theoretical and evidence-based hypotheses and moderation analyses were tested. Possible mediators could not be tested due to nonsignificant findings. Future studies may also wish to test the mediational role of the biological markers and mood in the relationship between social support and cancer severity. Assessing and testing moderators such as conflictual aspects of relationships and social distress may also provide novel and interesting insights into this area of research.

Research on the role of proangiogenic cytokines in cancer has led to interesting approaches to the treatment of cancer. For instance, major clinical trails have examined anti-VEGF agents as part of cancer immunotherapy to treat patients with advanced colorectal cancer (Carrato, Gallego-Plazas, & Guillen-Ponce, 2006; Dranoff, 2004). Additional anti-angiogenic therapies currently being tested with reference to cancer include the use of agents such as soluble receptors which *trap* soluble circulating VEGF (Rudge et al., 2005), and anti-VEGF monoclonal

antibodies which bind to VEGF with high affinity and neutralise all human VEGF fragments (Ferrara, Hillan, Gerber, & Novotny, 2004). From the treatment point of view, it is important to actively select patients with certain molecular characteristics who are more likely to benefit from these anti-angiogenic therapies, and to determine the factors and pathways of resistance to such treatments. Psychosocial factors including social support have been found to be associated with some of the important proinflammatory and proangiogenic markers in cancer. The cytokines and psychosocial factors have also been found to play a significant role in cancer progression and survival. Therefore, it may be important to identify patients who may be more vulnerable due to these factors, in order to take that into account and to enhance the efficacy of targeted immunotherapeutic interventions for cancer patients. Future studies may need to test whether these anti-angiogenic therapies are particularly effective in patients with little social support, and could examine the effects of such agents on social support. Randomised control trials (RCTs) and studies using within-subjects design could also explore the relevance of improving social support to these markers, by employing psychosocial interventions such as cognitive behavioural therapy (CBT) and support groups.

There is growing evidence suggesting that oxytocin can lead to a reduction in cancer cell proliferation. For instance, Morita et al. (2004) found that the in vivo intraperitoneal administration of oxytocin resulted in the reduction of intraperitoneal dissemination of ovarian cancer cells and of average tumour burden as compared to the control group. Also, the evidence discussed in Chapter 4 suggested that lower levels of psychosocial stress-related oxytocin could lead to higher levels of migration and invasion of tumour cells through the HPA axis activation. The implications of these findings are two-fold: these may support psychosocial interventional trials for lonely cancer patients, and supplement these interventions with oxytocin therapy trials. However, further research is warranted to establish the anti-cancer effects of oxytocin and the effects of this hormone on loneliness.

8.5 Concluding Comments

This thesis has attempted to make a contribution to the field of health psychology by introducing the use of implicit testing of loneliness, and attempting to

test its relevance to various measures of well-being and health. The CVR study was the first of its kind which used this implicit test to investigate the relationship between social support, loneliness and CVR to stress. Future studies may wish to take this further in order to establish the reliability and validity of this implicit test in the context of other health outcomes. Another contribution of this thesis was the systematic evaluation of the evidence on the role of two important indices of social support in cancer progression. Despite nonsignificant findings, the main study of this thesis provided a unique impetus for future research in the areas of psycho-oncology and psychoneuroimmunology of cancer. While the only significant relation observed must be viewed with great caution, it is in line with that of Study 2, and suggested that loneliness may be related to an important proangiogenic factor in cancer. Future studies need to test these relations in larger and prospective studies with cancer progression (or prognosis) as the main outcome.

Appendices

Appendix A: Demographic Information Sheet

Please complete the following:

Gender: Male Female

Age (in years):

Implicit Association Test

Press [i] to continue

The tasks that you will be doing in this experiment involve CATEGORY JUDGMENT. On each trial, a stimulus will be displayed, and you must assign it to one of two categories. You should respond AS RAPIDLY AS POSSIBLE in categorising each stimulus, but do not respond so fast that you make many errors (occasional errors are okay).

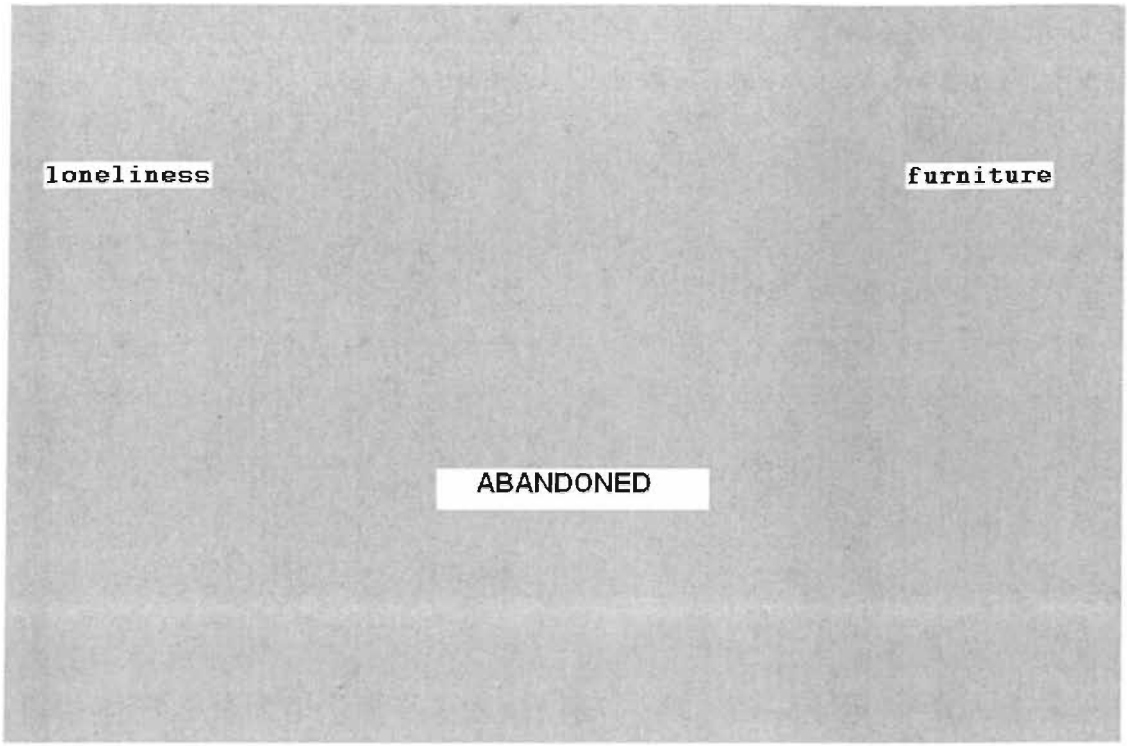
The two categories that you are to distinguish are:

LONELINESS vs. FURNITURE.

Press the 'e' key if the stimulus is a LONELINESS word.

But press 'i' key if the stimulus is a FURNITURE word.

Press [i] to continue



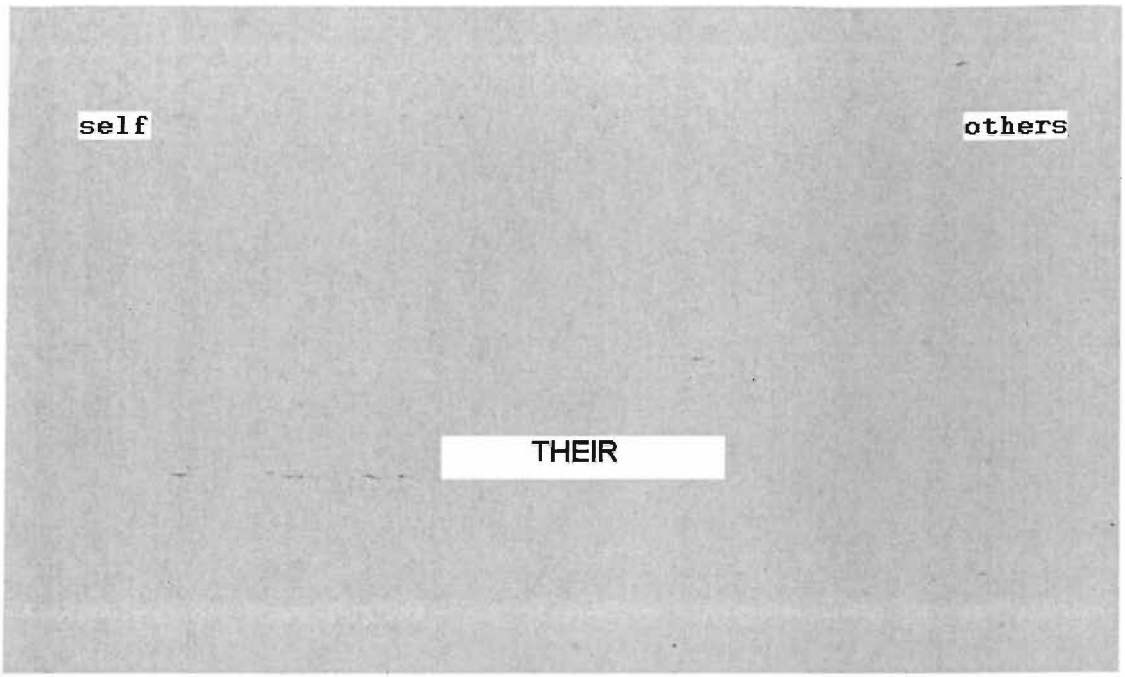
The two categories that you are to distinguish are:

SELF vs. OTHERS.

Press the 'e' key if the stimulus is a SELF word.

But press 'i' key if the stimulus is an OTHERS word.

Press [i] to continue



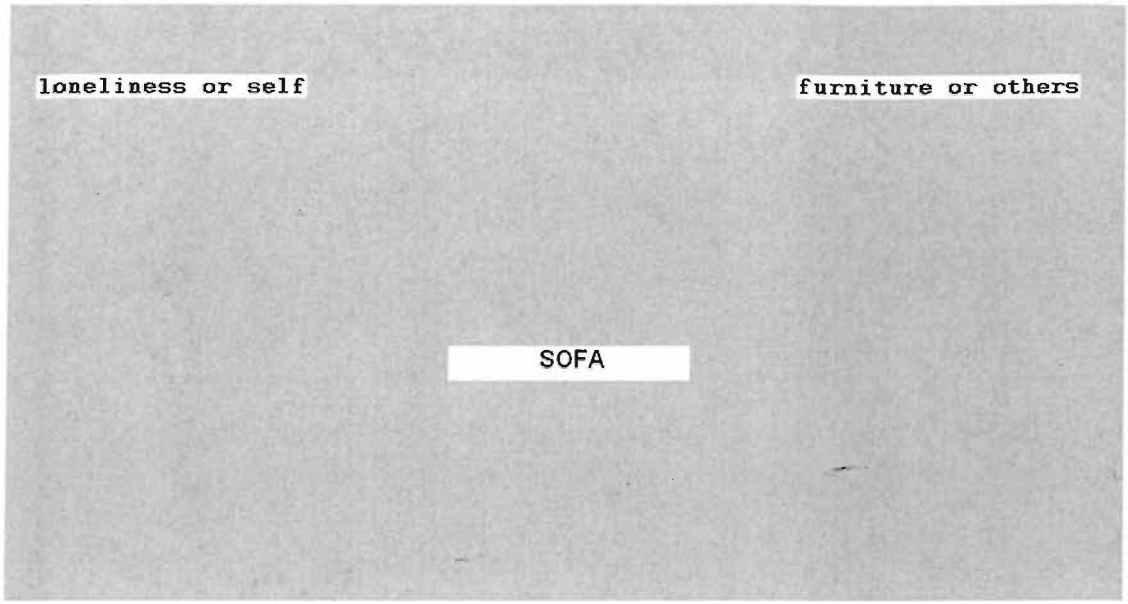
The four categories that you are to distinguish are:

LONELINESS vs. FURNITURE.
or
SELF vs. OTHERS.

Press the 'e' key if the stimulus is
a LONELINESS or a SELF word.

But press 'i' key if the stimulus is
a FURNITURE or an OTHERS word.

Press [i] to continue



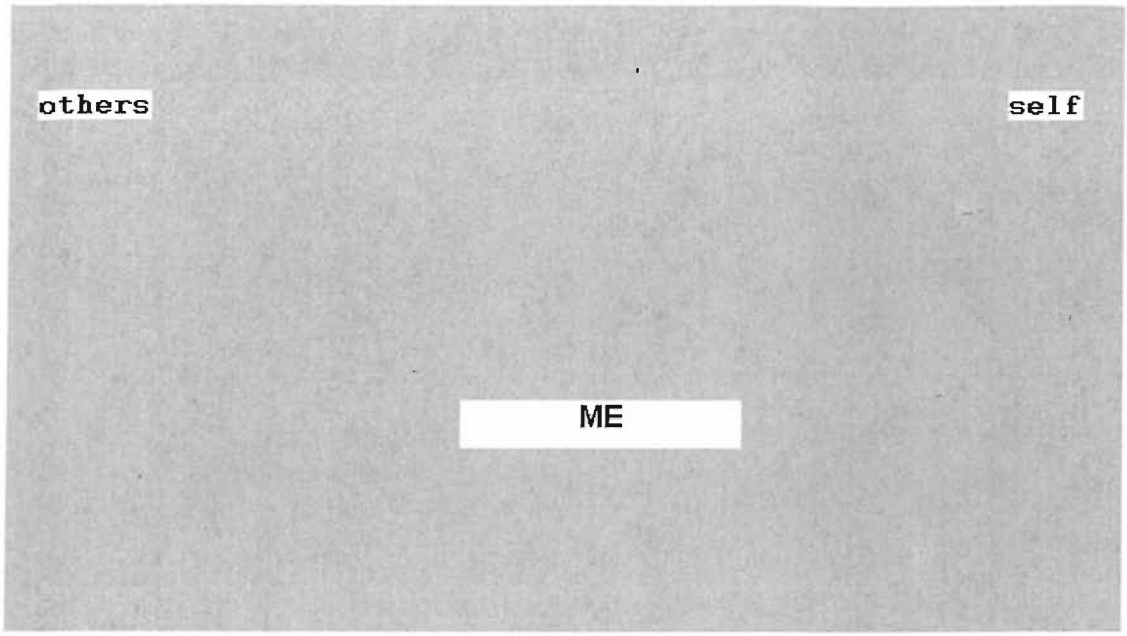
The two categories that you are to distinguish are:

OTHERS vs. SELF.

Press the 'e' key if the stimulus is an OTHERS word.

But press 'i' key if the stimulus is a SELF word.

Press [i] to continue



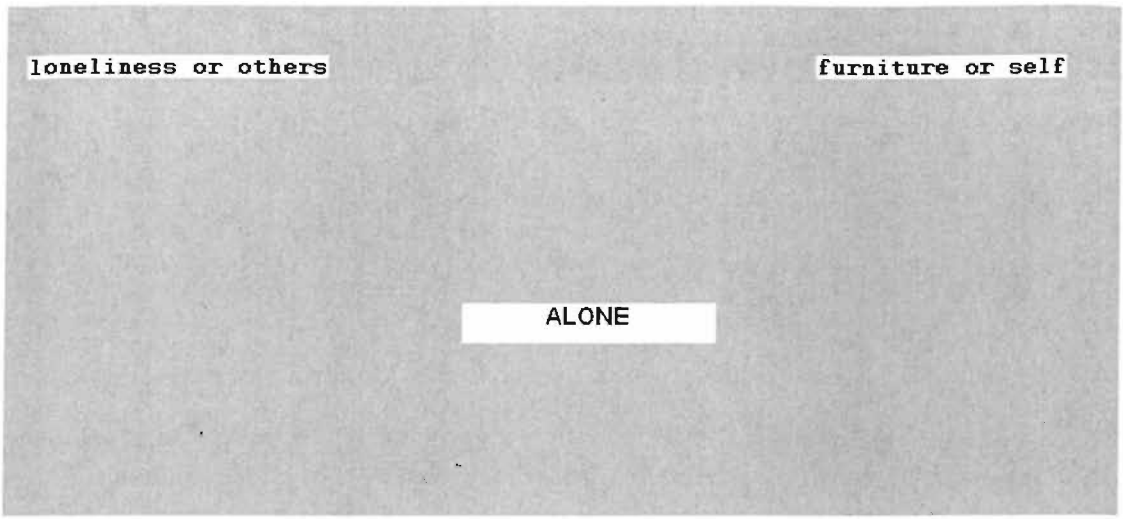
The four categories that you are to distinguish are:

LONELINESS vs. FURNITURE.
or
OTHERS vs. SELF.

Press the 'e' key if the stimulus is
a LONELINESS or an OTHERS word.

But press 'i' key if the stimulus is
a FURNITURE or a SELF word.

Press [i] to continue



The Implicit Association Test is now concluded. If you have any questions or reactions to the experiment, please discuss them with the experimenter.

Press [i] to continue

Appendix C: List of Stimulus Words – IAT-L

Category: SELF	Category: OTHERS
Me	Their
My	They
Mine	Them
I	Other

Category: LONELINESS	Category: FURNITURE
Lonely	Sofa
Alone	Cupboard
Isolated	Chair
Abandoned	Table

Appendix D: UCLA Loneliness Scale (Version 3)

Instructions: The following statements describe how people sometimes feel. For each statement, please indicate how often you feel the way described by writing a number in the space provided. Here is an example:

How often do you feel happy?

If you never felt happy, you would respond "never"; if you always feel happy, you would respond "always".

NEVER	RARELY	SOMETIMES	ALWAYS
1	2	3	4

____ 1. How often do you feel that you are "in tune" with the people around you?
____ 2. How often do you feel that you lack companionship?
____ 3. How often do you feel that there is no one you can turn to?
____ 4. How often do you feel alone?
____ 5. How often do you feel part of a group of friends?
____ 6. How often do you feel that you have a lot in common with the people around you?
____ 7. How often do you feel that you are no longer close to anyone?
____ 8. How often do you feel that your interests and ideas are not shared by those around you?
____ 9. How often do you feel outgoing and friendly?
____ 10. How often do you feel close to people?
____ 11. How often do you feel left out?
____ 12. How often do you feel that your relationships with others are not meaningful?
____ 13. How often do you feel that no one really knows you well?
____ 14. How often do you feel isolated from others?
____ 15. How often do you feel you can find companionship when you want it?
____ 16. How often do you feel that there are people who really understand you?
____ 17. How often do you feel shy?
____ 18. How often do you feel that people are around you but not with you?
____ 19. How often do you feel that there are people you can talk to?
____ 20. How often do you feel that there are people you can turn to?

Note: interviewer instructions are enclosed within parentheses. Responses should be recorded on ASSIS answer sheets.

(Read to subject):

In the next few minutes I would like to get an idea of the people who are important to you in a number of different ways. I will be reading descriptions of ways that people are often important to us. After I read each description, I will be asking you to give me the first names, the initials, or nicknames of the people who fit the description. These people might be friends, family members, teachers, priests, ministers, doctors, or other people who you might know.

If you have any questions about the descriptions I have read, please ask me to try to make it clearer.

A. Intimate Interaction

A1. If you wanted to talk to someone about the things that are very personal and private, who would you talk to? Give me the first names, initials, or nicknames of people who you would talk to about things are very personal and private.

(If the subject is unable to name a single person, go to A4).

(If the subject names one or more people, probe for any additional names by asking: is there anyone else you can think of?)

A2. During the last month, which of these people did you actually talk to about things that were personal and private?

(Inquire about people who were listed in response to A1, but who were not listed in response to A2)

A3. How would you rate your satisfaction or dissatisfaction with the times you talked to people about your personal and private feelings during the past month?

Look at this card (shows satisfaction card) and tell me which number best describes your rating. (Record a number 1-7 on the answer sheet)

A4. During the past month, how much do you think you needed people to talk to about things that were very personal and private?

Look at this card (show need card) and tell me which number best describes your need. (Record number 1-5 on answer sheet)

B. Material aid

B1. If you needed to borrow £25 or something valuable, who are the people you know who would loan or give you £25 or more, or would give you something (a physical object) that was valuable?

You can name some of the same people that you named before if they fit this description, or you can name some other people.

(If the subject is unable to name a single person, go to B4)

(If the subject names one or more people, probe for any additional names by asking: is there anyone else you can think of?)

B2. During the past month, which of these people actually loaned or gave you some money over £25 or gave or loaned you some valuable object that you needed?

(Inquire about people who were listed in response to B1 but who were not listed in response to B2)

B3. During the past month, how satisfied or dissatisfied were you with the things that people loaned or gave to you?

(Show satisfaction card; record response on answer sheet)

B4. During the past month, how much you think you needed people who could loan or give you things that you needed?

(Show need card; record response on answer sheet)

C. Advice

C1. Who would you go to if a situation came up when you needed some advice?

Remember, you can name some of the same people who you mentioned before, or you can name some new people.

(If the subject is unable to name a single person, go to C4)

(If the subject names one or more people, probe for any additional names by asking: Is there anyone else?)

C2. During the past month, which of these people actually gave you some important advice?

(Inquire about people who were listed in response to C1, but who were not listed in response to C2)

C3. During the past month, how satisfied or dissatisfied were you with the advice that you were given?

(Show satisfaction card; record response on answer sheet)

C4. During the past month, how much you think you needed to get advice?

(Show need card; record response on answer sheet)

D. Positive feedback

D1. Who were the people who could let you know you when they like your ideas or the things that you do? They might be people you mentioned before or new people.

(If the subject is unable to name a single person, go to D4)

(If the subject names one or more people probe for any additional names by asking: Is there anyone else?)

D2. During the past month, which of these people actually let you know that they liked your ideas or the things that you did?

(Inquire about people who were listed in response to D1, but who were not listed in response to D2)

D3. During the past month, how satisfied or dissatisfied were you with the times that people told you that they liked your ideas or the things that you did?

(Show satisfaction card; record response on answer sheet)

D4. During the past month, how much you think you needed to have people let you know when they liked your ideas or the things that you did?

(Show need card; record response on answer sheet)

E. Physical assistance

E1. Who are the people who you could call on to give up some of their time and energy to help to take care of something that you needed to do--things like driving you someplace you needed to go, helping you do some work around the house, going to the store for you, and things like that? Remember, you might have listed these people before or they could be new names.

(If the subject is unable to name a single person, go to E4)

(If the subject names one or more people, probe for any additional names by asking: Is there anyone else?)

E2. During the past month which of these people actually pitched in to help you do things that you needed some help with?

(Inquire about people who were listed in response to E1, but who were not listed in response to E2)

E3. During the past month, how satisfied or dissatisfied were you with the help you received in doing these things that you needed to do?

(Show satisfaction card; record response on answer sheet)

E4. During the past month, how much did you feel you needed people who would pitch in to help you do things?

(Show need card; record response on answer sheet)

F. Social participation

F1. Who are the people who you could get together with to have fun or to relax? These could be new names or ones you've listed before.

(If the subject is unable to name a single person, go to F4)

(If the subject names one or more people, probe for any additional names by asking: Is there anyone else?)

F2. During the past month, which of these people did you actually get together with to have fun or to relax?

(Inquire about people who were listed in response to F1, but who were not listed in response to F2)

F3. During the past month how satisfied or dissatisfied were you with the times that you got together with people just have fun and relax?

(Show satisfaction card; record response on answer sheet)

F4. How much do you think that you needed to get together with other people for fun and relaxation during the past month?

(Show need card; record response on answer sheet)

Satisfaction Card

1. very dissatisfied
2. moderately dissatisfied
3. slightly dissatisfied
4. neither satisfied or dissatisfied
5. slightly satisfied
6. moderately satisfied
7. very satisfied

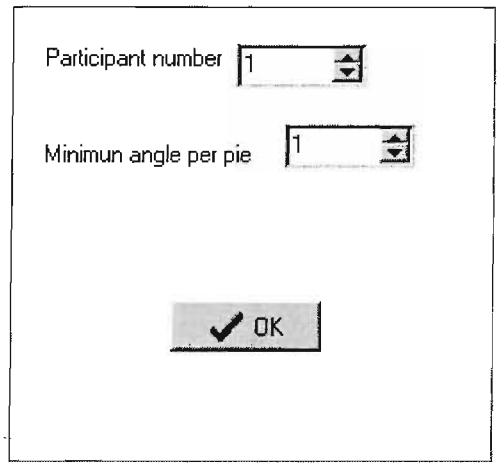
Need Card

1. no need at all
2. slight need
3. moderate need
4. great need
5. very great need

ASSIS Scoring Sheet

Participant #---------- Date:----------

	A		B		C		D		E		F	
Network Members												
1.												
2.												
3.												
4.												
5.												
6.												
7.												
8.												
9.												
10.												
11.												
12.												
13.												
14.												
15.												
Totals												
Support Satisfaction Support Need	3/4		3/4		3/4		3/4		3/4		3/4	

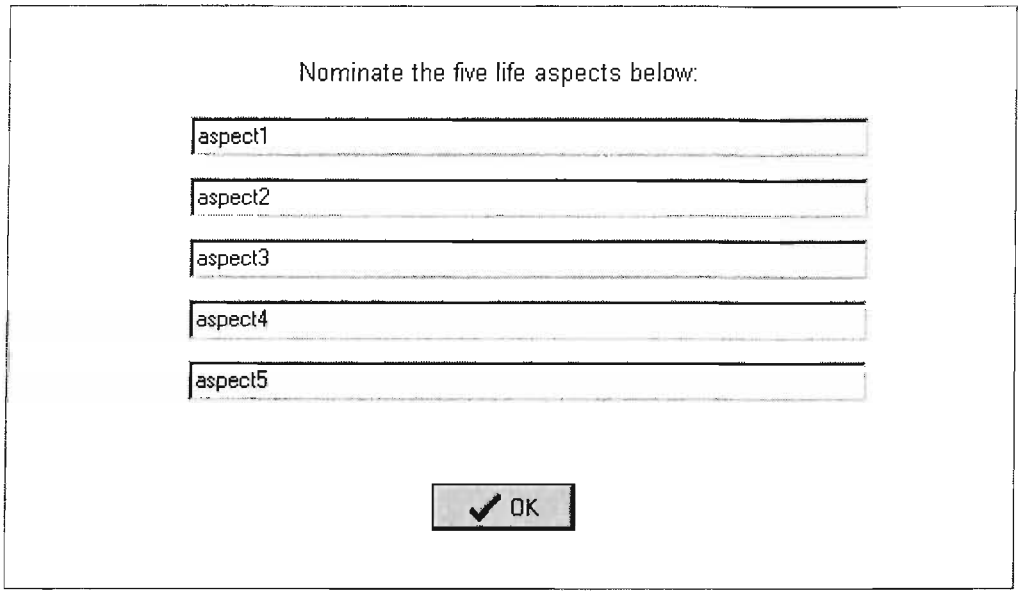


Dear Participant,

In the first step, you are asked to name the five most important aspects or areas in your life which determine your quality of life at the moment.

When you are ready, please click the button below to start.

Please click here when you are ready to start

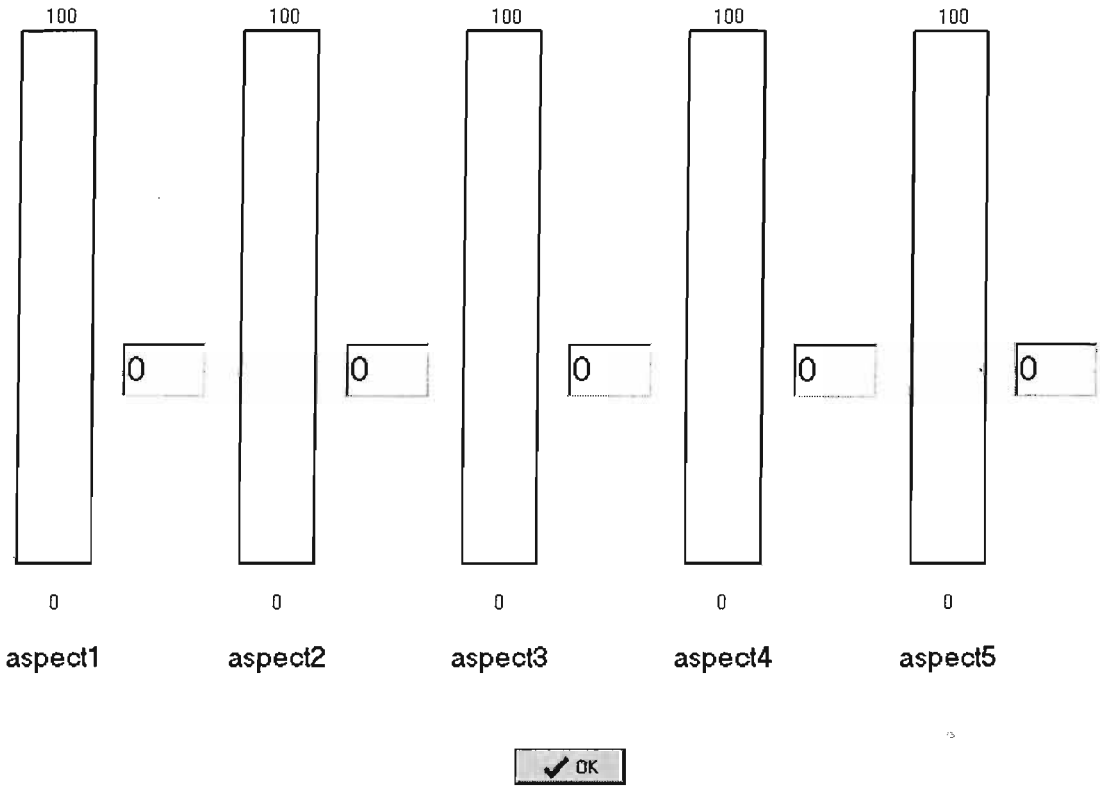


Please rate your current level of satisfaction on each of the aspects you just nominated.

Insert any number from 0 to 100 in the boxes provided, corresponding to your level of satisfaction, where 0 = "not at all satisfied" and 100 = "extremely satisfied".

When you are ready, please click the button below to start.

Please click here when you are ready to start

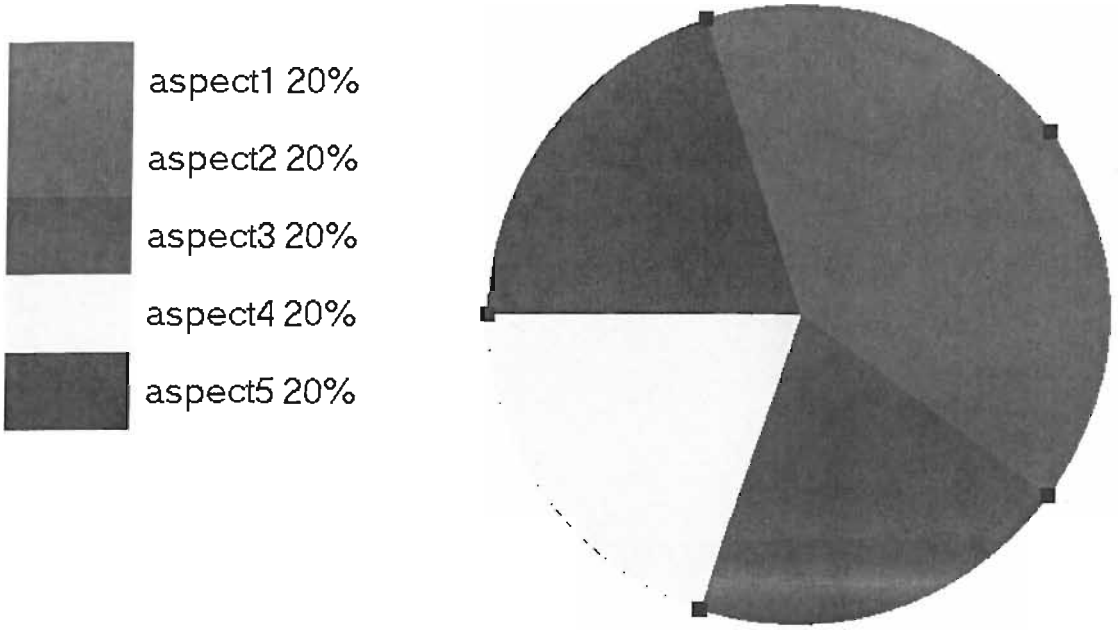


In this final step, we ask to determine the relative importance of each aspect of your life, by adjusting its size in a coloured circle.

The five colours depict your nominated aspects of life, and you can drag the small black square at the edge of each area, to adjust it until the size reflects each aspect's importance in your quality of life.

When you are ready, please click the button below to start.

Please click here when you are ready to start



OK

We thank you for your time and cooperation.

Please click here to end the experiment

Appendix G: Consent Form for Research Participants

Interactions in Daily Life

I am Bina Nausheen, a PhD research student at the School of Psychology. I am requesting your participation in a study regarding your social interactions in daily life. This will involve a reaction time test, a brief interview, a questionnaire and a quality of life measure. Your personal information will not be released to or viewed by anyone other than researchers involved in this project. Results of this study will not include your name or any other identifying characteristics.
Your participation is voluntary and you may withdraw your participation at any time. If you choose not to participate there will be no consequences to your grade or to your treatment as a student.
A debriefing statement will be supplied to you after you complete the study. If you have any questions please ask them now, or contact me at: 023 8059 4594 (internal: 24594) or email at bn1@soton.ac.uk

Sincerely
Bina Nausheen

Statement of Consent
I _____ have read the above informed consent form.

I understand that I may withdraw my consent and discontinue participation at any time without penalty or loss of benefit to myself. I understand that data collected as part of this research project will be treated confidentially, and that published results of this research project will maintain my confidentiality. In signing this consent letter, I am not waiving my legal claims, rights, or remedies. A copy of this consent letter will be offered to me.

(Circle Yes or No)

I give consent to participate in the above study Yes No

Signature Date
Name
I understand that if I have questions about my rights as a participant in this research, or if I feel that I have been placed at risk, I can contact the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ.
Phone: (023) 8059 3995.

Appendix H: Consent Form for Research Participants

Information Sheet

We are requesting your participation in a study regarding the social interactions and performance of tasks in daily life, and your response to them.

You will be randomly allocated to either the experimental or control group. The brief tasks that you will then be asked to perform will depend on the group you are in.

This study will also involve an interview, two questionnaires, and a computerised test. Your physiological state will also be monitored. However, you will not undergo any kind of pain.

This study will take maximum 70 minutes. Your personal information will not be released to or viewed by anyone other than researchers involved in this project. Results of this study will not include your name or any other identifying characteristics.

Your participation is voluntary and you may withdraw your participation at any time. If you choose not to participate there will be no consequences to your grade or to your treatment as a student.

A debriefing statement will be supplied to you after you complete the study. If you have any questions please ask them now, or contact at: 023 8059 4594 (internal: 24594) or email at hst103@soton.ac.uk

Sincerely

Bina Nausheen

Statement of Consent

I _____ have read the above informed consent form.
[participant's name]

I understand that I may withdraw my consent and discontinue participation at any time without penalty or loss of benefit to myself. I understand that data collected as part of this research project will be treated confidentially, and that published results of this research project will maintain my confidentiality. In signing this consent letter, I am not waiving my legal claims, rights, or remedies. A copy of this consent letter will be offered to me.

(Circle Yes or No)

I give consent to participate in the above study. Yes No

Signature Date

Name

I understand that if I have questions about my rights as a participant in this research, or if I feel that I have been placed at risk, I can contact the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ.
Phone: (023) 8059 3995.

Debriefing Statement

The aim of this research is to explore the quality of interactions and social support networks in daily life and their effect on physical health.

Previous research has shown that psychosocial aspects have a strong influence on physical health and well-being. This study also aims to develop tests, which may be able to predict these physiological outcomes better.

Once again results of this study will not include your name or any other identifying characteristics. You may have a copy of this summary if you wish. If you have any further questions please contact me at 023 8059 4594 or email at hst103@soton.ac.uk

Thank you for your participation in this research.

Bina Nausheen

If you have questions about your rights as a participant in this research, or if you feel that you have been placed at risk, you may contact the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ.
Phone: (023) 8059 3995.

Appendix J: Complete Protocol - Trier Social Stress Test (TSST)

Experimental Group

Initial instructions (before rest period) in Room 1:

Please take a seat and relax for a few minutes.

After 2-3 minutes, take the Participant to Room 2. Demonstrate the following:

- *There is a video camera that is directed towards the middle of the room.*
- *Behind this one-way mirror sits a committee that I'm going to tell you about in a minute.*

Speech task - Instructions (by the Experimenter):

- ***You will have to deliver a speech for a job application to the committee, for which you will have ten minutes to prepare.***
- ***Imagine you have applied for a job as a research assistant in this school and you were invited to present yourself before a committee which will evaluate you on the basis of your personal characteristics. Your task in this experiment is to convince the committee in a free speech that you are the best candidate for the vacant position.***
- ***The committee members are seated in an adjacent room and can see you though this one-way mirror.***
- ***This speech would be filmed and voice recorded.***
- ***Please note that we will record your speech for a subsequent voice frequency analysis to reveal any paraverbal signs of stress.***
- ***The camera recording is used for later behavioural analysis.***
- ***Members of the committee would take notes regarding the manner and contents of the speech.***
- ***A member of the committee is trained in behavioural observation and your behaviour would be accordingly documented.***
- ***As for the speech, you should imagine that you have applied for a position and are invited by this school to introduce yourself to the selection committee.***
- ***The speech should take about five minutes.***
- ***A second task will follow it, about which you would only learn more after delivering the speech.***
- ***Do you have any questions?***

Instructions (by the Experimenter) in Room 1 (pre-preparation):

- ***Your participant number is*** (tell the serial number).
- ***You can make written notes about your speech.***
- ***These notes may not be taken into the experimental room (2), but they are for your personal preparation.***
- ***It is important to make believable impression, because committee members will ask additional questions in case of disagreement.***
- ***You are now given ten minutes to prepare for the speech.***

- ***Your time starts now.***

Setup in Room 2 (speech task):

(The Participant is not informed that the committee includes only one member).

To committee members: *Could you turn the recording equipment on please.*

- The Committee opens up the session with the words: ***please step behind the line, name your participant number and begin your speech.***
- The Committee remains quiet, as long as the Participant continues to speak fluently.
- Let the Participant speak for the first three minutes. In most cases the Participant will come to the end of the speech even before three minutes have passed.
- Give the Participant then time to formulate additional elaborations.
- After about first 20 seconds pause alert the Participant to the remaining time, as with the phrase: ***you still have time, please continue...***
- Should it appear after another 10 seconds that the Participant has nothing further to say, then the Committee should ask questions until the end of the time period.
- The phrasing of these questions may be solely oriented on the Participant's previous statements.
- Typical questions in this context are:

1. Why do you think that you are the best applicant for this position?
2. What other experiences have you had in this area?
3. What about your studies identify a special aptitude and motivation for this position?
4. Where else did you apply? Why?
5. What would you do, if your application here would not succeed?

- It is not appropriate for the Participant to speak in great detail about specific lessons one may have learned in the course of one's training at university or elsewhere. Some Participants use their school-knowledge to distract from their own person. In that case the Committee should certainly intervene, for example, by saying: ***we believe you that you know how to execute ... but we would be more interested to find out why you were so involved in this area.***

Arithmetic task - Instructions (by the Committee):

- ***Thank you very much. We now want you to work on a second task, which is different and has nothing to do with the first one.***
- ***We now want you to solve a calculation task.***
- ***Please count aloud backwards from 1687 to zero in 13-step sequences.***
- ***Please calculate as quickly and correctly as possible.***
- ***Should you miscalculate, we will point out your mistake and you have to start all over again at 1687.***
- ***Do you have any questions?***

- ***Please begin then...***
- Should the participant miscalculated, the committee will respond with the standard phrase: ***ERROR, 1687.***
- The committee should note the number of errors and the number the participant eventually reached as a performance measure.
- At the end of the test period the committee should thank the participant for her participation.

Important points to remember (for the Experimenters):

- Before and during the rest period the Participant should not be informed in greater detail about the exact procedure of the experiment.
- If there should be any questions about the specific content of the experiment, the Experimenter should reply with a rather general statement about a psychological stress situation and refer to a later introduction for details.
- After the reception the Participant is led to the rest area; at this point the purpose of the rest can be explained to the Participant.
- Note the exact time of the beginning of the rest period.
- Introduction and preparation together should take about ten minutes; depending on the introduction (usually about 2 minutes) there should be about 8 +/- one minutes time for the Participant to prepare.
- The Experimenter should alert the Participant at this time to the fact that the written notes may not be taken into speech room and that they only serve for the Paricipant's mental organisation.
- The preparatory period should be spent by the Participant alone.
- There should be no laughing during the speech.
- The point of the asking questions is not to embarrass the Participant or be mean to them.

<u>Control Group</u>

Speech Task:

Participant No.
Imagine you have applied for a job as a research assistant in Psychology. Your task in this experiment is to write a letter of application to the school for this post. You have 15 minutes to perform this task.

Arithmetic Task:

Participant No.
In the present task you are required to perform simple paper-and-pencil arithmetic calculations. Your task is to calculate backwards to zero in 13-number steps, starting at 1687, and to do it as fast and correctly as possible.

1687 – 13 = 1674

1674 – 13 =

Appendix K: Demographic Information Sheet

1. Age:

2. Relationship status: (circle one)

Single With a partner Married/Living as married Divorced/Separated

Widowed

Appendix L: The Fear of Negative Evaluation (FNE) Scale-Brief Version

Please note that the questionnaire has no right or wrong answers. Your responses will be kept in the strictest confidence within our research team and will be used for research purposes only. I may contact you tomorrow to arrange a time convenient with you to take part in the remainder of the study.

Read each of the following statements carefully and indicate how characteristic it is of you according to the following scale:

	NOT AT ALL	SLIGHTLY	MODERATELY	VERY	EXTREMELY
1. I worry about what other people will think of me even when I know it doesn't make a difference.	1	2	3	4	5
2. I am unconcerned even if I know people are forming an unfavourable impression of me.	1	2	3	4	5
3. I am frequently afraid of other people noticing my shortcomings.	1	2	3	4	5
4. I rarely worry about what kind of impression I am making on someone.	1	2	3	4	5
5. I am afraid that others will not approve of me.	1	2	3	4	5
6. I am afraid that people will find fault with me.	1	2	3	4	5
7. Other people's opinions of me do not bother me.	1	2	3	4	5
8. When I am talking to someone, I worry about what they may be thinking about me.	1	2	3	4	5
9. I am usually worried about what kind of impression I make.	1	2	3	4	5

	NOT AT ALL	SLIGHTLY	MODERATELY	VERY	EXTREMELY
10. If I know someone is judging me, it has little effect on me.	1	2	3	4	5
11. Sometimes I am too concerned with what other people think of me.	1	2	3	4	5
12. I often worry that I will say or do the wrong things.	1	2	3	4	5

Appendix M: Visual Analogue Scale (VAS)

Participant No:

Pre:

Post:

Appendix N: Words for Judges & Final List of Stimulus Words for the IAT-L (M)

Instructions: Please rate the relevance of the following words to their respective "lonely" or "non-lonely" category on a 1-5 scale.

1 Not at all relevant	**2** Slightly relevant	**3** Moderately relevant	**4** Quite a bit relevant	**5** Extremely relevant

Lonely		**Non-lonely**	
Abandoned	_____	Accompanied	_____
All alone	_____	Beloved	_____
Alone	_____	Cared for	_____
By my self	_____	Grouped	_____
Companionless	_____	In-demand	_____
Deserted	_____	Liked	_____
Detached	_____	Looked-after	_____
Friendless	_____	Lovable	_____
Isolated	_____	Loved	_____
Lone	_____	Outgoing	_____
Lonesome	_____	Popular	_____
Unaccompanied	_____	Sociable	_____
Unaided	_____	Social	_____
Unassisted	_____	Supported	_____
Unattached	_____	Together	_____
Unloved	_____	Well-liked	_____

List of Stimulus Words – IAT-L (M)

Category: SELF	Category: OTHERS
I	They
Me	Them
My	Their
Mine	It
Myself	Other

Category: LONELY	Category: NONLONELY
All alone	Supported
Abandoned	Cared for
Unloved	Loved
Deserted	Looked after
Isolated	Beloved

Appendix P: Patient Information Sheet
(Printed on School of Psychology Letterhead)

Version: CL/05(ii)
Date: 12.07.2005

Covering Letter and Patient Information Sheet

A Research Project:

Social relationships and colorectal cancer.

This letter contains an invitation to take part in a research study. It is being given to you at the pre-assessment clinic (Southampton General Hospital). This study is entirely separate from your appointment. If you decide not to take part in the study, this will not affect your future screening or treatment in any way. Thank you for reading this letter.

This study is involves a short computer task, a brief interview and two questionnaires. It will take maximum 35-40 minutes and will be conducted in the ward where you will be admitted for your surgery. In order to help you to decide whether or not to take part in the study, we have enclosed an information sheet, outlining the background and aims of the study. This letter is being given to every patient diagnosed with colorectal cancer in the clinic you are attending.

Although you are unlikely to benefit directly from taking part in the study, the information gained may help us improve the treatment of patients in the future.

I encourage you to contact me at the following phone number or email address before you are admitted to the ward. I would be happy to discuss this study in detail with you or answer any queries that you may have regarding this study. A summary of study results will be available upon request at the end of the project.

If you do decide to take part, please remember that you are free to withdraw your consent at *any* time. Thank you for your time.

Bina Nausheen.
PhD research student,
School of Psychology,
University of Southampton.

Telephone: 023 8059 4719
Email: bn1@soton.ac.uk

TAKING PART IN RESEARCH

You are being invited to take part in a research project. Here is some information to help you decide whether or not to take part. Please take your time to read the following information carefully and discuss it with others if you wish. Please contact Bina (contact details given on the previous page) if there is anything that you do not understand or if you would like more information. Thank you for reading this.

It is up to you to decide whether or not to take part. Even if you decide to take part, you will be free to withdraw at any time and without giving a reason. This will not affect the standard of your care. If you decide not to take part, nobody will mind.

All of the information gathered about you during the course of this research will be kept strictly confidential. If the final report is published, it will not identify you.

Your consultant surgeon is informed that you have been requested to take part. Your GP will be notified about your participation. If this is a problem for you, you should discuss this with the researcher.

Social relationships and colorectal cancer

Information for Participants

Date: 12.07.2005
Version: PIS/05(ii)

1. What is the purpose of this study?

Research has shown associations between social relationships and physical health. The aim of this study is to investigate the relationship between the quality of social relationships and colorectal cancer. The development of better understanding of these associations may lead to some important implications for the well-being and treatment of cancer patients in the future.

2. Who is participating in this study?

This letter is being given to every patient diagnosed with colorectal cancer and undergoing surgery in the clinic you are attending. The study will include approximately 50 patients.

3. Who is organising the study?

This study has been organised by Bina Nausheen, who is a PhD research student at Southampton University, Dr Yori Gidron at Southampton University, and Prof Robert Peveler at School of Medicine, Southampton University. Co-investigators in this study are Miss Karen Nugent (Consultant Surgeon), Dr Liz Bruce, and Dr Clare Verrill (Registrars, Pathology) from Southampton University Hospitals Trust.

It is funded by the School of Psychology, University of Southampton.

4. What will I have to do if I take part?

After you are admitted to the ward 2 days before the surgery, the researcher will meet you and ask you if you would like to ask any questions or discuss the study. You can choose not to discuss and not to take part in the study and nobody will mind. If you choose to talk, she will discuss with you the procedures involved in the study and will answer your queries. Your consultant surgeon and a clinical nurse specialist will also be present.
Please remember that a decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

The study will take approximately 35-40 minutes and will be conducted in a private room at the ward.

You will be asked to sign a consent form before beginning the study. The study consists of the following steps:

Firstly, you will be asked to talk about your daily life interactions in a brief interview. You will then be asked to fill in a short questionnaire.

Next is a computerised task. It will involve responding as quickly as possible to some prompts on a computer screen by pressing keys on the computer keyboard. You don't need to be familiar with using the computer. The task will only involve pressing one of the two assigned keys after seeing different words on the screen. Complete instructions will be provided.

Finally, you will be asked to fill in another brief questionnaire.

You will be free to withdraw from the task at any point and you can have the opportunity for rests between the tasks.

Medical records

Information regarding your current medical state and treatment will be taken from your medical records for the purpose of this research. However, your name and other personal details will remain strictly confidential.

Tests on surgical excisions

Some further pathological tests will be carried out on the tissues after they are surgically removed. This surgery is a part of your routine treatment. You will not have to have any extra samples taken if you agree to take part in the study.

5. What are the possible benefits of taking part?

There will be no direct benefit to you. However, the results of this study may help to develop future treatments for patients.

6. What if something goes wrong?

It is highly unlikely that taking part in this study could harm you. However, in case of any discomfort, testing session will be terminated. If you have any grounds to complain about any aspect of the way you have

been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

7. Confidentiality – Who will know that I am taking part in this study?

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the clinic or hospital, will be anonymous, so you can not be recognised from it.

8. Surgeon/GP notification

Your surgeon is informed that you have been requested to take part in this study. If you agree to take part, your surgeon and GP will be notified. If this is of concern to you however, you should talk to the researcher about it.

9. LREC approval

This study has been approved as ethical by Southampton & South West Hampshire Local Research Ethics Committee (LREC).

10. What will happen to the results of this study?

The results of the study will be written-up to form part of a doctoral thesis to be submitted by the researcher in 2007. The results will only describe group/pooled data: individual participants will not be identified. If you want to receive a summary of completed report (this may not be for 2-3 years), it can be arranged through the researcher. If the report/article is published in an academic or practice-based journal, your name will not appear anywhere in the text and you will not be recognisable.

11. Further information

Further information about this study can be obtained from Bina Nausheen, who will be carrying out the research. She can be contacted at the School of Psychology, University of Southampton, Highfield, Southampton, SO17 1BJ.
Telephone: 023 8059 4719. Email: bn1@soton.ac.uk

Appendix Q: Consent Form
(Printed on School of Psychology Letterhead)

Version: CF/03
Date: 30.03.2005

Patient Identification Number for this trial:

CONSENT FORM

Title of Project: Social relationships and colorectal cancer.

Name of Researcher: Bina Nausheen.

1. I confirm that I have read and understand the information sheet dated 12.07.2005 (version CL/05-ii) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the University of Southampton or from regulatory authorities where it is relevant to my taking part in research. ☐

   I give permission for these researchers to have access to my records. ☐

4. I agree that some further pathological tests will be carried out on the tissues that are surgically removed as a part of my routine treatment. This will be done after the tissues are removed. ☐

5. I agree that my GP will be notified about my participation in this study. ☐

6. I agree to take part in the above study.

Name of Patient	Date	Signature
Researcher	Date	Signature

Version: D1/03

Date: 30.03.2005

Sociodemographic information & life-style habits

Are you taking part in any other research project at the clinic? Yes / No

1. Age:
2. Gender:
3. Marital status: (circle one)

Single Married / Living as married Divorced / Separated Widowed

4. The highest qualification you have reached (circle one):

Below GCSE GCSE / O level A level Vocational qualification or degree Higher degree

5. Ethnicity: (circle one)

White Black Asian Other Do not wish to answer

6. Are you a vegetarian? Yes / No If yes, go to 7.

Do you eat more fruits and vegetables than meat? Yes / No

Do you eat more white meat than red meat? Yes / No

7. Indicate the number of flights climbed, yards walked, and amount of light and strenuous sports engaged in, during a typical week.

Number of flights of stairs climbed:
Number of times approx. 100 yards/meters walked:
Number of times spent in doing light sports:
Number of times spent in doing strenuous sports:

8. Do you smoke? Yes / No

9. Have any members of your family (Blood relatives, not relatives by marriage) had bowel cancer? (circle one)

Mother Father Son (s) Daughter (s) Sister (s) Brother (s) No one

10. When did you first notice symptoms of colorectal cancer (e.g., in June 2004)?

Month: Year:

Specific symptoms:

Rectal bleeding Month:
Year:

Change in bowel habit especially without abdominal pain Month:
Year:

11. When did you first consult your GP about your symptoms?

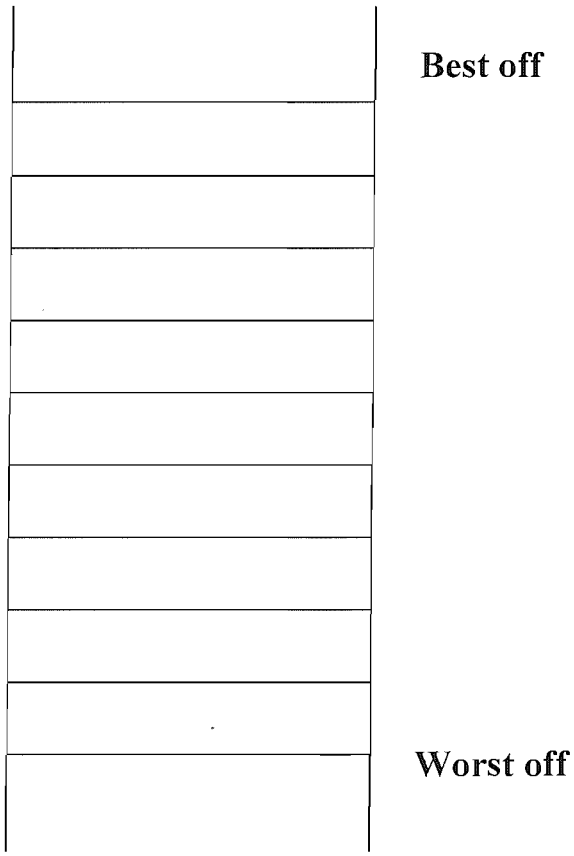
Month: Year:

12. When did you have your first appointment at the hospital?

Month: Year:

Social Ladder

Ten rungs of this ladder represent where people stand in society. At the top of the ladder are the people who are best off – those who have the most money, most education, and best jobs. At the bottom are the people who are the worst off, have the least money, least education, and the worst jobs or no job. Use an "X" to place yourself on the rung on which you feel that you stand.



Appendix S: Positive and Negative Affect Schedule (PANAS) Scales

Version: PANAS/01
Date: 23.11.2004

The PANAS

Instructions: This scale consists of a number of words that describe different feelings and emotions. Read each item and then mark the appropriate answer in the space next to that word. Indicate to what extent you felt this way in the past month. Use the following scale to record your answers.

1	2	3	4	5
very slightly or not at all	a little	moderately	quite a bit	extremely

___interested	___irritable
___distressed	___alert
___excited	___ashamed
___upset	___inspired
___strong	___nervous
___guilty	___determined
___scared	___attentive
___hostile	___jittery
___enthusiastic	___active
___proud	___afraid

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