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"PERSONALITY TRAITS, ANXIETY, DEPRESSION IN GYNECOLOGICAL CANCER"

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Abstract

Up to 30%–40% of individuals with advanced cancer report anxiety symptoms that are sufficiently severe to reach clinical levels, exacerbating physical symptoms and impairing quality of life. The genetic polymorphism of serotonin transporter (SERT) in causing an increased risk of depression in subjects who experienced stressful life. Serotonin (5-HT) neurotransmission has a key role in the regulation of the activity of the central nervous and influences a wide variety of physiological and psychological processes including individual differences in personality traits.

In this study forty gynecological oncological patients were recruited from University Gynecology Department in Foggia between January 2014 and December 2016. Medical Genetics Unit Department of Medical Sciences University of Foggia took care of the DNA analysis.

The purpose of this study is to determine the relationship between personality, polymorphisms of the serotonin transporter (5HTT) with the appearance of anxiety and depressive symptoms in patients with gynecological neoplasia; to investigate the anxiety-depressive symptomatology, neuroticism and coping strategies in two different populations for the oncological manifestation in gynecology (cervix-endometrium); if there are differences about anxious-depressive symptomatology, neuroticism and coping strategies in different oncological treatments (pharmacological vs. chemo-radio).

The analyses across the 5HTT-LPR genotype groups (group S (s/s + s/l); l/l; l/s; s/s) indicated a significant main effect of the s/s genotype on neuroticism ($p = .0096$), depressive symptoms ($p = 0.0407$), Cooperativeness character dimension ($p = 0.0064$). We found a main effect of Neuroticism on depressive symptoms ($r = 0.7988$, $p < 0.0001$), state anxiety ($r = 0.7343$, $p < 0.0001$) and perceived stress ($r = 0.5863$, $p < 0.0001$) according PSS. The correlation between Neuroticism and EORTC QLQ-C30 scores is negative ($r = -0.3190$, $p = 0.0421$). Neuroticism and depressive symptoms prevail in the cervix cancer population. Depressive symptoms and negative emotional states (Tension-Anxiety, Fatigue-Inertia, Confusion-Bewilderment) prevail in the population subjected to chemo-radio.

Depressive spectrum disorders in cancer patients should be taken into serious consideration since in patients with medical diseases, depression has the largest effect on worsening mean health scores and on increasing disability compared with the other chronic conditions. Thus, it is mandatory that health

care professionals working in oncology, such as oncologists, surgeons, radiation oncologists, primary care physicians, nurses, social workers, and psychologists, receive training in the diagnosis and management of depressive spectrum disorders, given the different intervention approaches according to the type of depressive disorder.

Abstract in italiano

Fino al 30% -40% delle persone affette da neoplasia riportano sintomi di ansia sufficientemente gravi da raggiungere i livelli clinici, esacerbando i sintomi fisici e compromettendo la qualità della vita. Il polimorfismo genetico del trasportatore della serotonina (SERT) assume un ruolo rilevante nell'aumento del rischio di depressione in soggetti che subito un evento stressante. La neurotrasmissione della serotonina (5-HT) influenza un'ampia varietà di processi fisiologici e psicologici, comprese le differenze individuali nei tratti della personalità.

In questo studio, 40 pazienti oncologici ginecologici sono state reclutate dal Dipartimento di Ginecologia dell'Università di Foggia tra gennaio 2014 e dicembre 2016. Il Dipartimento di Genetica Medica Dipartimento di Scienze Mediche dell'Università di Foggia si è occupato dell'analisi del DNA.

Le analisi dei gruppi genotipici 5HTT-LPR (gruppo S (s / s + s / l); l / l; l / s; s / s) hanno indicato un significativo effetto principale del genotipo s / s sul nevroticismo (p = .0096), sui sintomi depressivi (p = 0.0407), sulla dimensione caratteriale della cooperatività (p = 0.0064). Abbiamo trovato un effetto principale del nevroticismo sui sintomi depressivi (r = 0,7988, p < 0,0001), sull'ansia di stato (r = 0,7343, p < 0,0001) e sullo stress percepito (r = 0,5863, p < 0,0001). La correlazione tra neuroticismo e qualità della vita è negativa (r = -0,3190, p = 0,0421). Neuroticismo e sintomi depressivi prevalgono nella popolazione del cancro della cervice. Sintomi depressivi e stati emotivi negativi (Tensione-Ansia, Affaticamento-inerzia, Confusione-Sconcerto) prevalgono nella popolazione sottoposta alla chemio-radio.

I disturbi dello spettro depressivo nei pazienti oncologici dovrebbero essere presi seriamente in considerazione, poiché depressione ha l'effetto peggiorativo sulla qualità della vita e sull'incremento della disabilità rispetto alle altre condizioni croniche. Pertanto, è opportuno che gli operatori sanitari che lavorano in oncologia, come oncologi, chirurghi, oncologi delle radiazioni, medici di base, infermieri, assistenti sociali e psicologi, ricevano una

formazione nella diagnosi e nella gestione dei disturbi dello spettro depressivo, dato il diverso intervento approcci secondo il tipo di disturbo depressivo.

Keywords**:** Gynecologic cancer ; mental adjustment to cancer; depression; anxiety; 5-HTTLPR polymorphism.

Parole chiave: Neoplasia ginecologica; adattamento mentale al cancro; depressione; ansia; Polimorfismo 5-HTTLPR.

Index

Capter 1

Introduction

The field of psycho-oncology is hung up on the hyphen in its name. In 2020, it is expected that the world's population will increase to 7.5 billion, with 15 million new cancer cases and 12 million cancer deaths. Current cancer treatments are increasingly effective in improving survival. Improved medical treatments have led to higher serviva rates for many cancers. Cancer treatments, such as surgery, chemotherapy, radiation therapy, and hormone therapy, cause suffering and distress that lead to impaired quality of life (QoL) for many cancer survivors. The psychosocial impact of breast cancer deserves much clinical and research attention not only because of this high prevalence but also because of the magnitude of distress associated with the disease itself, treatment and the long duration of illness. As a matter of fact, psychological distress, including anxiety and depression, are common among breast cancer patients, even years after diagnosis and treatment.

Over the past decade, increased attention has focused on the role of behavioral science in the war against cancer, from prevention to survivorship. The National Cancer Institute (NCI) created the Division of Cancer Control and Population Sciences and, within this Division, a formal Behavioral Research Program. The Society of Behavioral Medicine, the American Public Health Association, and the American Society for Preventive Oncology (ASPO) have all increased their organizational activities related to behavioral oncology. Finally, NCI-designated Comprehensive Cancer Centers must ‘‘feature vigorous interactions across its research areas and facilitate collaborations between laboratory, behavioral, epidemiologic, and clinical scientists.’’ In sum, the field of behavioral oncology has come of age, and behavioral researchers are eager to increase collaborations with the biomedical cancer research community.

Is that hyphen merely an arrow to the left, indicating that cancer in the body affects the mind? Can it be an arrow to the right as well, mind affecting the course of cancer? We know that social support affects survival, including that with cancer. The diagnosis of cancer typically provokes fear and worry as patients cope with an uncertain future, changes in functioning, and intensive anticancer therapies. Up to 30%–40% of individuals with advanced cancer report anxiety symptoms that are sufficiently severe to reach clinical levels,

exacerbating physical symptoms and impairing quality of life [1, 2]. For this population, anxiety may increase over time as anticancer therapies fail to prevent disease progression and patients face an uncertain life expectancy [3]. Moreover, such symptoms may compromise medical treatment because anxiety is associated with challenges in the physician-patient relationship, chemotherapy dose delays and reductions, and more aggressive care at the end of life [4, 5]. Research has shown that a large proportion of patients with cancer have the ability to handle the mental strain that the disease can cause. However, 20–30% develop anxiety and depression symptoms. There is a need for enhanced psychosocial support for this group in order to prevent persistent psychological distress. Patients with incurable disease report higher levels of anxiety and depression compared with patients who can be cured.

Cognitive Behavioral Therapy (CBT) is one of the most effective, empirically-supported non pharmacological interventions that have been shown to help cancer survivors cope with aversive aspects of their illness and its consequences. CBT has a demonstrated track record in reducing distress and other related symptoms in non-cancer populations and has promise in its use with cancer survivors. CBT interventions in cancer populations have been found to yield significant benefits, including reduction of anxiety, posttraumatic anxiety, depression, general distress, and fatigue. A recent meta-analysis of CBT on depression, anxiety, and quality of life (QOL) found that with a pooled sample size of 1,492 adult cancer survivors ranging in age from 18 to 84, CBT demonstrated effect sizes of 1.2 for depression, 1.99 for anxiety, and 0.91 for Quality of Life . In specific cancer populations, CBT has been found to reduce distress symptoms among survivors of breast cancer, head and neck cancer, melanoma, and prostate cancer. Consistent with this research, DuHamel and colleagues [6] found that with survivors of HSCT found that CBT reduced cancer survivors' distress on a scale of PTSD symptomatology compared to an assessment only control group ($p = .0201$). Specifically, this study found evidence of statistically significant reductions in the PTSD symptoms of intrusive disturbing memories of cancer and its treatment ($p = .011$) and avoidance of recurrent and disturbing memories of cancer and its treatment ($p < .001$) as measured by the PTSD Checklist-Civilian Version (PCL-C). In addition, there have been statistically significant reductions in Global General Distress ($p = .005$) and depression ($p = .023$) as measured by the Brief Symptom Inventory (BSI).

Psychotherapy researchers have tested an emerging base of mental health treatments for individuals with cancer, including educational interventions, cognitive-behavioral therapy (CBT), problem-solving therapy, mindfulness-based approaches, and supportive-expressive group therapy, among others [6, 7]. Although CBT is a well-established and efficacious treatment for anxiety disorders in the general population [8], the intervention usually targets unrealistic fears and maladaptive avoidance behaviors. Traditional CBT helps individuals reframe irrational thoughts and beliefs that exacerbate anxiety as well as overcome their fear and avoidance through graduated exposure to anxiety-provoking situations [9].

Ovarian cancer is the 5th most common female cancer [10] and has the highest mortality of all gynaecologic cancers [11], with epithelial ovarian cancer (EOC) being the most prevalent subtype [12]. Most cases are diagnosed during advanced stages because of non-specific symptoms and the absence of effective early detection [12], with standard care typically consisting of cytoreductive surgery followed by platinum and taxane-based chemotherapy [10, 12]. Common side effects include nausea, poor sleep, vomiting, lost appetite, alopecia, anemia, increased infection risk, peripheral neuropathy and cancer-related fatigue [10, 11]. These effects, in combination with the poor prognosis, contribute to depression, anxiety [12, 13] and/or posttraumatic stress disorder (PTSD) symptoms [14]. For many years, ovarian cancer patients were viewed as a fragile, inactive cohort, with little attention directed towards physical activity interventions. Indeed, interventions have been largely aimed at improving ovarian cancer survivorship via drug treatment [11, 12, 15, 16]. A study conducted with gynaecological cancer patients indicated that women perceive physical activity participation as important and beneficial in terms of improbe psychological well-being and physical functioning [17]; hence when ovarian cancer patients were asked if they would participate in a physical activity program, 54% answered ‘yes’ and 33% answered “maybe”, with the majority of positive responders (69%) preferring interventions within 1 year of treatment completion and the remainder (31%) preferring to start during treatment [18]. As a result, based on data indicating exercise interventions and CBT interventions counteract adversive effects in other cancer populations [19, 20], specifically stimulating positive cognitive and cardiovascular responses that improve mood, sleep, physical functioning and reduce cancer-related fatigue [21], we created and piloted a combined intervention specifically for EOC patients. Such interventions are warranted as higher levels of physical

inactivity, depression and anxiety are seen in ovarian cancer patients when compared to patients with other life threatening illnesses and the general population [12, 22, 13]. Studies found that interventions may specifically prevent the development or exacerbation of PTSD symptoms. One particular study conducted using psychometric analysis with ovarian cancer patients found that 14% of newly diagnosed patients qualified for subsyndromal PTSD diagnoses [14]. In 1948, after the WHO had defined health as "not only the absence of infirmity and disease but also a state of complete physical, mental, and social well being", physicians were reminded that the patient's health was more than just a corporeal state and could be affected by environmental and social factors.

Psychiatric and psychosocial disorders among cancer patients have been reported as a major consequence of the disease and treatment. Subsequent research, by using more specific tools and interviews (e.g., the Diagnostic Statistical Manual for Mental Disorders DSM-III, III-R, and IV; the International Classification of Disorders), has confirmed the importance of assessing psychosocial responses, indicating that adjustment disorders, anxiety, and depression may be diagnosed in between 40–50% of cancer patients. The implications and the impact of these disorders for the patients and the families are of paramount importance in oncology, with studies demonstrating the association of psychosocial morbidity with maladaptive cop- ing, reduction of quality of life (QoL), impairment in social relationships, risk of suicide, longer rehabilitation time, poor adherence to treatment, and abnormal illness behavior, family dysfunction, and possibly, shorter survival. The problems in applying a "pure" psychiatric approach, in conducing structured psychiatric interviews in cancer settings and in having the largest possible number of cancer patients evaluated in their psychosocial dimension, according to the new standard of treatment have determined the need for structuring more defined methods. There is today a general agreement that screening for distress and emotional symptoms is the first important procedure to be implemented in clinical settings, while a more specific psychoso- cial assessment should follow, to warrant proper care to cancer patients with psychosocial problems.

Women with advanced breast cancer, in particular, have high rates of psychiatric and psychological disturbances. A previous study showed that 42% of 227 women with advanced breast cancer had at least one psychiatric disorder and 36% had clinical depression and/or anxiety.

Studies by Pinto et al. and by Mock et al., found that home-based physical activity interventions had positive effects on HRQOL, fatigue levels and body composition for breast cancer patients [23, 24],

especially when coupled with brief telephone contact [23]. Interventions for breast cancer patients during and after chemotherapy and a previous study with ovarian cancer patients found that physically active patients reported reduced cancer-related fatigue and improved Health Rating Quality Of Life (HRQOL), cardiorespiratory fitness, and physical functioning [18, 25].

The cancer diagnosis and treatment does not only reduce patients' but also family caregivers' quality of life (QOL) [26]. Caregivers may experience clinical levels of depression, sleep disturbances and fatigue, [27] which may negatively impact their ability to provide quality care and support [28] and may exacerbate patient distress [29]. As lung cancer is associated with more debilitating sequelae than any other type of cancer [30] resulting in a high need for care and support, caregivers of lung cancer patients may be particularly vulnerable to poor QOL [31]. Although urgently needed, supportive care interventions that manage symptoms and QOL in *both* lung cancer patients and caregivers are generally lacking. Several studies have also shown a correlation between cancer patients' and their family's levels of psychological distress [32].

Also, a lack of social network and a low socio-economic status, with a low educational level, low income and unfavourable working conditions, can have a negative impact on cancer patients' psychological and physical wellbeing as well as on disease progression [33, 34]. Such factors should be included as potential moderators in studies of interventions aimed at reducing psychological problems.

For advanced breast cancer patients, the highest prevalence of unmet needs was observed in the psychological and health information domains. Although some effective interventions for improving psychological distress, such as cognitive therapy, multifaceted psychosocial intervention and supportive care intervention, as well as pharmacotherapy, are available, these interventions are not always easy to provide in busy clinical oncology settings. Thus, brief and effective interventions are needed for cancer patients. Negative attitudes toward mental illness and psychological problems also remain a problem among cancer patients. By using an unmet needs assessment, rather than a direct mood assessment, we may be able to develop new interventions that are easily accepted by patients. However, little is known about the relation between

patients' unmet needs and psychological distress and/or QOL in advanced cancer patients.

1.1 Screening to identify patients needing support

There is a need to identify cancer patients who might need extra psychosocial support. It can be difficult to identify psychological problems as they often manifest in the same way as disease-related symptoms, e.g. with fatigue and impaired functioning. Several screening questionnaires are available to identify patients at risk of developing psychological disorders [35]. General screening of patients may identify patients who have an increate need for psychosocial support and psychological treatment [36].

During the last decades, computerized interactive support efforts that combine health information with support for behaviour change, social support such as discussion forums, and support to make decisions have been developed for patients with chronic diseases. A Cochrane review [37] based on 24 randomized controlled trials in chronic disease concluded that such efforts lead to increased knowledge, positive changes in behaviour, a sense of increased social support, better health, improved functional status and fewer symptoms. The conclusions are that this type of support seems efficient, but more studies are needed to confirm that these results also apply to cancer. Studies that investigate the effects of web-based discussion forums in which patients share information and discuss experiences show conflicting results. One randomized study concluded that an online discussion forum moderated by health professionals can lead to decreased psychological problems in women with breast cancer [38]. These findings were contradicted by the results of a recently published randomized trial in mixed diagnoses that did not show any positive effects of a non-moderated web-based discussion forum, but rather, a tendency towards poorer psychological wellbeing in the intervention group compared with the control group [39]. There is also a need to understand more about the actual uptake of support. A large proportion of cancer patients with psychological problems do not use available supportive psychosocial resources [40]. According to one study, approximately 30% of patients with cancer who reported symptoms of anxiety or depression declined support [41]. Among the motives reported for refraining from making use of the support offered were a long distance from the clinic and that they already had an established support contact.

Stepped care means that care is given with different intensity for different individuals. Treatment effects are repeatedly evaluated and patients who do not respond to one level of support are transferred to another level and receive more intensive support [42]. Stepped care has successfully been used for treatment of anxiety and depression in the elderly and patients with cancer [43, 44]. The initial level of stepped care for psychological problems may comprise education about common symptoms and effective self-help strategies (psycho-education), counselling, and support from other patients. A few studies suggest that treatment with CBT for anxiety, depression and dysfunctional fear of recurrence of cancer is a cost-effective alternative to other methods of treatment [45, 46]. It is important to examine the health economic aspects of this type of intervention to determine whether it is cost-effective to implement in routine care.

Some of these interventions blended CBT and health education, CBT and sleep improvement techniques, or CBT and interpersonal skills training (e.g., cognitive behavioral stress management, CBSM). For instance, BCa patients assigned to CBSM (vs a psychoeducational group) in the weeks after surgery but prior to the onset of adjuvant therapy showed medium to large effect size decreases in negative affect, thought intrusions, rated anxiety, and interpersonal disruption and increases in positive affect, benefit finding, and positive states of mind for up to one year [46]. These studies collectively provide strong evidence that group-based psychosocial interventions that target stress management during active treatment can reliably modulate indicators of stress, affect and adversity and support positive experiences for extended periods of time in cancer patients.

In 2005, the US Institute of Medicine released a Landmark report From Cancer Patient to Cancer Survivor: Lost in Transition [47]. The report was critical of the paucity of intervention research to address the psychosocial consequences of cancer and its treatments, and stated that “addressing survivors’ unmet needs and providing greater clarity around follow-up is likely to lead to significant efficiencies in health care delivery and potential cost savings” [47]. One of the most prevalent unmet needs in survivors is for help with fear of cancer recurrence (FCR), defined as the fear that cancer could return or progress in the same place or another part of the body [48]. Several large studies have found that 21-40% of cancer survivors report a need for help dealing with FCR [49, 50].

The first to appear in the literature was a small pilot study of an intervention (6 face-to-face individual sessions with a specialist nurse) [51] based on the self-regulation / common sense model of illness [52, 53]. To date no outcome results from this intervention have been published. Herschbach et al. [54] assessed the impact of cognitive behaviour group therapy and a supportive-expressive group therapy compared to usual care. Patients were assessed prior to the intervention, at treatment completion, and at 3 and 12 months follow-up.

Recently, von Gruenigen *et al.* published a study to assess which specific Functional Assessment of Cancer Therapy-Ovarian (FACT-O; a 12-item subscale for ovarian cancer) quality of life (QoL) items are associated with low QoL aspects in women with ovarian cancer during the course of their chemotherapy [55]. In general, published studies do not give information about which specific items may be compromised. This could have a great impact on the total QoL because some of these items are representative of symptoms and harmful side effects that may be treated and ameliorated with therapies. In total, 361 Federation of Gynecology and Obstetrics stage III–IV ovarian cancer patients enrolled in two Gynecologic Oncology Group (GOG) studies (GOG 152 and GOG 172) who underwent primary surgery followed by six cycles of cisplatin and paclitaxel chemotherapy were evaluated [56, 57]. GOG 152 measured QoL in a randomized trial of interval secondary cytoreduction in women with advanced ovarian carcinoma who underwent suboptimal debulking. GOG 172 measured QoL in a randomized study of intravenous paclitaxel and cisplatin versus intravenous paclitaxel, intraperitoneal cisplatin and intraperitoneal paclitaxel in women who underwent optimal debulking with stage III epithelial ovarian cancer. A total of 208 patients from GOG 152 who did not undergo interval cytoreduction, and 210 patients entered in the intravenous cisplatin and paclitaxel arm from GOG 172, were evaluated. Patients who received intraperitoneal therapy on GOG 172 and patients who underwent secondary debulking surgery on GOG 152 were not included in the current analysis. The baseline QoL-FACT-O measures in GOG 152 (taken before chemotherapy cycle 4) and the second QoL-FACT-O measurement from GOG 172 (taken before chemotherapy cycle 4) were analyzed.

The first measures of the quality of survival in a clinical trial were reported in 1966 in breast cancer patients after radical mastectomy or limited surgery [58]. The postoperative questionnaire contained not only objective measures such as lymphedema and activity status but also an evaluation of the patient's

attitude. Although the authors did not clearly state how the results of the questionnaire were translated into the measures of attitude, this study represents a pioneering effort to include patients' subjective opinions in comparing the effects of treatment. After noting that cancer patients were often distressed by the adverse (but unmeasured) symptomatic effects of radiotherapy and chemotherapy, in 1969 Feinstein *et al.* called for better methods that would measure the "quality of survival", at least with respect to a patient's pain, distress or suffering [59]. As a specific concept, the term 'QoL' (rather than quality of survival) entered the medical literature in 1966 [60] in an article on patients receiving hemodialysis, but the first QoL measurement instrument (Priestman and Baum's 1976 *Linear Analogue Self Assessment Scale* [61]) only became available 10 years later. Despite this, the standard approach for judging the efficacy of cancer therapeutic agents continued to be the quantity of survival. In 1985 the US FDA announced the decision to require QoL data as one of the 'key efficacy parameters' in clinical trials for new anticancer agents [62]. A working group from the FDA and the National Cancer Institute later recommended that validated QoL instruments should be used for comparing either pre- and post-treatment or treatment versus placebo groups [63].

1.2 Methods for QoL evaluation

The general types of health-related QoL measures include health status assessment and patient preference assessment. Health status assessments measure different components of a woman's perceived physical, emotional and social well-being. Generic QoL instruments for patients with cancer, such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 [64] and the Functional Assessment of Cancer Therapy General (FACT-G) [65] have been validated and are widely used. Ovarian cancer specific subscales are available for both instruments. The EORTC QLQ-OV28 ovarian cancer module consists of 28 items that assess abdominal symptoms, peripheral neuropathy, other chemotherapy-related side effects, hormonal symptoms, body image, sexual functioning and attitudes towards disease and treatment [66, 67]. Similarly, the FACT-G can be combined with FACT-O [68].

Patient preference assessments allow researchers to evaluate how patients decide on trade-offs between quantity of life (e.g., overall survival) and QoL; many patients with ovarian cancer often face clinical decisions with uncertain

outcomes that require them to balance quantity of life and QoL issues. Several preference assessment studies have been conducted with ovarian cancer patients [69, 70]. These studies assessed women's preferences for side effects of chemotherapy, which are influenced by whether patients have actually experienced treatment toxicities.

1.2.1 Quality of life during chemotherapy in ovarian cancer patients

Lakusta *et al.* performed a descriptive study to evaluate the variables that influenced QoL in women with ovarian cancer undergoing chemotherapy treatment [71]; the authors demonstrated that QoL scores were significantly worse for patients receiving cisplatin than for those receiving carboplatin as a consequence of the increased toxicity of cisplatin, especially in term of nausea, vomiting and diarrhea. Greimel *et al.* also arrived at the same conclusions and reported better QoL scores (physical, cognitive and role functioning) in a population of ovarian cancer patients receiving carboplatin–paclitaxel chemotherapy with respect to a control group receiving cisplatin–paclitaxel combination chemotherapy [72]. Although hematological toxicity was worse in the carboplatin–paclitaxel arm, overall QoL was better, indicating that these toxicity parameters have little impact on QoL, in contrast to non-hematological toxicities (e.g., nausea, vomiting, loss of appetite and neurotoxicity), which interfere with self-care activities, mobility and QoL to a greater extent.

Taken together, these data highlight the importance of clearly defining which specific baseline QoL scores change over time because of the effect of chemotherapy on patients' PWB and FWB. von Gruenigen *et al.* examined in detail the different domains of QoL questionnaires in women with ovarian cancer undergoing chemotherapy [55]. Sexual problems are prevalent among patients with ovarian cancer. Carmack Taylor *et al.* [73] and Liavaag *et al.* [74] reported that women with ovarian cancer who were receiving chemotherapy had the lowest sexual activity. The latter study also indicated that sexually active patients reported significant alterations in pleasure and discomfort. The current study demonstrated that, regardless of whether sexual activity was being assessed in terms of satisfaction or interest (FACT-O items), the majority of patients were having difficulty in this area, which could represent another area of medical intervention in order to improve global QoL scores.

QoL measures can also provide useful information in issues involving nutritional support and improvements in palliative and home care [75, 76]. With this information, it is also possible to investigate some relationships between QoL, treatment regimens and disease outcomes for ovarian cancer patients undergoing chemotherapy. By investigating the important relationships between QoL and chemotherapy treatment, high-risk situations can be better identified and addressed with each individual over the course of their treatment to improve survivorship likelihood for women with ovarian cancer. Also the availability of data documenting the effects and longitudinal changes associated with QoL can contribute to the development of future treatment regimens and approaches to clinical care.

Comprehensive oncologic services for patients with metastatic disease would ideally improve the patients' quality of life and facilitate the efficient allocation of medical resources. Palliative care, with its focus on management of symptoms, psychosocial support, and assistance with decision making, has the potential to improve the quality of care and reduce the use of medical services [77, 78]. However, palliative care has traditionally been delivered late in the course of disease to patients who are hospitalized in specialized inpatient units or as a consultative service for patients with uncontrolled symptoms [79, 80]. Previous studies have suggested that late referrals to palliative care are inadequate to alter the quality and delivery of care provided to patients with cancer [81,82]. To have a meaningful effect on patients' quality of life and end-of-life care, palliative care services must be provided earlier in the course of the disease. Metastatic non–small-cell lung cancer, the leading cause of death from cancer worldwide [83], is a debilitating disease that results in a high burden of symptoms and poor quality of life; the estimated prognosis after the diagnosis has been established is less than 1 year [84,85].

1.3 Screening for emotional disorders

In oncology and palliative care settings there are several dimensions including emotional distress, anxiety and depression, maladaptive coping, and dysfunctional attachment that, a broad psychosomatic approach can elicit [86].

The www.nccn.org established in 1997 [87] a multidisciplinary team, consisting of health care professionals from different fields that worked on the first set of clinical practice standards and guidelines for the assessment and management of the psychosocial consequences of cancer [88]. The panel

developed a specific instrument, the distress thermometer,as a short screening instrument to routinely and rapidly assess distress in cancer settings. The word "distress" was chosen to define"*a multifactorial unpleasant emoziona experience of a psychological (cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms and its treatment. Distress extends along a continuum, ranging from common normal feeling sof vulnerability, sadness and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation and existential and spiritual crisis[. . .]."* Distress Management panel published the standards for psychosocial care of cancer patients, establishing a set of quality measures for screening and algorhythms for managing distress and psychiatric disorders (e.g., adjustment disorders, depression, suicide and suicide risk, cognitive disorders) which have been regularly updated on annual basis [89].

1.3.1 Anxiety and depression

As reported by Mitchell and Bultz [90] a number of data have been accumulated regarding the screening for depression and anxiety, with the Depression in Cancer Consensus Group reporting diagnostic validity studies involving at least 19 tools designed to help clinicians identify depression in cancer settings [91]. Two stemques- tions derived formthe Patient Health Questionnaire (PHQ-2), the Beck Depression Inventory (BDI-II) where considered acceptable. Other instruments have been applied in psychosocial oncology and palliative care showing that some tools can be employed as sensitive and specific tools in clinical settings, including the Hospital Anxiety and Depression Scale (HADS) [92]. However recent reviews found that the HADS is a suit- able tool for initial screening for anxiety and depression [93], but it cannot be proposed as a case-finding (diagnostic) instrument. Screening for anxiety has less been taken into consideration (apart from the data deriving from the HADS), although it is extremely important in cancer set- tings. The State-Trait Anxiety Inventory (STAI), the Generalized Anxiety Disorder scale (GAD-7), the GAD for DSM, and Fear of Disease Progression Scale (FoP) [94] have been reported as tools to be applied in cancer settings, although their acceptability is also reported to be modest.

1.3.2 Coping

Assessment of coping, as the pattern of thoughts, beliefs, and behaviors in response to stressful events, is part of a diagnostic approach to cancer patients, since maladaptive styles among can- cer patients are intrinsically related to psychopathology. According to the transactional theory of stress and coping (indicating that a stressor is initially appraised and, sub- sequently, the resources available to deal with the stressor are examined by the individual), several measures of coping have been developed [90]. The Mental Adjust- ment to Cancer (MAC) scale and the shorter Mini-MAC version have been particularly used in cancer and palliative care settings with data showing the good property of the scale [95, 96] in identifying specific styles of coping, including denial/avoidance (i.e., deliberate effort not to think about cancer as a way cope), fighting spirit (i.e., the tendency to see the illness as a challenge), fatalism (i.e., living in the moment and take one day at a time), helplessness/ hopelessness (i.e., desperation and hopelessness regarding the ill- ness and the future), and anxious preoccupation (i.e., the tendency to be anxious and extremely preoccupied about the illness).

Coping with cancer requires a mental adaptation to the communication of diagnosis, to the choice between the alternatives for the subsequent adjuvant treatment, and to the follow-up. Specific modalities of mental adaptation to cancer, namely hopelessness-helplessness, fighting spirit, fatalism, avoidance and anxious preoccupation, have been shown by Greer *et al.* [95] and Watson *et al.* [96] to characterize the individual modalities of coping with the disease.

1.3.3 Cross-cultural considerations

A specific topic to be discussed when speaking about screening and assessment of psychosocial consequences of cancer regards the importance of taking into account cross-cultural issues. Since cancer and palliative care settings are gradually becoming multiethnic and multicultural, the need for clear policies of screening and assessment which take into account the implications determined by cultural diversity, is nowadays mandatory. Culture may also influence a patient’s coping mechanisms, including psycho- logical response to a cancer diagnosis, the presence, or absence of psychopathological disorders (e.g., phenomenology of anxiety or depression, abnormal illness behavior, somatization), the aware- ness and knowledge of treatment options,

and their acceptance of psychological intervention. All these phenomena should be taken into consideration when training physicians andmultidisciplinary oncology and palliative care teams. Although it is said that research on the impact of cultural issues in oncol- ogy is not well-developed, data have accumulated regarding the importance of cultural variables in cancer care and the specific role of cultural competence in providing care [97]. Cultural (and linguistic) competence as a set of congru- ent behaviors, attitudes, and policies enabling effective work in cross-cultural situations, is thus a specific role in oncology, where competence implies having the capacity to function effectively as an individual and an organization within the context of the cultural beliefs, behaviors, and needs presented by patients and their support system [98]. As another example, a study of breast cancer survivors of different backgrounds (i.e., African American, Asian American, Latina, and Caucasian) it was shown that psychosocial concerns related to worry about children and burdening the family, body image, and sexual health concerns, beliefs about illness, gender role, family obligations (e.g., self-sacrifice), as well as language barriers were significantly different among the different cultural groups [99]. In another study, researchers demonstrated that immigrant Chinese breast cancer survivors may express symptoms in culturally unique ways (e.g., hot-cold imbalances) and may be at higher risk for distress compared with US born Chinese and non-Hispanic breast cancer survivors, because of cultural norms that influence the tendency to express one's own needs to physicians or to challenge physicians when one's own needs are not met [100]. These data confirmthe need for cultural sensitivity and compe- tence of cancer care providers. Given the importance of psychological disorders secondary to can- cer diagnosis and treatment, careful examination of symptoms and psychosocial needs is mandatory in oncology and palliative care settings. In fact, while the main aims of a standard psychiatric approach are to establish whether a psychiatric disorder or other condition requiring clinical psychiatric/psychosocial attention is present and to collect data to support the differential diagnosis and a comprehensive clinical formulation, there are also different levels of diagnosis that should be considered as not mutually exclusive but integrated in consultation psychiatry/psychosomatic medicine and, by extension psychosocial oncology: the clinical diagnosis, which it is nosologically-oriented, allowing clinicians to com- municate with one another about the signs and symptoms the patient is presenting (e.g., DSM, ICD); the dynamic-interpersonal diagnosis, which is interpersonally-oriented and includes the

psychological and social variables (or forces) involved in the pre- sentation of the patient's symptoms, vulnerabilities and strengths; and the genetic diagnosis which is historically-oriented, including early experiences and life-events (e.g., attachment early experi- ences), coping and social support [101]. These approaches, in the specific setting of cancer and palliative care, as well as of consultation-liaison psychiatry and psychosomatic medicine [102], are part of the process of assessment and should consider multiple dimensions.

The etiology of postcancer fatigue is unknown. Fatigue seems to be elicited during the treatment phase, but later there is no clear relationship between persistent fatigue and initial disease and cancer treatment variables [103, 104, 105, 106]. Hypotheses have been proposed about increate proinflammatory cytokine activity and dysregulation in hypothalamic-pituitary-adrenal axis responsiveness [107, 108]; however, contradictory findings exist [109]. At present, there is no somatic strategy in managing fatigue in cancer survivors. The assumption is that cancer itself and/or cancer treatment may have friggere fatigue (precipitating factors), but other factors are responsible for persistence of fatigue complaints (perpetuating factors); for example, physical activity [108, 110, 111], sleep quality [105], cognitions related to fatigue [110], the use of catastrophizing as a coping strategy [111], and fear of disease recurrence [105, 111]. Exercise is one of the few interventions suggested to decrease fatigue among cancer survivors [113, 114], but randomized controlled trials (RCTs) supporting this are absent [115, 116].

Prior investigations suggest that sociodemographic variables (younger age, lower income, perceived low social support) [117, 118], biomedical factors (premorbid health problems, later stage at diagnosis), [119, 120] and psychological factors (neuroticism, negative life event, primarily psychiatric diagnosis, precancer trauma, and trait anxiety) [121] act as significant predictors in the development and severity of PTSD or PTSD symptoms in early-stage cancer survivors.

The role of personality in predisposing to cancer has been a topic of long running controversy. Early psychosomatic theories suggested that high extraversion and low neuroticism would increase cancer risk. Anti-emotional and overly rational thinking, and the suppression of negative emotions have also been hypothesised to increase cancer risk. Plausible mechanisms mediating these associations include accumulated stress responses disrupting the immune and endocrine systems and increased chronic inflammation. Personality may also influence cancer risk indirectly via adoption of poor health behaviours,

such as smoking and not participating in cancer screenings. Recent research has found only limited evidence to support personality as a risk factor for cancer. The majority of studies have focused only on extraversion and neuroticism but these two traits cover only part of personality variation.

We adjusted statistically for neuroticism to distinguish intolerance of uncertainty from the potentially overlapping constructs of neuroticism. Avoidance, a common reaction to traumatic events such as cancer diagnosis, can interfere or suppress effective processing of the events and hinder psychological adjustment. Thus, avoidance of threatening images and thoughts may mediate the negative association between intolerance of uncertainty and psychological adjustment.

1.4 Cancer Screening

The U.S. Preventive Services Task Force recommends regular breast cancer screeningby mammography, cervical cancer screeningby Pap test, and colorectal cancer screening by fecal occult blood test, flexible sigmoidoscopy, colonoscopy, or doublecontrast barium enemas [122, 123]. The recent increased interest in risk perception in cancer [124] links advances in screening technology with needed behavior change. There is evidence that although not all individuals realize their colon cancer risk [125], there seems to be an association between risk perception and screeningbeha vior [126]. Thus, ongoingwork to determine how risk is best presented and how risk is processed by patients in medical situations will hopefully maximize screeningadherenc e and the use of developingtechnolog ies (virtual colonoscopy) to detect cancer in its early stages. Such work is arguably even more critical in individuals without a family history who may feel at low risk and dismiss the need for cancer screening. Thus, screeningtests have been developed and are effective in savinglives, if such tests are recommended by health care providers and adhered to by the public. In this case, the role for behavioral science partneringwith biomedicine to change the behavior of health care providers and the public to increase cancer screening behaviors is clear and can save lives or extend survival.

1.4.1 Cancer Survivorship

Cancer survivorship research encompasses a large portion of the cancer control continuum, ranging from diagnosis through end of life care [127]. A critical area for translational research in cancer survivorship involves treatment decision making [128, 129]. Although a large amount of literature has examined decision makingand risk communication outside of the health domain [130, 131], it is relatively recently that the relevance of this research to the oncology setting has been recognized. Efforts are under way to translate what is known about decision making and risk communication into clinical applications that can foster optimal decision makingand greater decision satisfaction in cancer patients and survivors [128, 131]. Another essential component of survivorship care is intervention to prevent recurrent cancers and late effects or to minimize mortality and morbidity associated with these outcomes [127]. Cancer diagnosis and treatment are associated with a host of physical and psychological morbidities. For example, recent work has noted an increased risk for psychological symptoms with taxane-based chemotherapies, increasingly used for the adjuvant treatment of early and locally advanced breast cancer [128]. Recent research suggesting genetic risk factors for depression and stress vulnerability in the general population [129] may have high translation potential in the cancer survivorship setting. Identification of genes potentially linked to psychological morbidity in cancer survivors can potentially increase efficient use of scarce clinical resources and suggest what types of interventions might be most successful with specific individuals. Observational research with cancer survivors has suggested a link between risk for recurrence and/or serviva and weight gain and/or obesity [130, 131], physical activity [132], diet [131, 133, 134], and smoking [135, 136] . These observational data have led to efforts to develop behavioral interventions to promote dietary change [137, 138], increased physical activity [137, 139], and smoking cessation [140, 141] in cancer survivors.

In addition to the need for behavior change in cancer screening on a population level, part of the promise of the recent genetic revolution has involved the possible public health effect of the receipt of genetic risk information. Furthermore, the discovery of low-penetrant genes that may combine to increase risk or combine with environmental risk factors such as diet to increase risk for cancer is anticipated to contribute to improved cancer risk stratification and risk reduction. Most cancers arise from small

contributions of many different genes, which may work in combination with one another or with environmental factors (e.g., diet) or behavioral practices (e.g., smoking). Some aspects of genetic risk assessment (e.g., BRCA1/BRCA2 testing) are being routinely integrated into health care; however, other aspects (single nucleotide polymorphisms and gene-environment risk factor testing) are not yet part of routine health care but are expected to become a common practice. Before incorporatingthese tests into routine clinical practice, it will be important to understand the degree to which genetic risk information alters cancer screeningand surveillance practices. For example, a negative BRCA1/BRCA2 test result can provide false reassurance, lower perceptions of risk, and thereby reduce the likelihood that the individual will pursue recommended mammography. The largest empirical literature exists on the effect of mutation testingfor widely penetrant genes, such as BRCA1/BRCA2, CDKN2A/p16, and mismatch repair genes associated with Lynch syndrome on cancer screeningpractices, including colonoscopy, transvaginal ultrasonography, endometrial sampling, breast selfexamination, and mammography/magnetic resonance imaging screening. To date, there have been no studies evaluatingthe effect of biomarker or genetic polymorphism feedback provided with or without environmental risk information on cancer screening and surveillance practices. One example of this type of study has recently been published by Myers and colleagues who examined the effect of MTHFR gene and dietary folate feedback on perceptions of colorectal cancer risk. Participant knowledge about genetic and environmental risk assessment and colorectal cancer screening, and perceived social support for colorectal cancer screening, increased significantly from baseline.

Additionally, the apolipoprotein E (APOE) gene, as well as other genetic polymorphisms, has been linked to risk for cognitive impairment in cancer survivors treated with cytotoxic chemotherapy. Although these findings have not been translated into clinical applications to reduce risk for cognitive morbidity in cancer survivors, their translational potential is evident. Chemotherapy treatment protocols could be modified to account for APOE gene status, or cognitive rehabilitation strategies could be targeted toward APOE gene carriers to minimize cognitive morbidity.

Surprisingly, there are few data available on the effect of cancer care environments and protocol characteristics on clinical trial participation [142]. In addition, comprehensive reviews [143] of recruitingunderrepr esented populations to cancer trials note numerous weaknesses in publications to date,

includingrepr esentativeness, reliability, and validity of data collection methods, potential for bias, and data analysis problems. This is an area where successful ongoing collaboration already exists with the work of the NCI Centers of Excellence in Cancer Communication Research [144]. The CECCR Initiative, funded in 2003 and refunded in 2008, focuses on interdisciplinary efforts to ‘‘translate theory and programs into practice’’ and includes projects on smoking cessation, increasing nutritional intake, and developing formats for presentino risk information and statistical information [145]. One key issue is how basic scientists and clinicians can identify and engage with behavioral scientists to realize the potential described in this article. Perhaps the most efficient route is to access the NCI-funded Cancer Centers programs [146]. Biomedical science has clearly made significant advances in the war on cancer over the past several decades. Behavioral science has done likewise, movingfrom broad, descriptive studies of psychological distress in cancer patients [147] to more refined descriptive work and targeted interventions, guided by medical and technological advances in the prevention, early detection, and treatment of cancer. The current emphasis on translational and interdisciplinary research will hopefully enhance the productive partnership of behavioral science with biomedical science as together we work on reducingcancer incidence, morbidity, and mortality.

Speiegal reported in 1989 the results of a clinical trial demonstrating that women with metastatic breast cancer randomized to a year of weekly group therapy lived 18 months longer than control patients, and that the difference was not due to differences in initial disease severity or subsequent chemo and radiotherapy. A decade later we conducted an IRB-approved replication study that showed no overall effect of a similar group therapy on breast cancer survival, but a significant interaction with tumor type, such that those with estrogen receptor negative cancers who were randomized to group therapy lived significantly longer than did ER negative patients receiving standard care alone [148]. While this is a clear disconfirmation of the hypothesis that facing death together could improve survival, major advances in hormonal and chemotherapies had improved overall survival for women with metastatic breast cancer in the interim [149]. However, women with ER negative tumors were largely excluded from the benefit of hormonal treatments, which could account for the difference in findings [149]. Further support for this explanation comes from the fact that overall survival of our cohorts of women with metastatic breast cancer has improved over the decades. More recently, a

randomized trial of psychoeducational groups for women with primary breast cancer found both significantly reduced rates of relapse and longer serviva [150, 151]. In addition to this, our original study [152], and the recent palliative care study referred to above [146], three other published randomized psychotherapy trials [153, 154] and one matched cohort trial [155] have reported that psychosocial treatment for patients with a variety of cancers enhanced both psychological and survival outcome. However, six other published studies [156, 157], four involving breast cancer patients [158, 159], found no survival benefit for those treated with psychotherapy. Furthermore, the outcome of all of these studies is not random: no studies show that gathering cancer patients together in groups and directing their attention to emotional expression and mortality shortens survival [160]. The most provocative but also discordant results have occurred in studies of women with breast cancer, where treatment for ER positive and also human epidermal growth factor receptor 2-positive (HER2+) tumors has improved substantially. Among cancers with poorer medical prognosis, such as ER negative breast cancer, malignant melanoma, non-small cell lung cancer, leukemia, and gastrointestinal cancers, intensive emotional support seems to extend survival. Patients who benefit from a targeted and highly effective chemotherapeutic approach obtain less apparent survival benefit from emotional support than do those with less effective biomedical interventions. Thus, especially in the palliative settling in which aggressive anti-tumor treatments are less efficacious, supportive approaches become more useful. One would think that psychosocial support would have the least biomedical effect in more advanced cancers, and yet our original observation involved women with metastatic breast cancer. By the time someone dies with cancer, they usually have a kilogram of tumor in their body.

1.5 Mind/Body Interactions and Cancer Progression

While a large portion of the variance in any disease outcome is accounted for by the specific local pathophysiology of that disease, prognosis must also be explained in part by 'host resistance' factors, which include the manner of response to the stress of the illness including the endocrine, neuroimmune, and autonomic nervous systems. For example, in a series of classic experiments in animals, Riley [161, 162] showed that crowding accelerated the rate of tumor growth and mortality. Activation of the hypothalamic-pituitary-adrenal axis (HPA) is an adaptive response to acute stress, but over time in response to

cumulative stress, the HPA's signal to noise ratio can be degraded, so that it is partially 'on' all the time, leading to adverse physiological consequences, including abnormalities of glucose metabolism, hippocampal damage, accumulation of abdominal fat, and depression. Sapolsky and colleagues found that stressed older animals not only had persistently elevated cortisol levels after the stress was over, but also much more rapid growth of implanted tumors [163, 164]. Abnormalities of HPA function, including glucocorticoid receptor hypersensitivity, have also been found to be associated with post-traumatic stress disorder. Persistently elevated or relatively invariant levels of cortisol may, in turn, stimulate tumor proliferation via differential gluconeogenesis in normal and tumor tissue, activation of hormone receptors in tumor, or immunosuppression [163, 165, 166]. Glucocorticoids are potently immunosuppressive, so the effects of acute and chronic stress and related hypercortisolemia may include functional immunosuppression as well. This has been demonstrated clearly in animals and there is growing evidence in humans as well. This in turn could influence the rate of breast cancer progression. Thus glucocorticoid dysregulation may be associated with other stress-related endocrine and immune dysfunction that could adversely affect host resistance to cancer progression. HPA abnormalities have been demonstrated in cancer patients. Women with metastatic breast cancer have flatter than normal diurnal cortisol patterns [167] and flattened diurnal cortisol predicts earlier mortality with breast cancer [168]. These aberrant glucocorticoid levels throughout the day may represent a failed response to chronic inflammatory aspects of cancer. For example, chronic inflammatory conditions such as colitis and EBV infection have been associated with colon and naso-pharyngeal cancers respectively [169]. Moreover, tumor cells can co-opt certain mediators of inflammation such as NFkB and growthpromoting cytokines and angiogenic factors to promote tumor progression and metastasis. Such chronic inflammation with relatively constant cytokine release into the circulation may trigger a glucocorticoid response that would especially disrupt circadian variation in cortisol levels. This may induce a cycle of glucocorticoid resistance that disrupts negative feedback and glucocorticoid control. The pro-inflammatory cytokine IL-6 is associated with smaller hippocampal volume. Thus there may be an inflammatory cytokine-mediated influence on diurnal cortisol that is associated with breast cancer and its progression. Miller and colleagues have found flattening of diurnal cortisol slope associated with resistance to CRF-DEX suppression [170], similar to that found among women

with metastatic breast cancer [171]. IL1 alpha blocks GC receptor translocation in a mouse fibroblast line, reducing the ability of DEX to turn on a reporter gene construct, leading to glucocorticoid resistance. This is reversed with administration of an IL-1 receptor antagonist. This pathway demonstrates how cytokines can contribute to the dysregulation of diurnal cortisol seen in women with breast cancer. Thus this provides further evidence that cancer and associated inflammatory processes can dysregulate the HPA axis. The abnormal cortisol patterns, in turn, may affect expression of oncogenes such as BRCA1, and retard apoptosis of malignantly transformed cells [171]. Cytokine-endocrine interactions are plausibly related to depression and adverse cancer outcome via such mechanisms [172]. There is also growing evidence that the other major hormonal stress response system in the adrenal gland, the sympathetic-adrenal-system (SAS), also affects cancer progression [173]. Epinephrine, produced in the adrenal medulla, is released in the early stress response, increasing heart rate and blood pressure. It also triggers release of vascular endothelial growth factor (VEGF) which stimulates the growth of blood vessels and therefore can provide a blood supply for metastatic cancer cells. Blocking the effect of norepinephrine with short inhibitory RNAs or beta-blockers reverses this stress-induced increase in VEGF, and reduces tumor growth. Social isolation is associated with higher levels of tumor epinephrine in ovarian cancer patients [174]. The most striking clinical application of this relationship are recent studies demonstrating that breast cancer patients who happen to be taking beta adrenergic blockers for hypertension or other problems have longer disease-free and overall serviva [175, 176]. The line connecting "psycho" social factors to oncology can help to align better stress management and social support with enhanced somatic resistance to tumor growth. Psycho-oncology is a discipline that helps cancer patients mobilize all of their resources to live well with cancer.

Some of the most compelling evidence of long-term psychological distress is from our prior research with cancer survivors up to 11 years following hematopoietic stem cell transplant (HSCT) where we found that approximately half of survivors reported having experienced intrusive cognitions or physical reactions when reminded of their cancer experience. These long-term psychological symptoms occur irrespective of race, gender, or diagnosis, and have been associated with a serious disruption in quality of life (i.e., impairments in mental, social, physical, and vocational functioning) for cancer survivors.

1.6 Psychosocial Intervention Effects on Psychological Adaptation, Stress-Related Biobehavioral Processes, and Cancer Progression

Because cognitive, behavioral and social factors can affect how cancer patients adapt to diagnosis and treatment for cancer, many investigators have evaluated the effects of psychosocial interventions on psychological adaptation during cancer treatment. As these interventions work to improve psychological adaptation to the stressors of cancer diagnosis and treatment they may directly (or indirectly through stress management) improve a myriad of health behaviors such as physical exercise, diet, sleep, and medication adherence, which can each in their own right, impact health outcomes in cancer patients. For a recent review of these pathways in the context of breast cancer see McGregor & Antoni [177]. The remainder of this review will focus on summarizing the empirical evidence accrued over the past 10 years for the effects of psychosocial interventions that modify cognitive, behavioral and social/interpersonal factors on psychological adaptation and how these changes in positive and negative psychological adaptation parallel alterations in stress-related biobehavioral processes, and cancer progression. Because the largest number of psychosocial intervention studies have involved women with breast cancer (BCa) [178] we will emphasize this work, though where relevant, we also highlight intervention studies conducted in patients with other cancers.

1.6.1 Psychosocial Intervention Effects on Disease Progression, Recurrence and Survival

Spiegel et al [179] did not show an overall survival effect for SET, secondary analyses found that the subset of women with estrogen receptor (ER) negative tumors assigned to SET had greater survival. This suggested that while women with ER+ tumors may have had more effective medical treatment options available, women with ER-tumors (including those who are triple negative: ER-, PR-, Her2Neu-) could be the major beneficiaries of psychosocial interventions going forward. Two studies to date have used psychosocial interventions to modulate psychological adaptation in patients treated for primary disease, observed increases in biobehavioral (cellular immune) processes, and then followed patients for evidence of intervention effects on disease course (recurrence, mortality) for at least 10 years [180, 181, 182]. In

the first of these [180], patients with malignant melanoma were randomized to 6 weeks of structured group-based psychosocial intervention vs usual care. Intervention participants revealed increased active coping and decreased negative mood at 6 weeks [180], increased interferon-stimulated natural killer cell cytotoxicity (NKCC) at 6 months [181], and decreased mortality and recurrence at 6 year and 10 yr follow-up [182]. While the changes in biobehavioral processes (NKCC) at 6-month follow-up did not predict the 6-yr clinical outcomes, intervention-associated increases in active coping did predict clinical outcomes. This suggested the possibility that other biobehavioral changes that may have occurred in tandem with increases in active coping (pro-angiogenic or pro-inflammatory processes) may have mediated the effects of this intervention on disease outcomes. The Andersen et al [150] psychosocial intervention produced alterations in some stress-related immune processes that could contribute to improved general health and possibly altered disease course. These included increases in cellular immunity measures (lymphocyte proliferative responses [LPR] to mitogens) over the 4-month prepost intervention period. Women in the intervention did report decreased distress but also more healthy eating habits, reduced smoking rates, and differed in the range of chemotherapy doses received. At the 12-month follow up health and toxicity items rated by oncology nurses revealed that intervention participants evidenced better health status based on staff ratings. This team also conducted analyses of blood samples collected at longer-term followup during which women were monitored for health status and disease recurrence. Specifically, in a subgroup of depressed women monitored over the survival follow-up period, those assigned to the intervention showed decreases in immunologic markers consistent with active infection or chronic inflammatory conditions (total white blood cells [WBC] and neutrophils) compared to controls. Women whose cancer ultimately recurred revealed greater serum cortisol and greater levels of WBC and neutrophils 17 months prior to their recurrence compared to those who remained disease free suggesting that these immunological changes in the intervention group may have been relevant in explaining differences in clinical outcomes between groups. Interestingly those women who experienced a distal recurrence at this point had weaker cellular immune responses (NKCC, LPR to mitogens) and greater elevations in WBC compared to those who experienced a local recurrence.

1.6.2 Psychosocial Intervention Effects on Stress-Related Biobehavioral Processes during Breast Cancer treatment

Briefly, the effects of CBSM and MBSR have included decreases in late afternoon serum cortisol levels and increases in lymphocyte proliferative response and Th1 cytokine production and Th1/Th2 production ratio [183]. Women completed questionnaires and provided blood samples at 6 and 12 month follow-up. Women in CBSM reported improvements in negative and positive mood and a wide variety of quality of life indicators as well as decreases in late afternoon serum cortisol, and increases in IL-2 and IFN-γ production from anti-CD3 stimulated peripheral blood mononuclear cells (PBMCs). Thus this form of intervention, which was previously associated with decreases in distress states, and increases in positive states, was also related to reductions in cortisol and increases in cellular immune function that are consistent with a hastened recovery from cancer treatment. Intervention effects on Th1 cytokine production may be important for supporting cellular immune processes that are involved in tumor eradication, such as antigen presenting cells, cytotoxic- T-cells, and T regulatory cells. Some biological processes that remain to be studied to explain the effects of psychosocial interventions on clinical outcomes in cancer patients include inflammation and those processes that may play a role in directly supporting tumor growth and metastasis, such as angiogenesis, tumor cell migration, tissue remodeling, and anoikis and resistance to apoptosis. There is growing evidence that neuroendocrine hormones such as glucocorticoids and adrenergic hormones can influence communications between tumor, endothelial, and stromal cells which appears to be critical in modulating downstream signaling pathways important for disease progression. One paradigm for examining the effects of psychosocial interventions on cell signaling pathways that are relevant to human cancer progression is to examine whether psychosocial interventions with cancer patients are associated with transcriptional changes in circulating leukocytes reflecting molecular pathways that affect inflammation and cellular immune signaling as well as those that promote invasion and metastasis. For instance, given that chronic stress and negative affect are related to other biological processes such as inflammation, which may have relevance for cancer progression [183], it is important to examine whether stress reduction interventions (e.g., CBSM) can affect inflammatory indicators and stress-sensitive neuroendocrine processes (e.g., glucocorticoid receptor sensitivity)

that control inflammation within circulating leukocytes. It would also be intriguing to show that these interventions are associated with transcriptional changes in genes controlling cellular immunity (e.g., interferon activation pathways) within these cells.

1.6.3 Intervention Effects on Stress-Related Leukocyte Transcriptional Changes in Cancer Patients Undergoing Treatment

Using frozen cells from women who had previously participated in an RCT testing the effects of a 10-week CBSM intervention vs an active control we conducted genome-wide transcriptional profiling and bioinformatic analysis at study entry, and 6- and 12-month follow-up [184]. Greater negative affect and less positive affect was associated with greater than 50% differential expression of 201 genes, including upregulated expression of proinflammatory cytokines (IL1A, IL1B, IL6, TNF) and metastasis-promoting genes (e.g., those involved in tissue remodeling and epithelial-mesenchymal transition, LMNA, MMP9). Gene Ontology analyses confirmed that these transcripts were disproportionately involved in pro-inflammatory cytokine function and wound healing. This is the first evidence that individual differences in psychological adaptation status early in BCa treatment (2–10 weeks after surgery) are significantly associated with a leukocyte transcriptional profile reflecting an up-regulation of signaling pathways associated with inflammation, invasion and metastasis. Women assigned to CBSM showed decreases in negative affect and increases in positive affect, and also showed altered expression of 91 genes by > 50% at 6–12 month follow-up. These changes included down-regulation of 62 genes encoding pro-inflammatory cytokines, the prostaglandin-synthesis enzyme COX2, inflammatory chemokines and their receptors, and mediators of tissue remodeling and epithelial-mesenchymal transition. Women in CBSM also revealed 29 upregulated genes relevant for cellular immune responding including Type I interferon response, Type II interferon signaling, and interferon signal transduction. Real-time Polymerase Chain Reaction (RT-PCR) analysis confirmed microarray-indicated group differences in the between-group relative expression of a sample of transcripts audited. Women in CBSM showed increased expression of genes controlling the glucocorticoid receptor (GR) relative to controls. Parallel analyses of gene transcription controlling for concurrent serum cortisol levels showed an over-representation of GR response elements in the promoters of CBSM-up-regulated genes. Differential

transcription of genes bearing GR response elements was not attributable to differential expression of genes encoding the GR. These findings are provocative and suggest that the effect of CBSM on gene profiles reflecting a down-regulation of inflammatory signaling co-occur in tandem with an upregulation of GR. Since chronic stress has been proposed to down-regulate GR and up-regulate inflammatory (NFκB) signaling in other populations it is plausible that the transcriptional changes in neuroendocrine and inflammatory factors observed after CBSM are mediated by the decreases in chronic stress and negative affect as noted above. Transcript Origin Analyses [188] implicated monocytes and plasmacytoid dendritic cells (pDCs) as the most likely cells involved in CBSM induced transcriptional changes with up-regulated genes deriving predominately from monocytes and downregulated transcripts associated with both monocytes and pDCs. The effects of CBSM on gene expression profiles persisted when controlling for clinicopathological, cancer treatment-related, and psychiatric medications, as well as potential sociodemographic and behavioral confounders. Importantly, the genes down-regulated by CBSM included many of the transcripts that were also up-regulated in women with greater negative and less positive affect at baseline. This suggests a specificity of CBSM impact on psychological adaptation-associated genes, specifically those involved in inflammation and tissue remodeling. The immune cell types most likely mediating CBSM transcriptional alterations--antigen presenting myeloid cells — have previously been linked to distress states [188]. Bioinformatic inferences of TF activity (GATA- and NF-κB/Rel-family TFs) associated with CBSM-induced transcriptional alterations have been linked to stress and SNS signaling in prior work as well [185, 186]. Findings also suggest that CBSM induced GR activation, possibly representing a reversal of the distress related GR transcriptional down-regulation shown in other work on chronic stress [185]. Because these effects persisted after controlling for individual differences in circulating cortisol levels [187], they suggest that CBSM affects GR target gene expression primarily by enhancing GR functional sensitivity (i.e., reversing stress-induced GR desensitization) [188]. If this is true it opens the possibility that CBSM and other stress reduction interventions may modulate inflammatory signaling by mitigating stress-induced GR downregulation in the context of cancer treatment, and possibly in other chronic medical and psychiatric conditions. If in fact CBSM was capable of causing the changes in gene expression observed in this study it is unclear whether the accompanying

changes in CNS-mediated mood changes precede or follow from changes in leukocyte signaling. It is plausible that pro-inflammatory cytokines derived from activated monocytes may signal to the brain to causally affect neural function and, thus inducing a bi-directional regulatory circuit that could explain associations between inflammation and CNS-mediated distress processes. These results justify future randomized trials of similar psychosocial interventions in cancer patients utilizing transcriptional analyses of specific leukocyte subsets, possibly along with functional assays designed to probe the communication between neuroendocrines (e.g., glucocorticoids) and specific leukocyte subpopulations (e.g., monocytes) and their association with longer-term clinical outcomes in order to explore whether the effects of psychosocial interventions on these signaling pathways are relevant to cancer disease progression. It also appears that the women receiving CBSM show contemporaneous increases in gene expression associated with a recovery of interferon-mediated cellular immunity, which may be relevant for immunosurveillance of cancer micro-metastases [189] or opportunistic infections during and after adjuvant treatment.

1.6.4 Psychosocial Intervention Effects in Other Cancer Populations

One study showed a 2-session stress management intervention (deep breathing, guided imagery and adaptive coping skills) offered to men prior to surgery for prostate cancer related to decreases in mood disturbance and increases in NKCC one week pre- to 48 hrs post-surgery [190]. This is an interesting finding in view of prior work showing that a psychosocial intervention initiated prior to surgery was associated with improved 10-year survival in patients treated for gastrointestinal cancer [191]. Another study showed that telephone-delivered psychosocial counseling intervention is associated with improved QoL and a shift toward a more Th1/Th2 cytokine bias in women with cervical cancer [192].

1.6.5 Exploring Other Clinical Health Outcomes in Cancer Patients

It has also been established that comorbidities before cancer treatment can affect clinical outcomes (decreased survival, increased disease recurrence) [193]. For instance, conditions such as diabetes mellitus, may increase the risk for disease recurrence in colon cancer [194], while obesity, another sign of

altered insulin metabolism, has been associated with reduced efficacy of aromatase inhibitors in ER + breast cancer patients [195]. Interestingly metformin, an insulin metabolism modulator, has been shown to have potential as a cancer therapeutic, especially in breast and colon cancers, which are associated with hyperinsulinemia [196]. To the extent that psychosocial factors and stress physiology can affect the pathogenesis of comorbidities related to insulin metabolism [197, 198, 199] then psychological interventions, including stress management, may mitigate the risk of and effects of these conditions in cancer survivorship. It seems reasonable that psychosocial intervention may be able to affect the risk of opportunistic disease and some of the co-morbidities listed here in treated cancer patients and may yield definitive results in much shorter follow-up periods than are requie for documenting effects on disease recurrence and survival.

1.6.6 Caveats and Methodological Considerations

Using the example of breast cancer, differences in clinicopathological characteristics can have prognostic significante (stage, HER2-neu+/−, ER/PR+/−) [200, 201], and in at least one trial, were found to moderate the effects of a psychological intervention on clinical outcomes. There is likely inter-individual variation in neuroimmunological responses attributable to surgery, chemotherapy, radiation, immunomodulators, anti-emetics, and hormonal treatments (e.g, Tamoxifen), to name a few of the major classes of treatment. Because some have hypothesized that the critical period for stress-mediated immunosuppression increasing the risk of breast cancer metastatic spread is in the weeks after surgery, it seems as though some intervention research in breast cancer patients may benefit by contending with these timing issues head on as in the case of the Andersen et al [150] trial. Going forward, potential confounds might be minimized in psychosocial intervention trials by controlling for elapsed days since diagnosis and surgery for the pre-intervention measures, elapsed days since most recent adjuvant treatment for intercurrent follow-ups, as well as careful monitoring of frequency/dosage of regimen, treatment actually received, corticosteroids, anti-emetics, nonsteroidal anti-inflammatory agents, and other medications patients are receiving at each time point. As attention in cancer research has shifted to a greater emphasis on the tumor microenvironment, it is now reasonable to examine how psychosocial processes and interventions affect the stromal cells (e.g., circulating and tumor-

associated myeloid cells) that could interact in the tumor microenvironment and how such changes relate to the clinical course of disease.

Emerging technologies now allow us to expand biobehavioral research in oncology by applying microarray and bioinformatics analyses of immune and tumor cell transcriptional activity. This could illuminate the juncture of neuroimmune communications underlying inflammatory and tumor promoting cell signaling. It is reasonable to propose that psychosocial interventions that address cancer patient's focal concerns in the period before and after surgery for primary disease may reduce stress associated exacerbations of biobehavioral processes that could promote disease progression. Basic research and preliminary intervention studies suggest that stress factors and psychological interventions may modulate biobehavioral processes in patients diagnosed with ovarian, cervical and prostate cancers.

Multidisciplinary Team (MDT) and Team Oncology Medicine are international medical hot topics in recent years. MDT is usually composed of specialists from two or more related disciplines, which work together to discuss some kinds of malignant tumors, and to form a clinical treatment plan [202]. Team Oncology Medicine is patient-centered, the relevant specialists aim at patients' Obvious achievements have been made in breast cancer, ovarian cancer, rectal cancer, prostate cancer, and lung cancer using the MDT treatment model [203, 204].

There are many international large-scale cancer centers such as M. D. Anderson Cancer Center (Houston, TX, USA), Philadelphia Veterans Affairs Medical Center (Philadelphia, PA, USA), the Netherlands Cancer Institute of Antoni van Leeuwenhoek Hospital (Amsterdam, Netherlands), and the National Cancer Action Team of St Thomas' Hospital (London, UK) which have set up a MDT treatment model [205, 206]. In this treatment model, the specialists from two or more departments such as oncosurgery, department of tumor medicine, tumor radiotherapy department, medical imaging department, pathology department, actual conditions and needs to guide patients with a team advantage, and provide extensive information, resources, and support and other related departments get together to discuss a patient's condition and form a treatment plan. A finding from University of Leeds (Leeds, UK) emphasized the importance of MDT in malignant tumor treatment [207]. This study was a retrospective analysis of 7,602 surgically resected colorectal cancer patients for whom colorectal pathology minimum data sets had been collected. A threshold for an adequate lymphadenectomy was defined as retriva of 12 nodes. The

operating surgeons and reporting pathologists were identified for each tumor. Surgeons and pathologists were then assigned to be team or nonteam members according to the results of the National Cancer Peer Review process. In recent years, cancer morbidity and mortality are not optimistic in a worldwide scope.

In the "Biology-Psychology-Society Medical Model", with the scientific and technological progress and people's understanding of solid tumors, the malignant tumor treatment model has basically changed from single-subject treatment to multidisciplinary collaboration treatment which was led by a Multidisciplinary Team. On this basis, a more consummate malignant tumor treatment – Team Oncology Medicine has been set up, which pays close attention to patients' actual demand to improve the quality of life.

When a child is diagnosed with cancer, it is quickly understood that he or she will die without treatment. Typically, treatment protocols require hospitalization, painful and invasive diagnostic and monitoring procedures, and surgery, chemotherapy, and/or radiation therapy. This model recognizes the life threat inherent in cancer and explains symptoms such as intrusive thoughts, physiological arousal, hypervigilance and avoidance. The time and physical demands of treatment prompt strain and disorganization; Horwitz and Kazak [208] found that families of children with cancer 6 to 41 months post-diagnosis were more likely to fall into the chaotic and rigid ranges of flexibility when compared to community controls. For example, Cohen and colleagues [209] found that significantly more families of children with cancer up to 4 years postdiagnosis scored in the enmeshed range when compared to norms (21% vs. 14%). Research specifically concerning family functioning and posttraumatic reactions in survivors of childhood cancer is scant. In summary while it is widely recognized in the general trauma literature that a child's response to a traumatic event is greatly influenced by family context [210], the evidence linking family functioning and cancer-related PTSD in adolescent survivors is weak.

Many parents of children with cancer explore the use of integrative therapies (IT) to help manage the side effects associated with cancer therapy, to augment the efficacy of conventional medications, and to provide psychological support for coping with the diagnosis of cancer. Children with cancer are significant consumers of modalities classified as IT, with international surveys demonstrating 31% to 84% reportedly using such terapie [211]. Specific prevalence data on the use of IT among children with hematological malignancies has generally not been reported in the surveys, although IT were

used by 53 of 60 children with leukemia in a recent Malaysian study [212]. Most children use these therapies in an “integrated” approach with conventional therapies; relatively few reports describe the use of alternative therapies in lieu of conventional medicine, although 5 of 6 cases involved children with good prognosis hematological malignancies [213]. Parents pursue IT in order to ensure that they have left “no stone unturned” and to feel as if they are doing all they can to help their child be cured or support them during cancer therapy. Although there has been a significant increase in research on IT for cancer, there is still a paucity of data to guide clinical practice incorporating IT for children with hematological malignancies.

Despite limitations, evidence is available from research studies including randomized controlled trials to support the use of some IT for symptom control among children with hematological malignancies [214, 215].

In addition to evaluation of direct anti-cancer activity, the investigation of the interactions of specific dietary supplements with conventional chemotherapy and radiation therapy is an area of pressing need. Antioxidants are one of the most common classes of supplements used by patients with cancer; these supplements are used for direct cytotoxic effects, for synergy with conventional therapy or to mitigate conventional therapy-induced toxicity.

Children also tend to tolerate chemotherapy better, as they are less likely to have comorbid conditions. Therefore, it is critical that therapies that may interfere with or encourage refusal or delay of conventional therapies be avoided in the child with cancer. Several types of integrative therapies can be considered for symptom control in the care of the child with hematological malignancies at this time Massage therapy. Glutamine is safe and beneficial in reducing the severity of mucositis in children undergoing stem cell transplantation.

Survivors are challenged with issues not limited to energy balance, fatigue, bone health, pain syndromes, and anxiety and are at increased risk for many long-term sequelae, including cardiac dysfunction, stroke, osteoporosis and osteonecrosis, infertility, and second malignancies. For example, yoga and meditation may help to reduce the feelings of anxiety associated with cancer recurrence, may lessen the functional impact of disturbances in balance or gait, or assist with maintenance of a healthy weight.

1.7 Chemotherapy as a contributor to disturbed sleep and insomnia

The greater rate of insomnia experienced by cancer patients has not only been attributed to the emotional consequences of being diagnosed with cancer but also to the direct effects of cancer treatments and their side effects, particularly chemotherapy [216, 217, 218]. In a prospective study of 823 patients undergoing chemotherapy, 39.8% reported moderate or severe insomnia symptoms after their first chemotherapy treatment, with symptoms persisting throughout subsequent cycles in two-thirds of patients. A systematic review of 21 articles further suggested that sleep disturbances can persist for up to 1 year post-chemotherapy. The most commonly reported sleep problem by patients undergoing chemotherapy is the inability to maintain sleep (63.3%), with disruptions being attributed to the anxiety and worry related to the cancer diagnosis/treatments and the effects of cancer treatments themselves (ie, postsurgical pain/discomfort, overall fatigue, nausea, nocturnal hot flashes, increased bathroom use, and steroid-induced agitation) [219, 220].

The pattern is a functional property of all living matter, including humans, and is controlled by two primary factors: the amount, timing, and placement of sleep across the day (i.e., sleep homeostasis) and the underlying intrinsic circadian rhythm. The role of homeostatic factors and circadian rhythm in sleep regulation is best understood when sleep is examined as a physiologic as well as a behavioral process controlled by a system based in the brain and central nervous system. The process of sleep onset also is modulated by the sympathetic nervous system and by the hypothalamic-pituitary-adrenal (HPA) axis. Input from the systems is filtered out by the thalamus as sleep occurs, a process that must be filtered continually to maintain uninterrupted sleep. The circadian oscillator resides in the suprachiasmatic nuclei, where rhythms are generated and synchronized with the environment by light and dark cues from the retina of the eye. Additional timing modifications are provided by interaction with the paraventricular nuclei and the ventromedial hypothalamus. Marker rhythms of the circadian oscillator are the core temperature rhythm and the rhythmic secretion of the hormone melatonin. At sleep onset, sleep initiation is most likely to occur during the falling phase of the endogenous component of the temperature rhythm. Timing of the circadian component is aduste by melatonin secreted from the pineal gland during the dark and inhibited by light exposure. Circadian timing also is adjusted by levels of plasma and central nervous system neurotransmitters and neuroendocrine

factors such as gamma-amino-butyric acid; dopamine; growth hormone releasing hormone; prostaglandins D2, E2, and F2a; vasoactive inhibitory peptide; and growth hormone. Final awakening typically occurs when body temperature is rising (approximately one to two hours after the minimum temperature of the endogenous circadian rhythm) and sleep pressure (Process S) has decreased. An absent or blunted rhythm of melatonin secretion also has been noted in patients with lung or colorectal cancer. Changes over time in nighttime melatonin levels in patients with breast or ovarian cancer also have been reported. In addition, cancer cells produce and induce production of cytokines, substances that promote sleep. More detailed summaries have been published. Further research is needed to understand more fully the extent to which the pathophysiology of cancer affects sleep and wakefulness.

Mormont et al reported that metastatic colorectal cancer patients with dysregulated sleep/wake patterns (ie, poorly differentiated activity levels during wake and sleep) were five times more likely to die within 5 years than patients with a more distinguishable circadian rhythm [221]. When assessed using actigraphy, people with a dampened circadian rhythm, characterized by flat profiles with less activity during the day and more activity during the night, reported more depressive symptoms and worse overall quality of life than those with more robust circadian rhythms.

Compared with good sleepers, individuals with insomnia exhibit cognitive, physiological, and cortical hyperarousal; demonstrate particular cognitive patterns and attentional biases; and strongly endorse problematic sleep-related beliefs. Relaxation training (the original behavioral intervention for insomnia) is no longer regularly incorporated into CBT-I but is sometimes utilized to reduce peripheral autonomic arousal and facilitate mental de-arousal.

Modern techniques in molecular genetics are being used in insect and animal models to begin to elucidate the genetic basis for circadian rhythms and sleep disturbances. From 2003–2004, an increasing volume of descriptive studies was published that included the variable of sleep in some context in patients with cancer. A search of MEDLINE, CINAHL, and PsycINFO was conducted to identify all nonpharmacologic intervention studies that examined sleep disturbance or sleep quality outcomes in adults with cancer; the search revealed 20 studies that met the criteria. Few of the approaches have been studied in populations with cancer, although the drugs are used commonly clinically in people with cancer. Antidepressants including serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants also may aid sleep, depending

on dosages used. SSRIs have varying effects on anxiety and daytime activity. The identified substances primarily included the herbal supplements valerian kava, and St. John's wort, plus the hormone supplement melatonin. Although patients with cancer were included as participants in a few studies, research testing pharmacologic complementary and alternative substances to treat sleep disturbances that focused specifically on people with cancer is almost nonexistent. St. John's wort may have anxiolytic effects with relevance to sleep, but herb-drug interactions with chemotherapeutic agents and other common drugs make the herb a potentially dangerous choice for use in patients with cancer [222].

A continued need exists for well-designed, large sample, double-blind, placebo-controlled clinical trials to determine the efficacy and safety of complementary and alternative therapies for sleep/wake disturbances in people with cancer.

This state-of-the-science summary of sleep/wake disturbances in people with cancer and their caregivers provides information to guide evidence-based practice, the "conscientious explicit and judicious use of theory-derived research-based information in making decisions about care delivery to people or groups of patients and in consideration of people needs and preferences" [223]. Because of the high incidence of sleep/wake disturbances in people with cancer, sleep-screening tools, such as the Clinical Sleep Assessment (Adult) and Clinical Sleep Assessmen (Child), should be integrated into oncology clinical practice. Not all patients report disturbed sleep; however, a subset of patients report problems at varying times throughout the cancer experience [224, 225, 226].

1.8 Serotonin

The role of the genetic polymorphism in the response to treatment and survival for oncological patients is well known. However, the genetic polymorphism of serotonin transporter (SERT) in causing an increased risk of depression in subjects who experienced stressful life events is also known and it has been initially reported by Caspi *et al.* Serotonin (5-HT) neurotransmission has a key role in the regulation of the activity of the central nervous and influences a wide variety of physiological and psychological processes including individual differences in personality traits [227, 228]. The serotonin transporter gene (SLC6A4) encodes the serotonin transporter protein (5-HTT),

which acts as a key regulator by removing serotonin from the synaptic cleft. The promoter region of the SLC6A4 gene contains a polymorphism with short (s) and long (l) repeats in a region: 5-HTT-linked polymorphic region (5-HTTLPR). The long form was shown to be associated with higher and the short form with lower expression of the gene product [229]. Several studies have provided strong evidence for an association between the 5-HTTLPR short allele and neuroticism, defined as proneness to negative emotionality, including depression and anxiety. Individual with either one or two copies of the short allele had significantly greater levels of neuroticism than those homozygous for the long allele [229]. The analysis of the association between the 5-HTTLPR polymorphism and neuropsychiatric disorders, including anxiety and depressive syndromes, has shown some positive but contradictory findings. Significant associations between the short variant and susceptibility for mood disorders have been reported [230, 231, 232] but other studies did not confirm these findings [233]. The original results of Caspi et al. [234] suggested that individuals carrying the short (s) allele are more likely to develop major depression following exposure to early life stress (e.g., childhood maltreatment). More recently, many investigators found that this polymorphism confers risk for psychopathology in the presence of stress during adulthood [235, 236], which has been confirmed in mouse models [237]. Individuals with one or two copies of the s allele exhibited higher levels of depressive symptoms following exposure to stressful events than did individuals who were homozygous for the l allele. Perhaps most notably, a number of studies have shown that neuroticism mediates the association between the serotonin transporter gene polymorphism and stress-reactive phenotypes like depression and anxiety by increasing the magnitude of emotional reactivity to stressful events [238, 239]. Taken together, these findings suggest that this genetic polymorphism produces an increased sensitivity to the impact of stressful events that in turn increases the likelihood of anxiety and depression. Although there is evidence that athletes are highly vulnerable for developing mental health problems due to the level of stress they experience [240] little is known about the association between the 5-HTTLPR polymorphism and the development of depressive and anxiety symptoms in the athlete population. In addition research suggests that an episode of major depression increases trait neuroticism and it is possible that the mediating effect of neuroticism on the association between the 5-HTTPRL genotype and depression may be due, in part at least, to the fact that those who report a history of lifetime major

depression will also report elevated trait neuroticism, because of this history [241]. However, several researchers suggested that depression and anxiety may best be viewed as dimensional, not a categorical, constructs and explored the influence of the 5-HTTLPR genotype on affective disorders treating anxiety and depression as continuous variables [242, 243].

We had the opportunity to use diagnosis of colorectal cancer, known to increase risk for depression, as the severely stressful life event [244, 245]. In addition, we applied use of antidepressants as a measure of pharmacologically treated depression. Using exact dates of diagnosis of colorectal cancer and redeemed prescriptions of antidepressants, we tested the hypothesis that risk for use of antidepressants following diagnosis of colorectal cancer is associated with bi- and triallelic genotypes of 5-HTTLPR.

SERT-P polymorphism results from a 44 base-pair insertion/deletion, approximately 1 kb upstream of the serotonin transporter gene. The polymorphism results in an insertion (L) and a deletion (S) allele [246]. In functional studies using a transfected cell line, homozygous deletion (S/S) and heterozygous (L/S) SERT genotypes were associated with lower transcriptional activity compared with that of the homozygous insertion (L/L) genotype, leading to a reduction in 5-HT reuptake [247]. Several studies have investigated the association between SERT gene polymorphism and irritable bowel syndrome (IBS), with contradictory results [248, 249]. Two twin studies support a genetic and environmental basis for pathophysiology [250, 251]. In a study of 54 patients with IBS and 91 healthy subjects, it was found that the presence of the S/S genotype in IBS patients carries an increased risk of the constipation-predominant type of IBS (C-IBS) [252] .

The objective of this exploratory study was to identify the determinants of intrusive recollections in breast cancer survivors; furthermore, Determine the relationship between personality, polymorphisms of the serotonin transporter (5HTT) with the anxiety and depressive symptoms in patients with gynecological cancer. We investigated the anxious-depressive symptomatology, neuroticism and coping strategies in two different populations for the oncological manifestation in gynecology (cervix vs endometrium). We asked if there are differences about anxious-depressive symptomatology, neuroticism and coping strategies in different oncological treatments (pharmacological vs chemo-radio). We expected that our study could be useful both in recommending clinical strategies for more easily evaluating our patients'

expected psychological distress and in developing appropriate supportive communication and/or intervention.

Capter 2

Methods/Design

2.1.1 Study design

In this study forty gynecological oncological patients were recruited from University Gynecology Department in Foggia between January 2014 and December 2016.

Study protocol approval and trial registration Participation in the study was voluntary and written informed consent was obtained. Patients were informed that they could withdraw their consent to participate at any time, with no negative consequences on their future medical treatment. Patients who wished to withdraw from the study received care as usual. Eligible patients received an explanation of the study procedures and were asked to sign an informed consent.

2.1.2 Inclusion and exclusion criteria

Participant eligibility criteria included a diagnosis of a curable solid tumor. We enrolled participants at least 4 weeks after cancer diagnosis to ensure that the anxiety symptoms persisted beyond the initial adjustment to a new cancer diagnosis. Patients prescribed psychotropic medications were eligible to participate because benzodiazepines in particular are a standard component of many chemotherapy regimens for alleviation of symptoms, such as nausea. Study referrals came from oncology clinicians, palliative care specialists, psychiatrists, or patients themselves through advertisements in the University Gynecology Department in Foggia.

No report of suicidal ideation, thought disorder, or psychosis.

2.1.3 Psychometric Evaluation

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [253] and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID II) [254], were administrated to assess current and previous psychiatric diagnoses. The clinical assessment was conducted by psychiatrists

and/or licensed research psychologists who were trained to a minimum interclass correlation of 0.80.

Personality traits were measured with two scales from the Eysenck Personality Questionnaire—Revised: the extroversion and neuroticism scales, each with 12 dichotomous items. The concept of neuroticism refers to a general emotional over responsiveness and liability to develop neurotic disorders under stress. The concept of extroversion refers to outgoing, sociable, uninhibited, impulsive inclinations. The NEO Five-Factor Inventory (NEO-FFI) was used to assess of personality [255]. The personality description is given in 5 dimensions: neuroticism, extraversion, agreeableness, openness and conscientiousness. The structure of this test has been validated in a variety of populations and cultures [256, 257, 258] using various personality inventories [259].

The POMS is a standard validated psychological test formulated by McNair et al. [260] consisting of 65 items that fit into 6 categories: tension-anxiety (T/A), depression-dejection (D/D), angerhostility (A/H), vigor-activity (V/A), confusion-bewilderment (C/B) and fatigue-inertia (F/I). The Temperament and Character Inventory (TCI) is an inventory for personality traits devised by Cloninger et al. [261]. It is closely related to and an outgrowth of the Tridimensional Personality Questionnaire (TPQ), and it has also been related to the dimensions of personality in Zuckerman's alternative five and Eysenck's models [262] and those of the five factor model [263] TCI operates with seven dimensions of personality traits: four so-called temperaments [264]: Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), Persistence (PS), and three so-called characters Self-Directedness (SD), Cooperativeness (CO), Self-Transcendence (ST). Each of these traits has a varying number of subscales. The dimensions are determined from a 240-item questionnaire. The TCI is based on a psychobiological model that attempts to explain the underlying causes of individual differences in personality traits [264].

The State-Trait Anxiety Inventory (STAI) is a commonly used measure of trait and state anxiety [265]. It can be used in clinical settings to diagnose anxiety and to distinguish it from depressive syndromes. It also is often used in research as an indicator of caregiver distress Form Y, its most popular version, has 20 items for assessing trait anxiety and 20 for state anxiety. State anxiety items include: “I am tense; I am worried” and “I feel calm; I feel secure.” Trait anxiety items include: “I worry too much over something that really doesn’t

matter" and "I am content; I am a steady person." All items are rated on a 4-point scale (e.g., from "Almost Never" to "Almost Always"). Higher scores indicate greater anxiety. The STAI is appropriate for those who have at least a sixth-grade reading level. Internal consistency coefficients for the scale have ranged from .86 to .95; test-retest reliability coefficients have ranged from .65 to .75 over a 2-month interval.

The Italian version of COPE (Coping Orientations to Problems Experienced) [266] was administered to assess coping styles. The COPE is a self-report questionnaire that measures 15 coping strategies: five scales that measure problem-focused coping (active coping, planning, suppression of competing activities, restraint coping, and use of instrumental social support); six scales that measure emotion-focused coping (use of social-emotional support, positive reinterpretation and growth, acceptance, humor, focusing on and venting of emotions, and turning to religion); four scales that measure potentially disadaptive strategies/less useful coping responses (denial, behavioral disengagement, alcohol and drug disengagement, and mental disengagement). This questionnaire is usually used in medical settings. The COPE can be used as a measure of dispositional coping or as a situational measure of coping with a specific stressful event.

The Perceived Stress Scale (PSS) is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress. The PSS was designed for use in community samples with at least a junior high school education. The items are easy to understand, and the response alternatives are simple to grasp. Moreover, the questions are of a general nature and hence are relatively free of content specific to any subpopulation group. The questions in the PSS ask about feelings and thoughts during the last month. In each case, respondents are asked how often they felt a certain way. Cohen et al. [267] show correlations with PSS and: Stress Measures, Self Reported Health and Health Services Measures, Health Behavior Measures, Smoking Status, Help Seeking Behavior.

The EORTC QLQ-C30 is a validated 30-item questionnaire containing both single- and multi-item measures [268]. These include five functional scales (Physical, Role, Cognitive, Emotional, and Social Functioning), three symptom scales (Fatigue, Pain, and Nausea/Vomiting), a Global Health Status/QoL scale,

and six single items (Constipation, Diarrhea, Insomnia, Dyspnea, Appetite Loss, and Financial Difficulties). Scores for each scale and single-item measure are averaged and transformed linearly to a score ranging from 0–100. A high score for functional scales and for Global Health Status/QoL represent better functioning ability or HRQoL, whereas a high score for symptom scales and single items represents significant symptomatology.

2.1.4 DNA analysis

Medical Genetics Unit Department of Medical Sciences University of Foggia took care of the DNA analysis.

A blood sample was collected in ethylenediaminetetraacetic acid or sodium citrate from each participant and DNA was extracted from peripheral blood leukocytes according to standard protocols [269].

DNA amplification was amplified using the 2 flanking primers suggested in 1996 by Heils et coll: 5-HTTU:5'GGCGTTGCCGCTCTUAATGC3', nt-1416,-13975-HTTL:5'GAGGGACTGAGCTGGACAACCAC, nt-910,-889. This set of primers amplifies a 484/528 fragment corresponding to the SLC6A4_C short and long allele, respectively. The PCR conditions were slightly modified from Heils et coll. [270]. The PCR reaction was carried out in a total volume of 20 µL consisting of 100 ng of genomic DNA, 0.1 µmol of primers per liter, 40-µmol/L deoxynucleotide triphosphates, 20-µmol/L 7-deaza-2'deoxyguanosine, and 1 unit of AmpliTaq with the appropriate buffer in a Mastercycler polymerase chain reaction thermal cycler (Eppendorf, Hamburg, Germany). Cycling conditions were as follows: 1 denaturing cycle at 95°C for 5 minutes, 2 cycles with a touchdown annealing temperature of 63°C and 62°C, respectively for 30 seconds, and 38 cycles with an annealing temperature at 61°C. Final DNA elongation was at 72°C for 10 minutes. DNA bands were visualized in prestained (0.4-µg/mL ethidium bromide) 3% agarose gels that were run for 1 hour at 120 V.

2.1.5 Mediation analyses

A path method was applied to test the hypothesis that the association between 5-HTTLPR genotype and symptoms of anxiety and depression was mediated by trait neuroticism. In particolar a series of linear regression models was run to assess the fourth criterion for mediation proposed by Baron and

Kenny [271] as described by Frazier et al. [272]. This approach involves testing three equations. First, the outcome variable is regressed on the predictor (Path c) (Fig.1). Second, the mediator is regressed on the predictor variable (Path a). In the third equation, the outcome variable is regressed on both the predictor and the mediator. This provides a test of whether the mediator is related to the outcome (Path b) as well as an estimate of the relation between the predictor and the outcome controlling for the mediator (Path c'). If the relation between the predictor and the outcome is significantly smaller when the mediator is in the equation (Path c') than when the mediator is not in the equation (Path c), the data suggest a mediation effect [272]. Second, the neuroticism (NEO-FFI) score (the mediator) was regressed on the 5-HTTLPR genotype (the predictor variable) to show that the predictor was related to the mediator (Path a). To assess the significante of the mediating variable effect we used the method proposed by Baron and Kenny [271]. Specifically, the product of paths a and b is divided by a standard error term. The mediated effect divided by its standard error yields a z score of the mediated effect. If the z score is greater than 1.96, the effect is significant at the .05 level.

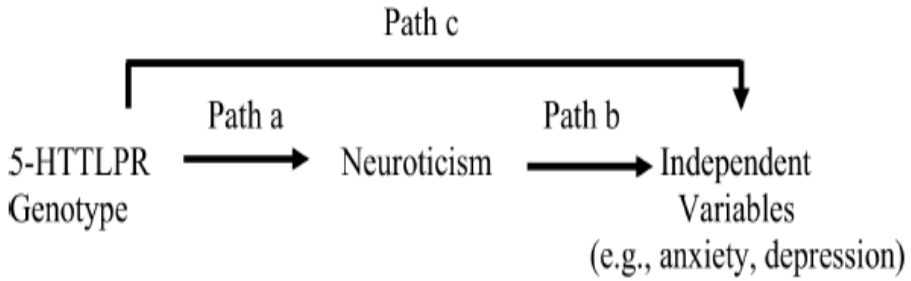


Fig 1. Paths in mediation model.

2.2 Outcomes

The purpose of this study is to determine the relationship between personality, polymorphisms of the serotonin transporter (5HTT) with the appearance of anxiety and depressive symptoms in patients with gynecological neoplasia; to investigate the anxiety-depressive symptomatology, neuroticism and coping strategies in two different populations for the oncological manifestation in gynecology (cervix-endometrium); if there are differences about anxious-depressive symptomatology, neuroticism and coping strategies in different oncological treatments (pharmacological vs. chemo-radio).

Capter 3

Results

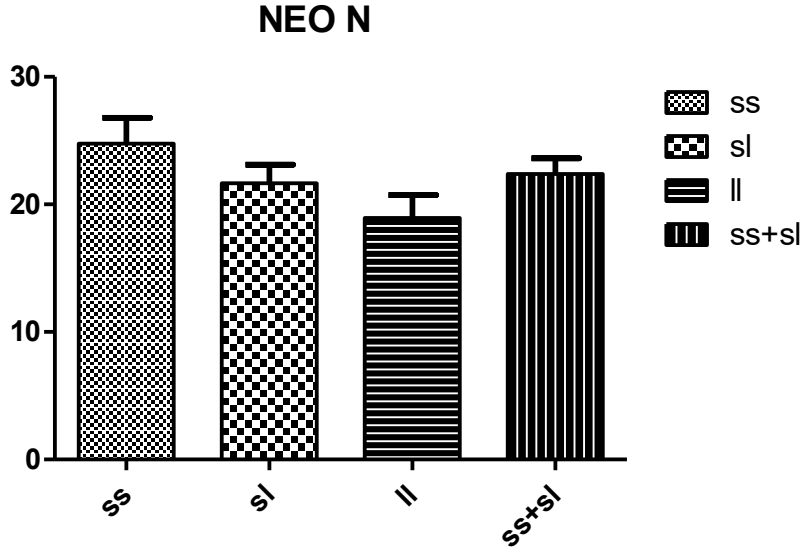
Participants had no history of neurologic, psychiatric disorders or alcohol and other drugdependence disorders. The average age of the participants was 58.15 (SD = 14.01), ranged from 18–65 years. The genotype subgroups did not differ significantly in age (s/s = 65 (SD = 12.36); s/l = 58.86 (SD = 11.14); l/l = 64.09 SD = 13.59), all $p > 0.05$. All participants reported high levels of stress related to competition (e.g. pressure to perform well and pressure of meeting expectations). 5-HTTLPR genotype and allele frequencies are shown in Table 1.

Table 1: Frequiences of the genotypes and alleles of the 5-HTTLPR

Genotypes		
l/l	l/s	s/s
N = 11	N = 23	N = 7

The distribution of allele in the sample was in the Hardy-Weinberg equilibrium ($p > 0.05$).

The mean scores on the Neuroticism personality trait, sub-scale of the NEO-FFI for each genotype group are presented in Graph 1. The analyses across the 5HTT-LPR genotype groups (group S (s/s + s/l); l/l; l/s; s/s) indicated a significant main effect of the s/s genotype on neuroticism ($p = .0096$). Post-hoc analyses revealed a recessive effect of the short allele of the 5-HTTLPR gene with increased neuroticism score in the s/s genotype group and in the S group compared with the s/l and l/l groups (all, $p < 0.05$). There was no association with the other major personality subscales of the NEO-FFI.

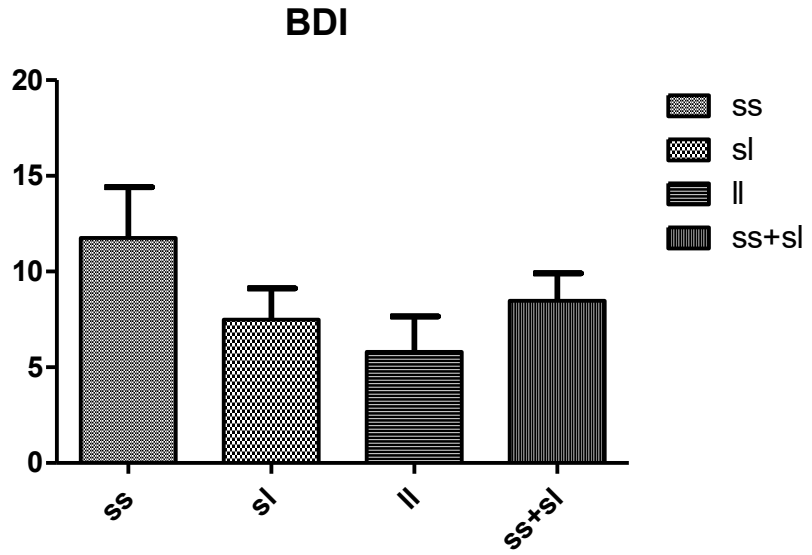


Graph. 1: anova Neo Neuroticism

Kruskal-Wallis test			
P value	0,0096		
Exact or approximate P value?	Gaussian Approximation		
P value summary	**		
Do the medians vary signif. (P < 0.05)	Yes		
Number of groups	4		
Kruskal-Wallis statistic	11,44		
Dunn's Multiple Comparison Test	Difference in rank sum	Significant? P < 0.05?	Summary
ss vs sl	10,74	No	Ns
ss vs ll	29,32	Yes	*
ss vs ss+sl	8,233	No	Ns
sl vs ll	18,58	No	Ns
sl vs ss+sl	-2,506	No	Ns
ll vs ss+sl	-21,08	Yes	*

Tab. 2: Description anova NEO Neuroticism

The mean scores on the depression symptoms, BDI scales for each genotype group are presented in Graph 2. The analyses across the 5HTT-LPR genotype groups (group S (s/s + s/l); l/l; l/s; s/s) indicated a significant main effect of the s/s genotype on depressive symptoms ($p = .0407$). Post-hoc analyses revealed a recessive effect of the short allele of the 5-HTTLPR gene with increased depressive score in the s/s genotype group and in the S group compared with the s/l and l/l groups (all, $p < 0.05$).

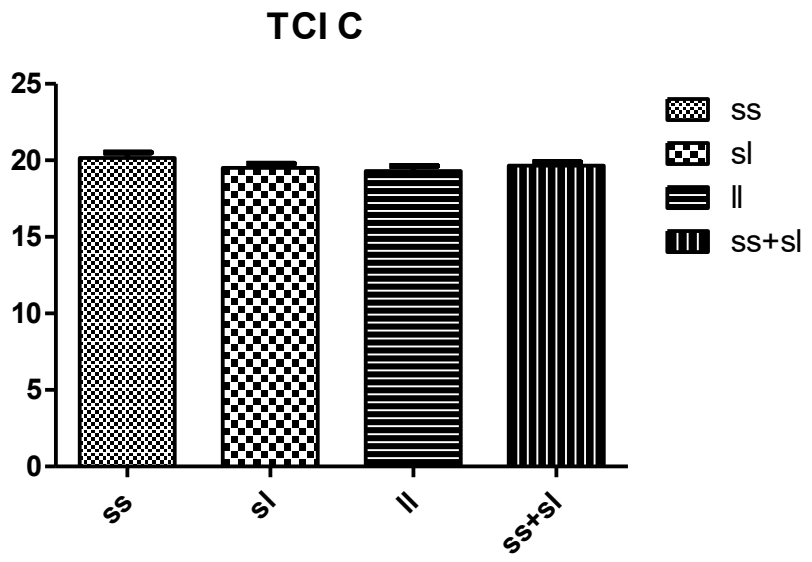


Graph 2: anova BDI depressive symptoms

Kruskal-Wallis test			
P value	0,0407		
Exact or approximate P value?	Gaussian Approximation		
P value summary	*		
Do the medians vary signif. (P < 0.05)	Yes		
Number of groups	4		
Kruskal-Wallis statistic	8,271		
Dunn's Multiple Comparison Test	Difference in rank sum	Significant? P < 0.05?	Summary
ss vs sl	17,80	No	Ns
ss vs ll	26,99	Yes	*
ss vs ss+sl	13,65	No	Ns
sl vs ll	9,186	No	Ns
sl vs ss+sl	-4,154	No	Ns
ll vs ss+sl	-13,34	No	Ns

Tab. 3: Description anova BDI depressive symptoms.

The mean scores on the Cooperativeness character dimension, TCI scales for each genotype group are presented in Graph 3. The analyses across the 5HTT-LPR genotype groups (group S (s/s + s/l); l/l; l/s; s/s) indicated a significant main effect of the s/s genotype on neuroticism (p = .0064). Post-hoc analyses revealed a recessive effect of the short allele of the 5-HTTLPR gene with increased neuroticism score in the s/s genotype group and in the S group compared with the s/l and l/l groups (all, p < 0.05). There was no association with the other major personality subscales of the TCI.



Graph.3: anova TCI Cooperativeness

Kruskal-Wallis test			
P value	0,0064		
Exact or approximate P value?	Gaussian Approximation		
P value summary	**		
Do the medians vary signif. (P < 0.05)	Yes		
Number of groups	4		
Kruskal-Wallis statistic	12,32		
Dunn's Multiple Comparison Test	Difference in rank sum	Significant? P < 0.05?	Summary
ss vs sl	15,55	No	Ns
ss vs ll	30,42	Yes	**
ss vs ss+sl	11,92	No	Ns
sl vs ll	14,88	No	Ns
sl vs ss+sl	-3,628	No	Ns
ll vs ss+sl	-18,50	Yes	*

Tab.4: Description anova TCI Cooperativeness

A significant correlation was observed between Neuroticism and moods state, clinical symptoms, level of perceived stress and level of qualitu of life. (Table 5).

There was a significant main effect of Neuroticism on anxiety symptoms according to the POMS ($r = 0.5229$, $p = 0.0005$). Post-hoc analyses revealed that participants with two copies of s allele had significantly higher POMS tension /anxiety (T/A) scores than those with the l/l genotype ($p<0.05$). Furthermore, we found a main effect of Neuroticism on depressive symptoms ($r = 0.7988$, $p < 0.0001$) according the BDI, and state anxiety ($r = 0.7343$, $p < 0.0001$) according STAI Y1, and perceived stress ($r = 0.5863$, $p < 0.0001$) according PSS. The correlation between Neuroticism and EORTC QLQ-C30 scores is negative ($r = -0.3190$, $p = 0.0421$)..

Table 5: Association between Neuroticism and psychological dimensions about anxious-depressive symptoms

	Neuroticism	BDI	POMS Tension-Anxiety	STAI Y1	PSS	EQ
Pearson r		0.7988	0.5229	0.7343	0.5863	-0.3190
P		< 0.0001	0.0005	< 0.0001	< 0.0001	0.0421

Subsequently, the analysis of the t test was applied with the correction parameter of Welsh for non-paired data both for the different type of cancer (Table 6) and for the different treatment (Table 7).

Table 6 shows how both neuroticism and depressive symptoms prevail in the cervix cancer population. However, this same population tends to give importance to coping strategies centered on emotional and social aspects (Focusing Expression Emotions, Use Instrumental Social Support, Use Emotiol Social Support, Acceptance).

Table 6: Assotiation between gynecological cancer nd psychological dimensions about anxious-depressive symptoms. Means ± SD P = level of significance.

Gynecological Cancer	N	BDI	Neroticism	COPE 3 Focusing Expression Emotions	COPE 4 Use Instrumental Social Support	COPE 11 Use Emotiol Social Support	COPE 13 Acceptance
Cervix	11	16.00±2.576	25.50±2.283	12.80±0.593	12.40±0.949	12.00±0.873	13.80±0.282
Endometrium	19	3.40± 0.320	16.50±0.923	9.221±0.457	9.77± 0.560	9.11± 0.504	10.56±0.607
P		0.0007	0.0029	0.0001	0.0292	0.0112	< 0.0001

Table 7 shows that both depressive symptoms and negative emotional states (Tension-Anxiety, Fatigue-Inertia, Confusion-Bewilderment) prevail in the population subjected to chemo-radio treatment compared to the population subjected to pharmacological treatment.

Table 7: Assotiation between cancer treatment and psychological dimensions about anxious-depressive symptoms. Means ± SD P = level of significance.

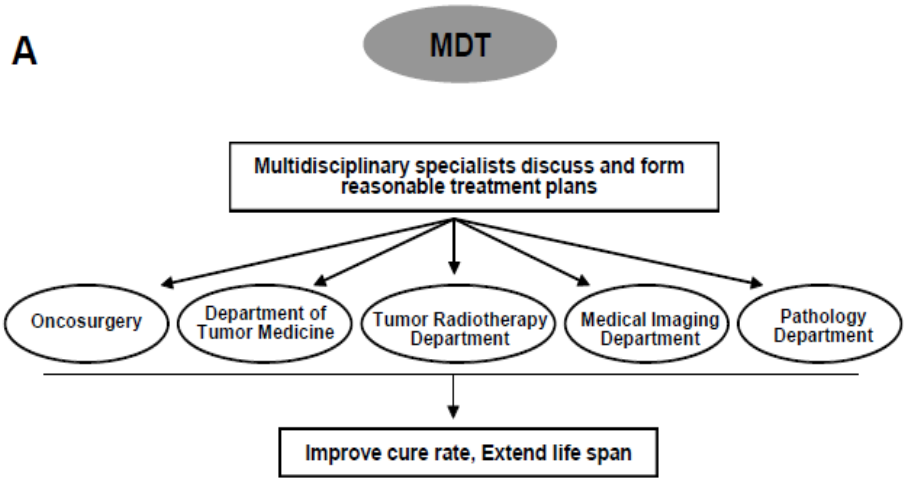
Cancer treatment	N	BDI	POMS Tension-Anxiety	POMS Fatigue-Inertia	POMS Confusion-Bewilderment
Pharmachological treatment	9	2.00±0.333	6.25 ± 0.977	4.75± 0.510	13.50±1.253
Radio - Chemio tretment	25	11.38±1.322	12.15±1.001	8.53±0.521	21.15±1.080
P		< 0.0001	0.0003	< 0.0001	0.0002

Capter 4

Discussion

The aim of the present study was that to examine in cancer patients the role of 5-HTTLPR in the mental adaptation to the disease, where diagnosis and treatment were considered to be the stressful life events requiring adequate coping by the patients.

The central findings of this exploratory cross-sectional study were that multidimensional factors, that is, biomedical (receiving radiotherapy), psychological (neuroticism, precancer intrusive recollections), and social characteristics, were associated with cancer-related intrusive recollections at the early survival stage (Fig.2). Having precancer intrusive recollections about prior trauma was a strong determinant of cancer-related intrusive recollections.



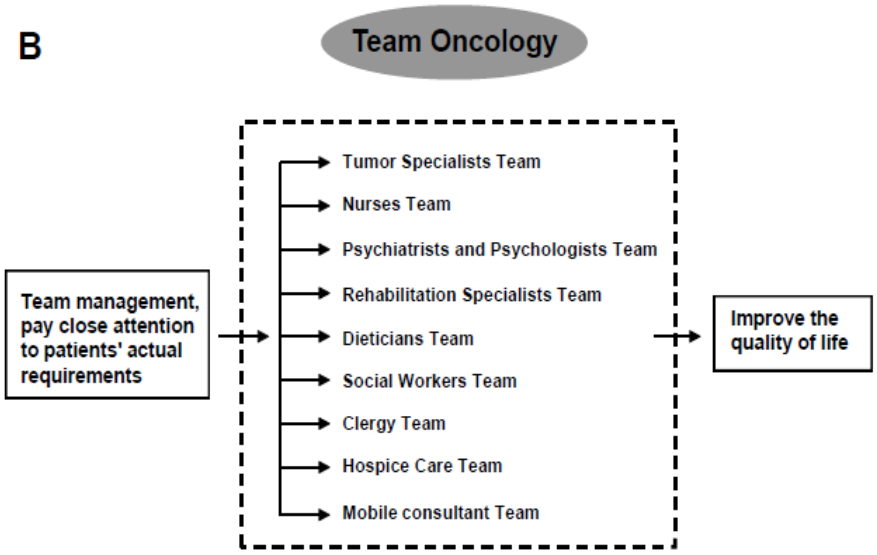


Fig. 2: The composition and purpose of MDT (A) and Team Oncology (B)

The prevalence of unmet needs found in our study is nearly two times as high as those in previous reports examining patients with advanced cancer (273, 274). A British study showed that the prevalence of unmet needs among 246 patients with mixed advanced incurable cancer assessed using the Need Assessment for Advanced Cancer Patients (NA-ACP) was 39–40% for unmet needs in the psychological or emotional domain and 31–35% for unmet needs in the medical communication and information domain (273). A larger number of unmet needs were observed in the present study, compared with previous studies. The findings may indicate that there are fewer social supports available for patients with advanced breast cancer in Japan (275). This is the rare study to examine the association between the unmet needs of patients with advanced cancer and psychological distress and/or QOL.

We found a significant correlation between unmet needs and psychological distress and/or QOL. However, our findings suggested that interventions based on unmet needs might reduce the distress of advanced cancer patients and enhance their QOL. Most treatment interventions have associated side effects. It is vitally important to document whether the interventions have an impact on QOL while attempting to palliate specific symptoms. Though external beam radiation therapy is a local treatment, studies including ours have shown it can improve patient QOL too.

The present study investigated the hypothesis that 5-HTTLPR modifies the association between cancer and depression, doubling the total number of cancer patients evaluated.

Although the use of postcancer personality measures may be problematic as a reliable representation of pretrauma personality, based upon this assumption, intrusive recollections could be expected in these cancer patients. The possibility that personality may be a risk factor for the development of malignant tumors has been suggested [276, 277, 278]. The results of recent prospective studies by Nakaya et al. suggest that psychological elements do not significantly influence the progression or mortality of cancer [279, 280]. Although personality is considered to have little influence on the development, progression, or mortality of malignant tumors, personality is strongly associated with the quality of life of patients [281]. Thus, it is very important for health professionals to assess the personalità of patients with malignant tumors. Because few studies have investigated the personality of patients with malignant tumors, the data from the present study are expected to be of value. With regard to the extroversion/introversion and neurotic tendencies of patients with malignant tumors, Kisen et al. [282] reported that male patients with lung cancer tended to be extroverted with a low neurotic tendency. Furthermore, Coppen et al. [283] found that patients with cancer were more extroverted and less neurotic than patients who did not have cancer.

Whereas neuroticism is likely to be an especially stable trait in individuals homozygous for the long allele, this may be less so the case for those carrying a short—and especially two short—alleles, given their apparent distinctive susceptibility to environmental influences.

Reporting bias could introduce error in the present results if personality was associated with decreased cancer risk but higher awareness of cancer, or vice versa (284, 285). Our findings are in agreement with previous studies reporting no associations between personality traits of extraversion and neuroticism with cancer. Our current study extends these studies by investigating all traits of the more comprehensive Five Factor Model of personality. With respect to the five personality traits, it is particularly notable that there was no association between conscientiousness and cancer risk. Low conscientiousness has been consistently associated with all-cause mortality [286], depression [287], and job-related stress [288] that have been robustly associated with various chronic diseases but not with cancer. Given the adverse psychological impact of cancer [286],

reverse causality should be considered carefully in studies of psychosocial risk factors and cancer [287].

Neuroticism was identified as a determinant of the intrusive recollections. Neuroticism may represent an alternative trajectory to the normal process of adaptation and recovery after traumatic events. Single-nucleotide polymorphism (SNP) refers to the variation between a single nucleotide base occurring on DNA sequences, in the population, the frequency of this mutation being at least 1%, otherwise it is considered to be a point mutation. Single-nucleotide polymorphisms are the most frequent type of variation in the human genome, and they provide powerful tools for a variety of medical genetic studies. Like many other studies we were not able to detect a direct association between the short allele of the 5-HTTLPR and neuroticism. As hypothesized, a significant interaction between the 5-HTTLPR and life events emerged in the prediction of neuroticism. Whereas neuroticism scores of individuals homozygous for the long allele proved unrelated to current life events, individuals with one or more short alleles scored higher or lower on the neuroticism scale depending on recent experiences; recall, though, that this association between life events and neuroticism only proved significant for those homozygous for the short allele. That is, such individuals manifested the highest neuroticism scores if they experienced many negative life events but also the lowest scores if exposed to many positive life events. Consequently, these results provide further empirical support for the reconceptualization of the short allele of the 5-HTTLPR as a marker of plasticity rather than just vulnerability to negative effects of adverse environments. However, the fact that neuroticism is heritable and has been found to predict exposure to adversity may also suggest an alternative interpretation of the interaction between the 5-HTTLPR and life events: Individuals scoring high on neuroticism and carrying short alleles may be more likely to encounter adverse experiences, as a function of neuroticism, and more likely to be negatively affected by such events, as a function of short alleles, compared to individuals with short alleles who score low in neuroticism and are therefore less prone to encounter adversity or any group with long alleles. With either explanation, however, the short allele of the 5-HTTLPR appears to be related to heightened susceptibility to environmental influences. It is the common understanding that personality traits tend to be stable in adulthood. However, some empirical work suggests that neuroticism can change over time and that there is considerable interindividual variation in neuroticism trajectories. The current analysis supports the notion that

personality traits may be less stable in some individuals compared to others—at least regarding neuroticism. For individuals carrying short alleles of the 5-HTTLPR neuroticism scores reflect, at least in part, the interaction between genetic susceptibility and environment, whereas the environment, at least as measured in this inquiry, seems to exert no apparent influence on the neuroticism scores of individuals homozygous for the long allele. This may pose a general but as of yet un-noted problem when evaluating the stability of neuroticism—and perhaps other personality traits, too. Indeed, the findings presented here lead to the prediction that neuroticism should be less stable in the case of more environmentally malleable individuals who carry short—and especially two short—alleles, yet highly stable in the case of those who carry only long alleles and appear impervious to at least some environmental effects.

Findings demonstrate that attitudes and perceptions of uncertainty, along with neuroticism, explained a noteworthy proportion of the variance in poor psychological adjustment in this sample of individuals with lung cancer. Specifically, perceived stress and emotional wellbeing were explained by both general intolerance of uncertainty and the perceived ambiguity of the cancer. Intolerance of uncertainty also predicted non-somatic depressive symptoms. Although an association between intolerance of uncertainty and illness-related ambiguity was found, perhaps because both ask participants to evaluate perceptions and thresholds of ambiguous or uncertain situations, they each contributed independently and similarly to explaining the variance in perceived stress and emotional well-being. One reason for our result may be that neuroticism was included in our models and was significantly associated with perceived stress. Removing neuroticism in the mediation models yielded a significant, positive relation between avoidance and perceived stress, as well as a significant indirect effect for avoidance.

Our findings may have therapeutic implications. Psychological adjustment may be influenced both by adopting alternative ways to process uncertainty cognitively and by addressing the factors that lead to perceived ambiguity. Applying cognitive skills and problem solving training and processing of traumatic material may improve adjustment. For example, promoting coping skills to manage the uncertainty about recurrence and metastatic disease has been demonstrated to be beneficial among long-term breast cancer survivors [288] and may be useful for survivors with lung cancer as well. A complementary approach is to address the specific characteristics of the cancer experience that induce the perception that the disease is ambiguous. For

example, future research to identify the extent to which adequate patient–clinician communication, awareness and attitudes about current symptoms, and religious/spiritual beliefs influence perceptions may be valuable. These areas of further study warrant empirical examination as they may have a clinically significant impact on psychological adjustment and quality of life. Our findings concur with this earlier research, and support a full discussion with women about the potential psychosocial benefits of surgery. To assist women in making surgical decisions about inherited risk management, the favorable effects of prophylactic gynecological surgery in terms of reducing worry and lowering perception of cancer risks will need to weighed against the increase in sexual and endocrine symptoms. Information about these potential risks could also be a part of patient-physician discussion. Finally, women's narratives highlighted the burden of ongoing screening and the lack of coordination amongst healthcare providers administering screening tests.

These results suggest that, for those caring for very ill people, an intervention which prompts them to reflect on their own needs may in fact draw attention to needs which had previously gone unattended. It is not clear whether this increased awareness constitutes harm or not. This intervention showed limited improvements for people with pre-existing anxiety and depression. There may be some benefit in administering it to people with pre-existing anxiety or depression. Further, it impacted positively on the physical wellbeing of non-anxious carers. Raising awareness of the impact of caring on the carers of very ill people may trigger extra help in a timely manner.

The implication of this study for clinical practice is that screening for prior trauma history, anxiety traits, and relevant family history would be helpful to address the high risk of developing intrusive recollections posttreatment. Indeed, it has been demonstrated that rapid screening for psychological problems with a self-report measure or checklist was useful to detect psychological distress in cancer patients [289, 290].

Result from the meta-analysis did not support a general association of 5-HTTLPR with depression after cancer. Even though colorectal cancer covers a wide spectrum of disease severities and treatment intensities, by using diagnosis of colorectal cancer as a stressor we made certain that all participants were exposed to stress that increases risk for depression [291, 292]. As colorectal cancer is depressionogenic we assume that such a diagnosis is distressing; however, we did not measure subjective perceptions of stress. As such, we were not able to capture wide individual differences in the perceived stress associated

with receiving a colorectal cancer diagnosis, and we necessarily assumed that the diagnosis was equally distressing to all individuals. This is a simplification as persons will react differently to being diagnosed with cancer, and colorectal cancer covers a wide spectrum of disease severities and treatment intensities. We were not able to determine the bi- and triallelic genotypes in all participants. However, the genotypes were in Hardy–Weinberg equilibrium, suggesting that unsuccessful genotyping was non-differential. The size of the study population was predefined and therefore power calculations had no purpose when planning our study. The present study is the seventh to investigate the hypothesis that 5-HTTLPR modifies the association between cancer and depression, doubling the total number of cancer patients evacuate [293, 294].

The finding that radiotherapy in the past acted as a protective factor against the intrusive recollections is intriguing. Patients may be confronted with realistically safe cancer experiences by frequent hospital visits related to radiotherapy, and it may offer patients an enhanced sense of control over an uncontrollable process as well as a perceived prevention of the threat to their lives. It is reported that affiliation among patients of similar emotional status has been found to reduce anxiety [295] and this may play a role in these patients spending time together while receiving their treatment. Only one of the previous studies about cancer patients was included in previous meta-analyses of the link between 5-HTTLPR, stress and depression [296]. The two studies that we were not able to include in meta-analysis comprise a total of 133 cancer patients, and both studies reported nonsignificantly higher risk of depression in cancer patients with a least one s allele [297, 298]. As meta-analysis is based on few studies consisting almost exclusively of breast and colorectal cancer patients, we advise that it is interpreted with caution. In addition, factors not accounted for, such as sex, age, ethnicity, timing of assessment of depression and type of depression measure, could affect the hypothesized association, in contrast to large meta-analyses that have provided substantial evidence of 5-HTTLPR being associated with vulnerability for depression after stressful life events. More studies based on larger populations as well as studies of patients with other types of cancer than colorectal and breast should be conducted before a definitive conclusion is warranted.

These results support the view that anxious preoccupation plays a significant role in patients with no advanced breast cancer during the early phase of the treatment of the disease. The data presently reported suggest that

the individual molecular-genetic information concerning 5-HTTLPR polymorphism can be usefully considered for identifying the patients at greater risk of anxious preoccupation, and may be considered for the choice of the agent in case of drug treatment on the basis of the pharmacogenetic evidence available.

In conclusion, the short allele of the 5-HTTLPR is associated with greater plasticity as evidenced by a higher susceptibility to both negative and positive effects of life events in the prediction of neuroticism. Whereas neuroticism is likely to be an especially stable trait in individuals homozygous for the long allele, this may be less so the case for those carrying a short—and especially two short—alleles, given their apparent distinctive susceptibility to environmental influences.

This study has several limitations. This study assessed psychological distress and quality of life findings through self-report questionnaires. With such a small sample size, the generalizability of these findings is limited. First, as our study used a cross-sectional design, we cannot be sure of the cause–effect relationship. Distress may create unmet needs, or unmet needs may generate distress; alternatively, a third factor may give rise to both unmet needs and distress. Second, the observed correlations among needs, distress and QOL may not be causal at all but simply represent conceptual overlaps among the respective measures. Third, because we invited outpatients to participate in the present study, most of the patients did not have any physical functioning impairments. Thus, our results do not reflect the unmet needs of advanced cancer patients with severe physical impairment. Finally, the sample size was not sufficiently large to use more rigorous statistical analyses such as multiple regression analysis, limiting the generalizability of these results to all advanced breast cancer patients. We used well-validated and reliable tools to assess psychological status and QOL, which should help to obtain generalizable results. We also selected the patients who have the same cancer type, similar physical status and advanced cancer to match QOL and needs, so we concentrated on a homogenous sample of patients. In addition, only a few patients refused to complete the questionnaires. The present study revealed close associations among the various domains of unmet needs, psychological distress and QOL among patients with advanced breast cancer but without several physical impairments.

Capter 5

5.1 Conclusions

In the "Biology-Psychology-Society Medical Model", with the scientific and technological progress and people's understanding of solid tumors, the malignant tumor treatment model has basically changed from single-subject treatment to multidisciplinary collaboration treatment which was led by a Multidisciplinary Team. On this basis, a more consummate malignant tumor treatment – Team Oncology Medicine has been set up, which pays close attention to patients' actual demand to improve the quality of life.

As cancer treatment becomes more scientifically sophisticated, the focus is increasingly on the treatments and less on the patient. If quality of life is an important goal of treatment, psychological symptoms should be recognized as sources of suffering that can be as debilitating as physical complaints. Discussion of mental health issues with a healthcare provider allows distress to be detected, and is the most important predictor of whether services will be received. More of these discussions need to occur in the oncology clinical care setting.

Depressive spectrum disorders in cancer patients should be taken into serious consideration since in patients with medical diseases, depression has the largest effect on worsening mean health scores and on increasing disability compared with the other chronic conditions [299]. However, the several clinical and phenomenological aspects of depressive disorders should be re-examined and recognized in terms of “spectrum” in order to screen the patients in a more specific way and to reach a more reliable diagnosis which makes referral and intervention more appropriate.

Recent consensus guidelines, algorithms, and reviews have been developed and proposed in the hope to promote integrated psychopharmacological and psychosocial treatment [300, 301] in order to reduce the burden of psychiatric morbidity on both the patient and the family.

Thus, it is mandatory that health care professionals working in oncology, such as oncologists, surgeons, radiation oncologists, primary care physicians, nurses, social workers, and psychologists, receive training in the diagnosis and management of depressive spectrum disorders, given the different intervention approaches according to the type of depressive disorder [302, 303].

The present study investigated the hypothesis that 5-HTTLPR modifies the association between cancer and depression, doubling the total number of cancer patients evacuate. All previous studies have been smaller (n=33–309), so much so that in some even large observed differences in depression between 5-HTTLPR genotype groups have not reached statistical significante [304, 305]. In conclusion, the short allele of the 5-HTTLPR is associated with greater plasticity as evidenced by a higher susceptibility to both negative and positive effects of life events in the prediction of neuroticism. Whereas neuroticism is likely to be an especially stable trait in individuals homozygous for the long allele, this may be less so the case for those carrying a short—and especially two short—alleles, given their apparent distinctive susceptibility to environmental influences.

5.2 Implications for research and practice

In addition to the formal analysis of this trial, the nature of carer needs and the way these needs change over time were explored.

Qualitative in depth interviews were also conducted to identify the impact in clinical practice. These will be reported in future publications.

This approach to the carers of people with serious illness should be tested in nonmalignant contexts. While a generic carer needs assessment tool is possible, there are also specific issues around specific conditions like dementia, which may require a specific approach.

While this intervention did not reduce the intensity or number of needs, there may be some benefit in administering it to people with pre-existing anxiety or depression. Further, it impacted positively on the physical wellbeing of non-anxious carers. Raising awareness of the impact of caring on the carers of very ill people may trigger extra help in a timely manner.

A complementary approach is to address the specific characteristics of the cancer experience that induce the perception that the disease is ambiguous. For example, future research to identify the extent to which adequate patient–clinician communication, awareness and attitudes about current symptoms, and religious/spiritual beliefs influence perceptions may be valuable. These areas of further study warrant empirical examination as they may have a clinically significant impact on psychological adjustment and quality of life. We hope study findings highlight useful areas for discussion in pre-operative settings and reveal some women’s desire for better follow-up support post-surgery.

The further research extended to include a larger cohort of patients, appears to be encouraged by the results reported and is currently being performer by the authors in the perspective of a further investigation of mental adaptation to cancer in relation to the genetic and cultural ethnic milieu of the patients, including the goal of a personalized and more effective intervention.

References

1. Hopwood P, Stephens RJ. Depression in patients with lung cancer: Prevalence and risk factors derived from quality-of-life data. J Clin Oncol 2000;18:893–903.

2. Delgado-Guay M, Parsons HA, Li Z et al. Symptom distress in advanced cancer patients with anxiety and depression in the palliative care setting. Support Care Cancer 2009;17:573–579.

3. Roth AJ, Massie MJ. Anxiety and its management in advanced cancer. Curr Opin Support Palliat Care 2007;1:50 –56.

4. Spencer R, Nilsson M, Wright A et al. Anxiety disorders in advanced cancer patients: Correlates and predictors of end-of-life outcomes. Cancer 2010;116:1810–1819.

5. Mack JW, Block SD, Nilsson M et al. Measuring therapeutic alliance between oncologists and patients with advanced cancer: The Human Connection Scale. Cancer 2009;115:3302–3311.

6. Jacobsen PB, Jim HS. Psychosocial interventions for anxiety and depression in adult cancer patients: Achievements and challenges. CA Cancer J Clin 2008; 58:214 –230.

7. Shennan C, Payne S, Fenlon D. What is the evidence for the use of mindfulness-based interventions in cancer care? A review. Psychooncology 2011;20:681–697.

8. Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: A meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry 2008;69:621– 632.

9. Barlow D. Anxiety and Its Disorders: The Nature and Treatment of Anxiety and Panic, 2nd ed. New York:Guilford Press, 2002.

10. Canada NClo: Canadian Cancer Statistics, C.N.D. Number, Editor. 2009.

11. Ovarian Cancer Canada: Ovarian Cancer Canada. 2012. [cited 2012 March]; Available from: http://www.ovariancanada.org/. Society AC; 2006. [updated 2006; cited]; Available from: http://www.cancer.org/.

12. Institute. NC: Epithelian Ovarian Cancer Treatment (PDQ). 2009. [cited 2009 Sept. 11]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/ovarianepithelial/healthprofessional Society CC: Treatment for Ovarian Cancer. 2009. [updated 2009 July 21, 2009; cited 2009 Sept. 11]; Available from: http://www.cancer.ca. Treatment and Recovery: Ovarian Cancer Canada. 2009. [updated 2009;cited 2009 Sept. 11]; Available from: www.ovariancanada.org/.

13. Bodurka-Bevers D, Basen-Engquist K, Carmack CL, Fitzgerald MA, Wolf JK, deMoor C, Gershenson DM: Depression, anxiety, and quality of life in patients with epithelial ovarian cancer. Gynecol Oncol 2000, 78(3 Pt 1):302–308.

14. Norton TR, Manne SL, Rubin S, Carlson J, Hernandez E, Edelson MI, Rosenblum N, Warshal D, Bergman C: Prevalence and predictors of psychological distress among women with ovarian cancer. J Clin Oncol 2004, 22(5):919–926.

15. Guglietti C, Rosen B, Murphy KJ, Laframboise S, Dodge J, Ferguson S, Katz J, Ritvo P: Prevalence and Predictors of PTSD in Women undergoing an Ovarian Cancer Investigation. Psychological Services 2010, 7(4):266–274.

16. Armstrong DK, Bundy B, Wenzel L, HJuang HQ, Baergen R, Lele S, Copeland LJ, Walker JL, Burger RA: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006, 354(1):34–43.

17. Hennessy BT, Coleman RL, Markman M: Ovarian cancer. Lancet 2009, 374(9698):1371–1382.

18. Donnelly CM, Lowe-Strong A, Rankin JP, Campbell A, Blaney JM, Gracey JH: A focus group study exploring gynecological cancer survivors' experiences and perceptions of participating in a RCT testing the efficacy of a home-based physical activity intervention. Support Care Cancer 2013. [cited 2013 March]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/23321934.

19. Stevinson C, Steed H, Faught W, Tonkin K, Vallance JK, Ladha AB, Schepansky A, Capstick V, Courneya KS: Physical activity preferences of ovarian cancer survivors. Psychooncology 2009, 18(4):422–428.

20. Coleman EA, Coon S, Hall-Barrow J, Richards K, Gaylor D, Stewart B: Feasibility of exercise during treatment for multiple myeloma. Cancer Nurs 2003, 26(5):410–419.

21. Korstjens I, May AM, van Weert E, Mesters I, Tan F, Ros WJ, Hoekstra-Weebers JE, van der Schans CP, van den Borne B: Quality of life after self-management cancer rehabilitation: a randomized controlled trial comparing physical and cognitive-behavioral training versus physical training. Psychosom Med 2008, 70(4):422–429.

22. Barnes EA, Bruera E: Fatigue in patients with advanced cancer: a review. Int J Gynecol Cancer 2002, 12(5):424–428.

23. Kornblith AB, Thaler HT, Wong G, Vlamis V, Lepore JM, Loseth DB, Hakes T, Hoskins WJ, Portenoy RK: Quality of life of women with ovarian cancer. Gynecol Oncol 1995, 59(2):231–242.

24. Pinto BM, Frierson GM, Rabin C, Trunzo JJ, Marcus BH: Home-based physical activity intervention for breast cancer patients. J Clin Oncol 2005, 23(15):3577–3587.

25. Mock V, Pickett M, Ropka ME, Muscari Lin E, Stewart KJ, Rhodes VA, McDaniel R, Grimm PM, Krumm S, McCorkle R: Fatigue and quality of life outcomes of exercise during cancer treatment. Cancer Pract 2001, 9(3):119–127.

26. McNeely ML, Frierson GM, Rabin C, Trunzo JJ, Marcus BH: Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. CMAJ 2006, 175(1):34–41.

27. Kim Y, Given BA. Quality of life of family caregivers of cancer survivors: across the trajectory of the illness. Cancer. 2008; 112:2556–2568. [PubMed: 18428199]

28. Swore Fletcher BA, Dodd MJ, Schumacher KL, Miaskowski C. Symptom experience of family caregivers of patients with cancer. Oncol Nurs Forum. 2008; 35:E23–44. [PubMed: 19405245]

29. Pawl JD, Lee SY, Clark PC, Sherwood PR. Sleep characteristics of family caregivers of individuals with a primary malignant brain tumor. Oncol Nurs Forum. 2013; 40:171–179. [PubMed: 23448742]

30. Milbury K, Badr H, Fossella F, Pisters KM, Carmack CL. Longitudinal associations between caregiver burden and patient and spouse distress in couples coping with lung cancer. Support Care Cancer. 2013

31. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology. 2001; 10:19–28. [PubMed: 11180574]

32. Bakas T, Lewis RR, Parsons JE. Caregiving tasks among family caregivers of patients with lung cancer. Oncol Nurs Forum. 2001; 28:847–854. [PubMed: 11421144]

33. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC: Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects. Psychological Bull 2008, 134(1):1.

34. Parker PA, Baile WF, Moor C, Cohen L: Psychosocial and demographic predictors of quality of life in a large sample of cancer patients. Psycho-Oncology 2002, 12(2):183–193.

35. Berglund A, Holmberg L, Tishelman C, Wagenius G, Eaker S, Lambe M: Social inequalities in non-small cell lung cancer management and survival: a population-based study in central Sweden. Thorax 2010, 65(4):327–333.

36. Pinquart M, Duberstein P: Depression and cancer mortality: a meta-analysis. Psychol Med 2010, 40(11):1797–1810.

37. Vodermaier A, Linden W, Siu C: Screening for emotional distress in cancer patients: a systematic review of assessment instruments. JNCI J Natl Cancer Inst 2009, 101(21):1464.

38. Murray E, Burns J, See TS, Lai R, Nazareth I: Interactive health communication applications for people with chronic disease. Cochrane Database Syst Rev 2005, 4:12–23.

39. Winzelberg AJ, Classen C, Alpers GW, Roberts H, Koopman C, Adams RE, Ernst H, Dev P, Taylor CB: Evaluation of an internet support group for women with primary breast cancer. Cancer 2003, 97(5):1164–1173.

40. Høybye M, Dalton SO, Deltour I, Bidstrup P, Frederiksen K, Johansen C: Effect of internet peer-support groups on psychosocial adjustment to cancer: a randomised study. Br J Cancer 2010, 102(9):1348–1354.

41. Spek V, Cuijpers P, Nyklícek I, Riper H, Keyzer J, Pop V: Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. Psychol Med 2007, 37(03):319–328.

42. Thalén-Lindström A, Larsson G, Glimelius G, Johansson B: Anxiety and depression in oncology patients; a longitudinal study of a screening, assessment and psychosocial support intervention. Acta Oncologica Jan 2013 2013, 52(1):118–127.

43. Bower P, Gilbody S: Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. Br J Psychiatry 2005, 186:11–17.

44. Fann J, Fan M, Unützer J: Improving primary care for older adults with cancer and depression. J Gen Internal Med 2009, 24:417–424.

45. van't Veer-Tazelaar PJ, van Marwijk HWJ, van Oppen P, van Hout HPJ, van der Horst HE, Cuijpers P, Smit F, Beekman ATF: Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. Archives Gen Psychiatry 2009, 66(3):297.

46. Myhr G, Payne K: Cost-effectiveness of cognitive-behavioural therapy for mental disorders: implications for public health care funding policy in Canada. Canadian J Psychiatry 2006, 51(10):662.

47. Sabariego C, Brach M, Herschbach P, Berg P, Stucki G: Cost-effectiveness of cognitive-behavioral group therapy for dysfunctional fear of progression in cancer patients. Eur J Health Econ 2011, 12(5):489–497.

48. Hewitt M, Greenfield S, Stovall E: From cancer patient to cancer survivor: lost in transition. Washington DC: Institute of Medicine (IOM); 2006.

49. Vickberg SMJ: The concerns about recurrence scale (CARS): A systematic measure of women's fears about the possibility of breast cancer recurrence. Ann Behav Med 2003, 25(1):16–24.

50. Armes J, Crowe M, Colbourne L, Morgan H, Murrells T, Oakley C, Palmer N, Ream E, Young A, Richardson A: Patients' supportive care needs beyond the end of cancer treatment: A prospective, longitudinal survey. J Clin Oncol 2009, 27(36):6172–6179.

51. Sanson-Fisher R, Girgis A, Boyes A, Bonevski B, Burton L, Cook P: The unmet supportive care needs of patients with cancer. Supportive Care Review Group. Cancer 2000, 88(1):226–237.

52. Humphris GM, Ozackinci G: The AFTER intervention: A structured psychological approach to reduce fears of recurrence in patients with head and neck cancer. Br J Health Psychol 2008, 13(2):223–230.

53. Easterling DV, Leventhal H: Contributions of concrete cognitionj to emotion: Neutral symptoms as elicitors of worry about cancer. J Appl Psychol 1989, 74(5):787–796.

54. Leventhal H, Nerenz DR, Steele DJ: Illness representations and coping with health threats. In Handbook of psychology and health: Social psychological apsects of health. Edited by Baum A, Taylor SE, Singer JE. Hillsdale: Lawrence Erlbaum Associates; 1984:219–252.

55. Herschbach P, Book K, Dinkel A, Berg P, Waadt S, Duran G, Engst-Hastreiter U, Henrich G: Evaluation of two group therapies to reduce fear of progression in cancer patients. Support Care Canc 2010, 18(4):471–479.

56. von Gruenigen VE, Huang HQ, Gil KM et al. Assessment of factors that contribute to decreased quality of life in Gynecologic Oncology Group ovarian cancer trials. Cancer 115(20), 4857–4864 (2009).

57. Wenzel L, Huang HQ, Monk BJ, Rose PG, Cella D. Quality-of-life comparisons in a randomized trial of interval secondary cytoreduction in advanced

ovarian carcinoma: a Gynecologic Oncology Group study. J. Clin. Oncol. 23(24), 5605–5612 (2005).

58. Wenzel LB, Huang HQ, Armstrong DK, Walker JL, Cella D. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. J. Clin. Oncol. 25(4), 437–443 (2007).

59. Eisenberg HS. A measurement of quality of survival of breast cancer patients. In: Clinical Evaluation in Breast Cancer Hayward JL, Bulbrook RD (Eds). Academic Press, London, UK (1966).

60. Feinstein AR. The epidemiology of cancer therapy: II. The clinical course: data, decisions, and temporal demarcations. Arch. Intern. Med. 123, 323–344 (1969).

61. Retan JW. Repeated dialysis of indigent patients for chronic renal failure. Ann. Intern. Med. 64(2), 284–292 (1966).

62. Priestman TJ, Baum M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. Lancet 1(7965), 899–900 (1976).

63. Johnson JR. Food and Drug Administration requirements for approval of new anticancer drugs. Cancer Treat. Reports 69, 1155–1157 (1985).

64. O'Shaughnessy JA, Wittes RE, Burke G et al. Commentary concerning demonstration of safety and efficacy of investigational anticancer agents in clinical trials. J. Clin. Oncol. 9(12), 2225–2232 (1991).

65. Aaronson NK, Ahmedzai S, Bergman B et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J. Natl Cancer Inst. 85(5), 365–376 (1993).

66. Cella DF, Tulsky DS, Gray G et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J. Clin. Oncol. 11(3), 570–579 (1993).

67. Cull A, Howat S, Greimel E et al. Development of a European Organization for Research and Treatment of Cancer questionnaire module to assess the quality of life of ovarian cancer patients in clinical trials: a progress report. Eur. J. Cancer 37(1), 47–53 (2001).

68. Greimel E, Bottomley A, Cull A et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur. J. Cancer 39(10), 1402–1408 (2003).

69. Basen-Engquist K, Bodurka-Bevers D, Fitzgerald MA et al. Reliability and validity of the functional assessment of cancer therapy-ovarian. J. Clin. Oncol. 19(6), 1809–1817 (2001).

70. Calhoun EA, Fishman DA, Lurain JR, Welshman EE, Bennett CL. A comparison of ovarian cancer treatments: analysis of utility assessments of ovarian cancer patients, at-risk population, general population, and physicians. Gynecol. Oncol. 93(1), 164–169 (2004).

71. Sun CC, Bodurka DC, Weaver CB et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. Support Care Cancer 13(4), 219–227 (2005).

72. Lakusta CM, Atkinson MJ, Robinson JW, Nation J, Taenzer PA, Campo MG. Quality of life in ovarian cancer patients receiving chemotherapy. Gynecol. Oncol. 81(3), 490–495 (2001).

73. Greimel ER, Bjelic-Radisic V, Pfisterer J, Hilpert F, Daghofer F, du Bois A. Randomized study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study group comparing quality of life in patients with ovarian cancer treated with cisplatin/ paclitaxel versus carboplatin/paclitaxel. J. Clin. Oncol. 24(4), 579–586 (2006).

74. Carmack Taylor CL, Basen-Engquist K, Shinn EH, Bodurka DC. Predictors of sexual functioning in ovarian cancer patients. J. Clin. Oncol. 22(5), 881–889 (2004).

75. Liavaag AH, Dorum A, Bjoro T et al. A controlled study of sexual activity and functioning in epithelial ovarian cancer survivors. A therapeutic approach. Gynecol. Oncol. 108(2), 348–354 (2008).

76. Ovesen L, Hannibal J, Mortensen EL. The interrelationship of weight loss, dietary intake, and quality of life in ambulatory patients with cancer of the lung, breast, and ovary. Nutr. Cancer 19(2), 159–167 (1993).

77. Payne SA. A study of quality of life in cancer patients receiving palliative chemotherapy. Soc. Sci. Med. 35(12), 1505–1509 (1992).

78. Ferris FD, Bruera E, Cherny N, et al. Palliative cancer care a decade later: accomplishments, the need, next steps —from the American Society of Clinical Oncology. J Clin Oncol 2009;27:3052-8.

79. Levy MH, Back A, Benedetti C, et al. NCCN clinical practice guidelines in oncology: palliative care. J Natl Compr Canc Netw 2009;7:436-73.

80. Follwell M, Burman D, Le LW, et al. Phase II study of an outpatient palliative care intervention in patients with metastatic cancer. J Clin Oncol 2009;27:206-13.

81. Jordhøy MS, Fayers P, Loge JH, Ahlner-Elmqvist M, Kaasa S. Quality of life in palliative cancer care: results from a cluster randomized trial. J Clin Oncol 2001; 19:3884-94.

82. Morita T, Akechi T, Ikenaga M, et al. Late referrals to specialized palliative care service in Japan. J Clin Oncol 2005;23:2637-44.

83. Zimmermann C, Riechelmann R, Krzyzanowska M, Rodin G, Tannock I. Effectiveness of specialized palliative care: a systematic review. JAMA 2008;299:1698-709.

84. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-49.

85. Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of life data. J Clin Oncol 2000;18:893-903.

86. Lutz S, Norrell R, Bertucio C, et al. Symptom frequency and severity in patients with metastatic or locally recurrent lung cancer: a prospective study using the Lung Cancer Symptom Scale in a community hospital. J Palliat Med 2001;4:157-65.

87. Grassi, L. (2013). Quam bene vivas referre: curing and caring in psychooncology. Psychooncology 22, 1679–1687.doi:10.1002/pon.3333

88. National Comprehensive Cancer Network (NCCN). (2003) .Distress management. Clinical practice guidelines. J. Natl. Compr. Cancer Netw. 1, 344–374.

89. Holland, J.C. (2013). Distress screening and the integration of psychosocial care into routine oncologic care. J. Natl.Compr.CancerNetw. 11(5 Suppl.),687–689.

90. Mitchell, A.J., and Bultz ,B.D. (2014). "Psychological assessment in psychopharma- cology," in Psychopharmacology in Oncology and Palliative Care, eds L.Grassi and M. Riba (Berlin:Springer), 49–68.doi:10.1007/978-3-642-40134-3_4

91. Mitchell, A.J., Meader, N., Davies, E., Clover, C., Crater, G., Loscalzo, M., et al. (2012). Meta-analysis of screening and case finding tools for depression in cancer: evidence based recommendations for clinical practice on be half of the DCC consensus group. J. Affect.Disord. 140, 149–160.doi:10.1016/j.jad.2011. 12.043

92. Zigmond, A.S., and Snaith, R.P.(1983). The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.doi:10.1111/j.1600-0447.1983.tb09716.x

93. Luckett, T., Butow, P.N., King, M.T., Oguchi, M., Heading, G., Hackl, N.A.,et al. (2010). A review and recommendations for optimal out come measures of anxiety, depression and general distress in studies evaluating psychosocial interventions for English-speaking adults with heterogeneous cancer diagnoses. Support. Care Cancer 18, 1241–1262.doi:10.1007/s00520-010-0932-8

94. Herschbach, P., Berg, P., Dankert, A., Duran, G., Engst-Hastreiter, U., Waadt, S., et al. (2005). Fear of progression in chronic diseases: psychometric properties of the fear of progression questionnaire. J. Psychosom. Res. 58, 505–511.doi: 10.1016/j.jpsychores.2005.02.007

95. Greer, S., Moorey, S.,and Watson, M. (1989). Patients' adjustment to cancer: the Mental Adjustment to Cancer (MAC) scale vs clinical ratings. J. Psychosom. Res. 33, 373–377.doi:10.1016/0022-3999(89)90027-5

96. Watson, M., and Homewood, J. (2008). Mental Adjustment to Cancer Scale: psychometric properties in a large cancer cohort. Psychooncology 17, 1146–1151.doi: 10.1002/pon.1345

97. Seeleman, C., Suurmond, J., and Stronks, K. (2009). Cultural competence: a conceptual frame work for teaching and learning. Med. Educ. 43, 229–237.doi: 10.1111/j.1365-2923.2008.03269.x

98. Surbone, A. (2004). Cultural competence: why? Ann. Oncol. 15, 697–699.doi: 10.1093/annonc/mdh194

99. Ashing-Giwa, K.T., Padilla, G., Tejero, J., Kraemer, J., Wright, K., Coscarelli, A.,et al. (2004). Understanding the breast cancer experience of women: a qualitative study of African American, Asian American, Latina and Caucasian cancer survivors. Psychooncology 6, 408–428.doi:10.1002/pon.750

100. Wang, J.H., Adams, I., Huang, E., Ashing-Giwa, K., Gomez, S.L., and Allen, L. (2012). Physical distress and cancer care experiences among Chinese-American and non-Hispanic White breast cancer survivors. Gynecol.Oncol. 124, 383–388. doi: 10.1016/j.ygyno.2011.11.029

101. Wise, T. (1986). “Clinical strategies for evaluating the medical patient,”in Clinical Psychopharmacology, ed.L.R. Derogatis (Menlo Park: Addison-Wesely Publishing Company),1–16.

102. Smith, F.A., Levenson, J.L., and Stern, T.A. (2011). “Psychiatric assessment and consultation,”in The American Psychiatric Publishing Text book of Psychosomatic Medicine Psychiatric Care of the Medically III, 2nd Edn (revised), ed. J.L. Levenson (Washington,DC: American Psychiatric Press), 3–17.

103. Servaes P, Verhagen C, Bleijenberg G: Fatigue in cancer patients during and after treatment: Prevalence, correlates and interventions. Eur J Cancer 38:27-43, 2002

104. Hjermstad SD, Fosså SD, Oldervoll L, et al: Fatigue in long-term Hodgkin’s Disease survivors: A follow-up study. J Clin Oncol 23:6587-6595, 2005

105. Young KE, White CA: The prevalence and moderators of fatigue in people who have been successfully treated for cancer. J Psychosom Res 60:29-38, 2006

106. Bower JE, Ganz PA, Dickerson SS, et al: Diurnal cortisol rhythm and fatigue in breast cancer survivors. Psychoneuroendocrinology 30:92-100, 2005

107. Bower JE, Ganz PA, Aziz N, et al: Fatigue and proinflammatory cytokine activity in breast cancer survivors. Psychosom Med 64:604-611, 2002

108. Bower JE, Ganz PA, Aziz N: Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue: Psychosom Med 67:277-280, 2005

109. Prue G, Rankin J, Allen J, et al: Cancer related fatigue: A critical appraisal. Eur J Cancer 42:846-863, 2006

110. Servaes P, Verhagen C, Bleijenberg G: Determinants of chronic fatigue in disease-free breast cancer patients, a cross-sectional study. Ann Oncol 13:589-598, 2002

111. Broeckel JA, Jacobsen PB, Horton J, et al: Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol 16:1689-1696, 1998

112. Servaes P, Verhagen S, Schreuder B, et al: Fatigue after treatment for malignant and benign bone and soft tissue tumors. J Pain Symptom Manage 26:1113-1122, 2003

113. Oldervoll LM, Kaasa S, Knobel H, et al: Exercise reduces fatigue in chronic fatigued Hodgkins disease survivors: Results from a pilot study. Eur J Cancer 39:57-63, 2003

114. Wilson RW, Jacobsen PB, Fields KK: Pilot study of a home-based aerobic exercise program for sedentary cancer survivors treated with hematopoietic stem cell transplantation. Bone Marrow Transplant 35:721-727, 2005

115. Courneya KS, Mackey JR, Bell GJ, et al: Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. J Clin Oncol 21:1660-1668, 2003

116. Schmitz KH, Holtzman J, Courneya KS, et al: Controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 14:1588-1595, 2005

117. Cordova MJ, Andrykowski MA, Kenady DE, McGrath PC, Sloan DA, Redd WH: Frequency and correlates of posttraumatic-stress disorder-like symptoms after treatment for breast cancer. J Consult Clin Psychol 1995; 63:981–986

118. Green BL, Krupnick JL, Rowland JH, Epstein SA, Stockton P, Spertus I, Stern N: Trauma history as a predictor of psychologic symptoms in women with breast cancer. J Clin Oncol 2000; 18:1084–1093

119. Andrykowski MA, Cordova MJ: Factors associated with PTSD symptoms following treatment for breast cancer: test of the Andersen model. J Trauma Stress 1998; 11:189–203

120. Bleiker EM, Pouwer F, van der Ploeg HM, Leer JW, Ader HJ: Psychological distress two years after diagnosis of breast cancer: frequency and prediction. Patient Educ Couns 2000; 40:209–217

121. Butler LD, Koopman C, Classen C, Spieger D: Traumatic stress, life events, and emotional support in women with metastatic breast cancer: cancer-related traumatic stress symptoms associated with past and current stressors. Health Psychol 1999; 18:555–560

122. U.S. Preventive Services Task Force. Screening for breast cancer. Available from: http://www.ahrq.gov/clinic/uspstf/uspsbrca.htm.

123. Sabatino SA, Habarta N, Baron RC, et al.; Task Force on Community Preventive Services. Interventions to increase recommendation and delivery of screening for breast, cervical, and colorectal cancers by healthcare providers systematic reviews of provider assessment and feedback and provider incentives. Am J Prev Med 2008;35 Suppl 1:S67–74.

124. Klein W, Stefanek M. Psychology of lay risk perception: lessons for cancer risk elicitation and communication. CA Cancer J Clin 2007;57:147–67.

125. Hay J, Coups E, Ford J. Predictors of perceived risk for colon cancer in a national probability sample in the United States. J Health Commun 2006;11 Suppl 1:S71–92.

126. Kim SE, Perez-Stable EJ, WongS, et al. Association between cancer risk perception and screening behavior among diverse women. Arch Intern Med 2008;168:728–34.

127. Institute of Medicine. From cancer patient to cancer survivor: lost in transition. Washington (DC): National Academies Press; 2005.

128. Blank T, Graves K, Supucha K, Llewellyn-Thomas H. Understanding treatment decision-making: contexts, commonalities, complexities, and challenges. Ann Behav Med 2006;32:211–7.

129. Nelson W, Stefanek M, Peters E, McCaul KD. Basic and applied decision makingin cancer control. Health Psychol 2005;24 Suppl:S3–8.

130. Gilovich T, Griffin D, Kahneman D. Introduction—heuristics and biases: then and now. In: Gilovich T, Kahneman D, editors. Heuristics and biases: the psychology of intuitive judgment. New York: Cambridge University Press; 2002. p. 1–18.

131. Loewenstein GF, Weber EU, Hsee CK, Welch N. Risk as feelings. Psychol Bull 2001;27:267–86.

132. O'Connor A, Fiset V, Degrasse C, et al. Decision aids for patients consideringoptions affectingcancer outcomes:evidence of efficacy and policy implications. J Natl Cancer Inst Monogr 1999;25:67–80.

133. Thornton LM, Carson WE III, Shapiro CL, Farrar WB, Anderson BL. Delayed emotional recovery after taxane based chemotherapy. Cancer 2008;113:638–47.

134. Levinson DF. The genetics of depression: a review. Biol Psychiatry 2006;60:84–92.

135. Amling CL, Riffenburgh RH, Sun L, et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. J Clin Oncol 2004;22:439–45.

136. ZhangS, Folsom AR, Sellers TA, Kushi LH, Potter JD. Better breast cancer survival for postmenopausal women who are less overweight and eat less fat. The Iowa Women's Health Study. Cancer 1995;76:275–83.

137. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2008; 17:379–86.

138. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. J Am Med Assoc 2007;298:754–64.

139. Saxe GA, Rock CL, Wicha MS, Schottenfeld D. Diet and risk for breast cancer recurrence and survival. Breast Cancer Res Treat 1999;53:241–53.

140. Aveyard P, Adab P, ChengKK, Wallace DMA, Hey K, Murphy MF. Does smokings tatus influence the prognosis of bladder cancer? A systematic review. BJU Int 2002;90:228–39.

141. Videtic GM, Stitt LW, Dar AR, et al. Continued cigarette smoking by patients receiving concurrent chemo-radiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. J Clin Oncol 2003;21:1544–9.

142. Lemieux J, Goodwin PJ, Pitchard KI, et al. Identification of cancer care and protocol characteristics associated with recruitment in breast cancer clinical trails. J Clin Oncol 2008;26:4458–65.

143. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruitingun derrepresented populations to cancer clinical trials: a systematic review. Cancer 2008;112:228–42.

144. NCI Centers of Excellence in Cancer Communication Research. Available from: http://dccps.nci.nih.gov/hcirb/ceccr/.

145. Gehricke JG, Loughlin SE, Whalen CK, et al. Smoking to self-medicate attentional and emotional dysfunctions. Nicotine Tob Res 2007;9 Suppl 4:S523–36.

146. Stefanek M, Derogatis LR, Shaw A. Psychological distress in an oncology outpatient population. Psychosomatics 1987;28:530–8.

147. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non small-cell lung cancer. N Engl J Med. 2010; 363:733–42. [PubMed: 20818875]

148. Spiegel D, Butler LD, Giese-Davis J, et al. Effects of supportive-expressive group therapy on survival of patients with metastatic breast cancer: a randomized prospective trial. Cancer. 2007; 110:1130–8. [PubMed: 17647221]

149. Peto R, Boreham J, Clarke M, et al. UK and USA breast cancer deaths down 25% in year 2000 at ages 20–69 years. Lancet. 2000; 355:1822. [PubMed: 10832853]

150. Andersen BL, Yang HC, Farrar WB, et al. Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. Cancer. 2008; 113:3450–8. [PubMed: 19016270]

151. Andersen BL, Thornton LM, Shapiro CL, et al. Biobehavioral, immune, and health benefits following recurrence for psychological intervention participants. Clin Cancer Res. 16:3270–8. [PubMed: 20530702]

152. Spiegel D, Bloom JR, Kraemer HC, et al. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. Lancet. 1989; 2:888–91. [PubMed: 2571815]

153. Fawzy F, Fawzy N, Hyun C, et al. Malignant Melanoma: Effects of an early structural psychiatric intervention, coping and affective state on recurrence and survival 6 years later. Arch Gen Psych. 1993; 50:681–689.

154. Richardson JL, Shelton DR, Krailo M, et al. The effect of compliance with treatment on serviva among patients with hematologic malignancies. J Clin Oncol. 1990; 8:356–64. [PubMed: 2299375]

155. McCorkle R, Strumpf NE, Nuamah IF, et al. A specialized home care intervention improbe survival among older post-surgical cancer patients. [see comments.]. Journal of the American Geriatrics Society. 2000; 48:1707–13. [PubMed: 11129765]

156. Linn MW, Linn BS, Harris R. Effects of counseling for late stage cancer. Cancer. 1982; 49:1048– 1055. [PubMed: 7059922]

157. Kissane DW, Grabsch B, Clarke DM, et al. Supportive-expressive group therapy for women with metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial. Psychooncology. 2007; 16:277–86. [PubMed: 17385190]

158. Cunningham AJ, Edmonds CVI, Jenkins GP, et al. A Randomized Controlled Trial of the Effects of Group Psychological Therapy on Survival in Women with Metastatic Breast Cancer. Psycho-Oncology. 1998; 7:508–517. [PubMed: 9885092]

159. Spiegel D. Effects of psychotherapy on cancer survival. Nat Rev Cancer. 2002; 2:383–9. [PubMed: 12044014]

160. Riley V. Mouse mammary tumors: alteration of incidence as apparent function of stress. Science. 1975; 189:465–7. [PubMed: 168638]

161. Riley V. Psychoneuroendocrine influences on immunocompetence and neoplasia. Science. 1981; 212:1100–9. [PubMed: 7233204]

162. Sapolsky RM, Donnelly TM. Vulnerability to stress-induced tumor growth increases with age in rats: role of glucocorticoids. Endocrinology. 1985; 117:662–6. [PubMed: 4017953]

163. Sapolsky RM, Krey LC, McEwen BS. The adrenocortical stress-response in the aged male rat: impairment of recovery from stress. Exp Gerontol. 1983; 18:55–64. [PubMed: 6683660]

164. Ben-Eliyahu S, Yirmiya R, Liebeskind JC, et al. Stress increases metastatic spread of a mammary tumor in rats: evidence for mediation by the immune system. Brain Behav Immun. 1991; 5:193–205. [PubMed: 1654166]

165. Spiegel D. Healing words: emotional expression and disease outcome [editorial; comment]. Jama. 1999; 281:1328–9. [PubMed: 10208150]

166. Abercrombie HC, Giese-Davis J, Sephton S, et al. Flattened cortisol rhythms in metastatic breast cancer patients. Psychoneuroendocrinology. 2004; 29:1082–92. [PubMed: 15219660]

167. Sephton SE, Sapolsky RM, Kraemer HC, et al. Diurnal cortisol rhythm as a predictor of breast cancer survival. Journal of the National Cancer Institute. 2000; 92:994–1000. [PubMed: 10861311]

168. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. Mol Cancer Res. 2006; 4:221–33. [PubMed: 16603636]

169. Raison CL, Borisov AS, Woolwine BJ, et al. Interferon-alpha effects on diurnal hypothalamicpituitary-adrenal axis activity: relationship with proinflammatory cytokines and behavior. Mol Psychiatry. 2008

170. Spiegel D, Giese-Davis J, Taylor CB, et al. Stress sensitivity in metastatic breast cancer: analysis of hypothalamic-pituitary-adrenal axis function. Psychoneuroendocrinology. 2006; 31:1231–44. [PubMed: 17081700]

171. Antonova L, Mueller CR. Hydrocortisone down-regulates the tumor suppressor gene BRCA1 in mammary cells: a possible molecular link between stress and breast cancer. Genes Chromosomes Cancer. 2008; 47:341–52. [PubMed: 18196591]

172. Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. Biol Psychiatry. 2003; 54:283–94. [PubMed: 12893104]

173. Sood AK, Lutgendorf SK. Stress influences on anoikis. Cancer prevention research. 2011; 4:481–5. [PubMed: 21464029]

174. Lutgendorf SK, DeGeest K, Dahmoush L, et al. Social isolation is associated with elevated tumor norepinephrine in ovarian carcinoma patients. Brain Behav Immun. 2011; 25:250–5. [PubMed: 20955777]

175. Barron TI, Connolly RM, Sharp L, et al. Beta blockers and breast cancer mortality: a population based study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011; 29:2635–44. [PubMed: 21632503]

176. Powe DG, Voss MJ, Zanker KS, et al. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget. 2010; 1:628–38. [PubMed: 21317458]

177. McGregor B, Antoni MH. Psychological intervention and health outcomes among women treated for breast cancer: a review of stress pathways and biological mediators. Brain Behav Immun. 2009; 23:159–66. [PubMed: 18778768]

178. Newell S, Sanson-Fisher R, Savolainen N. Systematic review of psychological therapies for cancer patients: Overview and recommendations for future research. J NCI. 2002; 94:558–84.

179. Spiegel D. Mind matters in cancer survival. JAMA. 2011; 305:502–503. [PubMed: 21285429]

180. Fawzy FI, Cousins N, Fawzy NW, Kemeny ME, Elashoff R, Morton D. A structured psychiatric intervention for cancer patients, I: changes over time in methods of coping and affective disturbance. Arch Gen Psychiatry. 1990; 47:720–725. [PubMed: 2378543]

181. Fawzy FI, Kemeny ME, Fawzy NW, Elashoff R, Morton D, Cousins N, Fahey JL. A structured psychiatric intervention for cancer patients, II: changes over time in immunological measures. Arch Gen Psychiatry. 1990; 47:729–735. [PubMed: 2143062]

182. Fawzy F, Canada A, Fawzy S. Malignant melanoma: Effects of a brief, structured psychiatric intervention on survival and recurrence at 10-year follow-up. Arch Gen Psychiatry. 2003; 60:100–103. [PubMed: 12511177]

183. Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhouser ML, Wener MH, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. J Clin Oncol. 2009; 27:3437–3444. [PubMed: 19470939]

184. Cole SW, Hawkley LC, Arevalo JM, Cacioppo JT. Transcript origin analysis identifies antigenpresenting cells as primary targets of socially regulated gene expression in leukocytes. Proc Natl Acad Sci U S A. 2011; 108:3080–3085. [PubMed: 21300872]

185. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009; 106:14716–14721. [PubMed: 19617551]

186. Lutgendorf SK, Degeest K, Sung CY, Arevalo JM, Penedo F, Lucci J 3rd, et al. Depression, social support, and beta-adrenergic transcription control in human ovarian cancer. Brain Behav Immun. 2009; 23:176–183. [PubMed: 18550328]

187. Phillips KM, Antoni MH, Lechner SC, Blomberg BB, Llabre M, Avisar E, Gluck S, Dehragopian R, Carver C. Stress management intervention reduces serum cortisol and increases relaxation during treatment for non-metastatic breast cancer. Psychosomatic Medicine. 2008; 70:1044–1049. [PubMed: 18842742]

188. Stark J, Avitsur R, Padgett DA, Sheridan JF. Social stress induces glucocorticoid resistance in macrophages. American J Physiol Reg Int Comp Physiol. 2001; 280:R1799–R1805.

189. Benish M, Ben-Eliyahu S. Surgery as a double-edged sword: A clinically feasible approach to overcome the metastasis-promoting effects of surgery by blunting stress and prostaglandin responses. Cancers. 2010; 2:1929–1951.

190. Cohen L, Parker O, Vence L, Savary C, Kentor D, Pettaway C, Babaian R, Pisters L, Miles B, Wei Q, Wiltz L, Patel T, Radvanyi L. Presurgical stress management improves postoperative immune function in men with prostate cancer

undergoing radical prostatectomy. Psychosomatic Medicine. 2011; 73 :218–225. [PubMed: 21257977]

191. Kuchler T, Bestmann B, Rappat S, et al. Impact of psychotherapeutic support for patients with gastrointestinal cancer undergoing surgery: 10-year survival results of a randomized trial. J Clin Oncol. 2007; 25:2702–2708. [PubMed: 17602075]

192. Nelson E, Wenzel L, Osann K, Dogan-Ates A, Chatana N, Reina-Patton A, Laust A, Nashimoto K, Chicz-DeMet A, DuPont N, Monk B. Stress, immunity and cervical cancer: biobehavioral outcomes of a randomized clinical trial. Clinical Cancer Research. 2008; 14(27):2111–2118. [PubMed: 18381952]

193. Patnaik JL, Byers T, DiGuiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J NCI. 2011; 103:1101–1111.

194. Pall SK, Hurria A. Impact of age, sex, and comorbidity on cancer therapy and disease progression. J Clinical Oncology. 2010; 28:4086–4093.

195. Sestak I, Distler W, Forbes JF, et al. Effect of body mass index on recurrences in tamoxifen and anastrozole treated women: An exploratory analysis from the ATAC trial. J Clin Oncol. 2010; 28:3411–3415. [PubMed: 20547990]

196. Dowling R, Goodwin P, Stambolic V. Understanding the benefit of metformin use in cancer treatment. PMC Medicine. 2011; 9:33.

197. Chrousos G. The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. Int J Obesity and Related Metabolic Disorder. 2000; 24:S550–555.

198. Vitaliano P, Scanlon J, Zhang J, Savage M, Hirsch I, Siegler I. A path model of chronic stress, the metabolic syndrome, and coronary heart disease. Psychosomatic Med. 2002; 64:418–435.

199. Schneiderman, N.; Antoni, MH.; Penedo, F.; Ironson, G. Psychosocial and Behavioral Interventions in the Treatment of Physical Illnesses and Disease Processes. In: Steptoe, A., editor. Handbook of Behavioral Medicine: Methods and Applications. N.Y: Springer; 2010. p. 989-1007.

200. Bovjberg D. Psychoneuroimmunology: Implications for oncology? Cancer. 1991; 67:828–832. [PubMed: 1986853]

201. van der Pompe G, Antoni MH, Heijen C. The effects of surgical stress and psychological stress on the immune function of operative cancer patients. Psychology and Health. 1998; 13:1015–1026.

202. Øvretveit J. Five ways to describe a multidisciplinary team. J Interprof Care. 1996; 10:163-171.

203. Specht J, Gralow JR. Neoadjuvant chemotherapy for locally advanced breast cancer. Semin Radiat Oncol. 2009; 19:222-228.

204. Serke M, Kollmeier J. Multimodal therapy of small cell and non-small cell lung carcinoma. Dtsch Med Wochenschr. 2007; 132:1221-1224.

205. Ang KK. Multidisciplinary management of locally advanced SCCHN: Optimizing treatment outcomes. Oncologist. 2008; 13:899-910.

206. Richards MA. The size of the prize for earlier diagnosis of cancer in England. Br J Cancer. 2009; 101:S125-S129.

207. Morris EJ, Maughan NJ, Forman D, Quirke P. Identifying stage III colorectal cancer patients: The influence of thepatient, surgeon, and pathologist. J Clin Oncol. 2007; 25:2573-2579.

208. Horwitz W, Kazak AE. Family adaptation to childhood cancer: Sibling and family system variables. Journal of Clinical Child Psychology 1989;19:221–228.

209. Cohen DS, Friedrich WN, Jaworski TM, Copeland D, Pendergrass T. Pediatric cancer: Predicting sibling adjustment. Journal of Clinical Psychology 1994;50:303–319. [PubMed: 8071436]

210. Kiser LJ, Black MM. Family processes in the midst of urban poverty: What does the trauma literature tell us? Aggression and Violent Behavior 2005;10:715–750.

211. Kelly KM. Complementary and alternative medical therapies for children with cancer. Eur J Cancer. 2004;40:2041-2046.

212. Hamidah A, Rustam ZA, Tamil AM, Zarina LA, Zulkifli ZS, Jamal R. Prevalence and parental perceptions of complementary and alternative medicine use by children with cancer in a multi-ethnic Southeast Asian population. Pediatr Blood Cancer. 2009;52:70-74.

213. Hord, JD, Rehman W, Hannon P, Anderson-Shaw L, Schmidt ML. Do parents have the right to refuse standard treatment for their child with favorableprognosis cancer? Ethical and legal concerns. J Clin Oncol. 2006;24:5454-5456.

214. Ladas EJ, Post-White J, Hawks R, Taromina K. Evidence for symptom management in the child with cancer. J Pediatr Hematol Oncol. 2006;28:601-615.

215. Myers C, Stuber ML, Bonamer-Rheingans JI, Zeltzer LK. Complementary therapies and childhood cancer. Cancer Control. 2005;12:172-180.

216. Savard J, Savard MH. Insomnia and cancer: prevalence, nature, and non-pharmacological treatment strategies. Sleep Med Clin. 2013;8: 373–387.

217. Savard J, Liu L, Natarajan L, et al. Breast cancer patients have progressively impaired sleep-wake activity rhythms during chemotherapy. Sleep. 2009;32(9):1155–1160.

218. Ancoli-Israel S, Liu L, Marler MR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. Support Care Cancer. 2006;14(3):201–209.

219. Savard MH, Savard J, Caplette-Gingras A, Ivers H, Bastien C. Relationship between objectively recorded hot flashes and sleep disturbances among breast cancer patients: investigating hot flash characteristics other than frequency. Menopause. 2013;20(10): 997–1005.

220. Beck SL, Berger AM, Barsevick AM, Wong B, Stewart KA, Dudley WN. Sleep quality after initial chemotherapy for breast cancer. Support Care Cancer. 2010;18(6):679–689.

221. Mormont MC, Waterhouse J, Bleuzen P, et al. Marked 24-h rest/activity rhythms are associated with better quality of life, better response, and longer survival in patients with metastatic colorectal cancer and good performance status. Clin Cancer Res. 2000;6(8):3038–3045.

222. Block, K.I., Gyllenhaal, C., & Mead, M.N. (2004). Safety and efficacy of herbal sedatives in cancer care. Integrative Cancer Therapies, 3, 128–148.

223. Ingersoll, G. (2000). Evidence-based nursing: What it is and what it isn't. Nursing Outlook, 48, 151–152.

224. Davidson, J.R., MacLean, A.W., Brundage, M.D., & Schulze, K. (2002). Sleep disturbance in cancer patients. Social Science and Medicine, 54, 1309–1321.

225. Engstrom, C.A., Strohl, R.A., Rose, L., Lewandowski, L., & Stefanek, M.E. (1999). Sleep alterations in cancer patients. Cancer Nursing, 22, 143–148.

226. Koopman, C., Nouriani, B., Erickson, V., Anupindi, R., Butler, L.D., Bachmann, M.H., et al. (2002). Sleep disturbances in women with metastatic breast cancer. Breast Journal, 8, 362–370.

227. Lieben CK, Blokland A, Westerink B, Deutz NE. Acute tryptophan and serotonin depletion usingan optimized tryptophan-free protein-carbohydrate mixture in the adult rat. Neurochemistry International 2004; 44:9–16. PMID: 12963083

228. Leonardo ED, Hen R. Genetics of affective and anxiety disorders. Annual Review of Psychology 2006; 57: 117–137. PMID: 16318591

229. Lesch KP, Balling U, Gross J, Strauss K, Wolozin BL, Murphy DL, et al. Organization of the human serotonin transporter gene. J Neural Transm Gen Sect 1994; 95: 157–62. PMID: 7865169

230. Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTPLR) and anxiety-related personality traits. Am J Med Genet B Neuropsychiatr Genet. 2004; 127:85–89.

231. Mossner R, Henneberg A, Schmitt A, Syagailo YV, Grassle M, Hennig T, et al. Allelic variation of serotonin transporter expression is associated with depression in Parkinson's disease. Mol Psychiatry 2001; 6: 350–352. PMID: 11326308

232.. Hauser J, Leszczynska A, Samochowiec J, Czerski PM, Ostapowicz A, Chlopocka M, et al. Association analysis of the insertion/deletion polymorphism in serotonin transporter gene in patients with affective disorder. Eur Psychiatry 2003; 18: 129–132. PMID: 12763299

233. Oo KZ, Aung YK, Jenkins MA, Win AK. Associations of 5HTTLPR polymorphism with major depressive disorder and alcohol dependence: A systematic review and meta-analysis. Aust N Z J Psychiatry 2016; pii: 0004867416637920.

234. Clarke H, Flint J, Attwood AS, Munafo MR. Association of the 5-HTTLPR genotype and unipolar depression: a meta-analysis. Psychol Med 2010; 12: 1–12.

235. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science 2003; 301: 386–389. PMID: 12869766

236. Gotlib IH, Joormann J, Minor KL, Hallmayer J. HPA Axis Reactivity: A Mechanism Underlying the Associations Among 5-HTTLPR, Stress, and Depression. Biol Psychiaty 2008; 63: 847–851.

237. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression. Arch Gen Psychiatry 2005; 62: 529–535. PMID: 15867106

238. Bartolomucci A, Carola V, Pascucci T, Puglisi-Allegra S, Cabib S, Lesch KP, et al. Increased vulnerabilità to psychosocial stress in heterozygous serotonin transporter knockout mice. Disease Models & Mechanisms 2010; 3: 459–470.

239. Lahey BB. Public Health Significance of Neuroticism. Am Psychol 2009; 64: 241–256. doi: 10.1037/a0015309 PMID: 19449983

240. Munafò MR, Clark TG, Roberts KH, Johnstone EC. Neuroticism Mediates the Association of the Serotonin Transporter Gene with Lifetime Major Depression. Neuropsychobiology 2006; 53: 1–8. PMID: 16319503

241. Bär KJ, Markser VZ. Sport specificity of mental disorders: the issue of sport psychiatry. Eur Arch Psychiatry Clin Neurosci. 2013; 263: 205–10.

242. Ormel J, Oldehinkel AJ, Nolen WA, Vollebergh W. Psychosocial disability before, during, and after a major depressive episode. Arch Gen Psychiatry 2004; 61: 387–392. PMID: 15066897

243. Brummett BH, Boyle SH, Siegker IC, Kuhn CM, Ashley-Koch A, Jonassaint CR, et al. Effects of Environmental Stress and Gender on Associations among Symptoms of Depression and the Serotonin Transporter Gene Linked Polymorphic Region (5-HTTLPR). Behav Genet. 2008; 38:34–43. PMID: 17955359

244. Ming Q, Zhang Y, Chai Q, Chen H, Hou CJ, Wang MC, et al. Interaction between a serotonin transporter gene promoter region polymorphism and stress predicts depressive symptoms in Chinese adolescents: a multi-wave longitudinal study. BMC Psychiatry 2013, 13:142 doi: 10.1186/1471-244X-13-142 PMID: 23683292

245. Dalton SO, Laursen TM, Ross L, Mortensen PB, Johansen C. Risk for hospitalization with depression after a cancer diagnosis: a nationwide, population-based study of cancer patients in Denmark from 1973 to 2003. J Clin Oncol 2009; 27: 1440–1445.

246. Quach C, Sanoff HK, Williams GR, Lyons JC, Reeve BB. Impact of colorectal cancer diagnosis and treatment on health-related quality of life among older Americans: a population-based, case-control study. Cancer 2015; 121: 943–950.

247. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, Lesch KP. Allelic variation of human serotonin transporter gene expression. J Neurochem 2002; 66: 2621-4.

248. Mortensen OV, Thomassen M, Larsen MB, Whittemore SR, Wiborg O. Functional analysis of a novel human serotonin transporter gene promoter in immortalized raphe cells. Brain Res Mol Brain Res 1999; 68: 141-8.

249. Borman RA, Burleigh DE. Evidence for the involvement of a 5-HT4 receptor in the secretory response of human small intestine to 5-HT. Br J Pharmacol 2012; 110: 927-8.

250. Turvill JL, Connor P, Farthing MJ. The inhibition of cholera toxin-induced 5-HT release by the 5-HT3 receptor antagonist, granisetron, in the rat. Br J Pharmacol 2009; 130: 1031-6.

251. Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Gastroenterology 2001; 121: 799-804.

252. Morris-Yates A, Talley NJ, Boyce PM, Nandurkar S, Andrews G. Evidence of a genetic contribution to functional bowel disorder. Am J Gastroenterol 1998; 93: 1311-7.

253. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. SCID- I: Structured Clinical Interview for DSM-IV Axis I Disorders. 2000; Giunti OS.

254. First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS. SCID- II: Structured Clinical Interview for DSM-IV Axis II Disorders. 2003; Giunti OS.

255. Costa PT Jr, McCrae RR. The NEO-PIINEO-FFl manual supplement. 1989; Odessa. FL: Psychological Assessment Resources.

256. Pulver A. Allik J, Pulkkinen L, Hamalainen M. A Big Five personality inventory in two non-Indo European languages. European Journal of Personality 1995; 9: 109–124.

257. Rolland JP, Parker WD, Stumpf H. A psychometric examination of the French translations of the NEOPI-R and NEO- FFI. Journal of Personality Assessment 1998; 7: 269–291.

258. Spirrison CL, Choi S. Psychometric properties of a Korean version of the revised NEO-Personality Inventory. Psychological Reports 1998; 83: 263–274.

259. Piedmont RL, McCrae RR, Costa PT. Adjective check list scales and the five factor model. Journal of Personality and Social Psychology 1991; 60: 630–637.

260. McNair DM, Lorr M, Droppleman LF. Manual for profile of Mood States. 1971; San Diego, CA: Educational and Industrial Testing Services.

261. C. Robert Cloninger CR (1994). The temperament and character inventory (TCI): A guide to its development and use. St. Louis, MO: Center for Psychobiology of Personality, Washington University. ISBN 0-9642917-1-1.

262. Zuckerman M and Cloninger CR (August 1996). "Relationships between Cloninger's, Zuckerman's, and Eysenck's dimensions of personality". Personality and Individual Differences. 21 (2): 283–285. doi:10.1016/0191-8869(96)00042-6.

263. De Fruyt, F.; Van De Wiele, L.; Van Heeringen, C. (2000). "Cloninger's Psychobiological Model of Temperament and Character and the Five-Factor Model of Personality". Personality and Individual Differences. 29 (3): 441–452. doi:10.1016/S0191-8869(99)00204-4.

264. Cloninger, C.R.; Svrakic, DM; Przybeck, TR (December 1993). "A psychobiological model of temperament and character". Archives of General Psychiatry. 50 (12):97590. doi:10.1001/archpsyc.1993.01820240059008. PMID 8250684.

265. Spielberger, C. D., Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. (1983). Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press.

266. Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. J Pers Soc Psychol. 1989;56:267-83.

267. Cohen, S. and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) The Social Psychology of Health. Newbury Park, CA: Sage, 1988.

268. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC, Kaasa S, Klee M, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw K, Sullivan M, Takeda F, for the European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for Use in international clinical trials in oncology. JNCI 1993, 85: 365–376. 10.1093/jnci/85.5.365

269. Miller SA, Dykes DD, Polesky HF. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res. 1988; 16:1215. PMID: 3344216

270. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D, et al. Allelic variation of human serotonin transporter gene expression. Neurochem 1996; 66: 2621–2624.

271. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. Journal of Personality and Social Psychology 1986; 51: 1173–1182. PMID: 3806354

272. Frazier PA, Barron KE, Tix AP. Testing moderator and mediator effects in counseling psychology research. Journal of Counseling Psychology. 2004 51: 115–134.

273. Rainbird K, Perkins J, Sanson-Fisher R, Rolfe I, Anseline P. The needs of patients with advanced, incurable cancer. Br J Cancer 2009;101:759–64.

274. Aranda S, Schofield P, Weih L, Yates P, Milne D, Faulkner R, et al. Mapping the quality of life and unmet needs of urban women with metastatic breast cancer. Eur J Cancer Care (Engl). 2005;14:211–22.

275. Shim EJ, Mehnert A, Koyama A, Cho SJ, Inui H, Paik NS, et al. Health-related quality of life in breast cancer: a cross-cultural survey of German, Japanese, and South Korean patients. Breast Cancer Res Treat 2006;99:341–50.

276. Eysenck HJ: The respective importance of personality, cigarette-smoking and interaction effects for the genesis of cancer and coronary heart disease. Pers Individ Dif 1988, 9:453–464.

277. Chida Y, Hamer M, Wardle J, Steptoe A: Do stress-related psychosocial factors contributeto cancer incidence and survival? Nat Clin Pract Oncol 2008, 5:466–475.

278. Temoshok L, Heller B, Sagebiel RW, Blois MS, Sweet DM, DiClemente RJ, Gold ML: The relationship of psychosocial factors to prognostic indicators in cutaneous malignant melanoma. J Psychosom Res 1985,29:139–153.

279. Nakaya N, Tsubono Y, Nishino Y, Hosokawa T, Fukudo S, Shibuya D, Akizuki N, Yoshikawa E, Kobayakawa M, Fujimori M, Saiti-Nakaya K, Uchitomi Y, Tsuji I: Personality and cancer survival: the Miyagi cohort study. Br J Cancer 2005, 92:2089–2094.

280. Nakaya N, Bidstrup PE, Saito-Nakaya K, Frederiksen K, Koskenvuo M, Pukkala E, Kaprio J, Floderus B, Uchitomi Y, Johansen C: Personality traits and cancer risk and survival based on Finnish and Swedish registry data. Am J Epidemiol 2010, 172:377–385.

281. Yamaoka K, Shigehisa T, Ogoshi K, Haruyama K, Watanabe M, Hayashi F, Hayashi C: Health-related quality of life varies with personality types: a comparison among cancer patients, non-cancer patients and healthy individuals in a Japanese population. Qual Life Res 1998, 7:535–544.

282. Kissen DM, Eysenck HJ: Personality in male lung cancer patients. J Psychosom Res 1962, 6:123–127.

283. Coppen A, Metacalfe M: Cancer and extraversion. BMJ 1963, 2:18–19.

284. Nakaya N, Bidstrup PE, Saito-Nakaya K, Frederiksen K, Koskenvuo M, Pukkala E, Kaprio J, Floderus B, Uchitomi Y, Johansen C (2010) Personality traits and cancer risk and survival based on Finnish and Swedish registry data. Am J Epidemiol 172: 377–385.

285. Ranchor AV, Sanderman R, Coyne JC (2010) Invited commentary: personality as a causal factor in cancer risk and mortality–time to retire a hypothesis? Am J Epidemiol 172: 386–388.

286. Jokela M, Batty GD, Nyberg ST, Virtanen M, Nabi H, Singh-Manoux A, Kivima¨ki M (2013a) Personality and all-cause mortality: individualparticipant meta-analysis of 3947 deaths in 76 150 adults. Am J Epidemiol 178: 667–675.

287. Lemogne C, Consoli SM, Geoffroy-Perez B, Coeuret-Pellicer M, Nabi H, Melchior M, Limosin F, Zins M, Ducimetiere P, Goldberg M, Cordier S (2013) Personality and the risk of cancer: a 16-year follow-up study of the GAZEL cohort. Psychosom Med 75: 262–271.

288. Mishel MH, Germino BB, Gil KM, et al. Benefits from an uncertainty management intervention for African–American and Caucasian older long-term breast cancer survivors. Psycho-Oncology. 2005; 14:962–978. [PubMed: 15712339]

289. Heikkila¨ K, Nyberg ST, Theorell T, Fransson EI, Alfredsson L, Bjorner JB, Bonenfant S, Borritz M, Bouillon K, Burr H, Dragano N, Geuskens GA, Goldberg M, Hamer M, Hooftman WE, Houtman IL, Joensuu M, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Madsen IE, Magnusson Hanson LL, Marmot MG, Nielsen ML, Nordin M, Oksanen T, Pentti J, Salo P, Rugulies R, Steptoe A, Suominen S, Vahtera J, Virtanen M, Va¨a¨na¨nen A, Westerholm P, Westerlund H, Zins M, Ferrie JE, Singh-Manoux A, Batty GD, Kivima¨ki M. IPD-Work Consortium (2013) Work stress and risk of cancer: meta-analysis of 5700 incident cancer events in 116 000 European men and women. BMJ 346: f165.

290. Ganz PA, Hirji K, Sim MS, Schag CA, Fred C, Polinsky ML: Predicting psychosocial risk in patients with breast cancer. Med Care 1993; 31:419–431

291. Roth AJ, Kornblith AB, Batel-Copel L, Peabody E, Scher HI, Holland JC: Rapid screening for psychologic distress in men with prostate carcinoma: a pilot study. Cancer 1998; 82:1904–1908

292. Reich M (2008) Depression and cancer: recent data on clinical issues, research challenges and treatment approaches. Curr Opin Oncol 20: 353–359.

293. Dalton SO, Laursen TM, Ross L, Mortensen PB, Johansen C. Risk for hospitalization with depression after a cancer diagnosis: a nationwide, population-based study of cancer patients in Denmark from 1973 to 2003. J Clin Oncol 2009; 27: 1440–1445.

294. Dunn J, Ng SK, Holland J, Aitken J, Youl P, Baade PD et al. Trajectories of psychological distress after colorectal cancer. Psychooncology 2013; 22: 1759–1765.

295. Grassi L, Rossi E, Cobianchi M, Aguiari L, Capozzo M, Martinis E et al. Depression and serotonin transporter (5-HTTLPR) polymorphism in breast cancer patients. J Affect Disord 2010; 124: 346–350.

296. Kim JM, Kim SW, Stewart R, Kim SY, Shin IS, Park MH et al. Serotonergic and BDNF genes associated with depression 1 week and 1 year after mastectomy for breast cancer. Psychosom Med 2012; 74: 8–15.

297. Kulik JA, Moore PJ, Mahler HI: Stress and affiliation: hospital roommate effects on preoperative anxiety and social interaction. Health Psychol 1993; 12:118–124

298. Heils A, Teufel A, Petri S, Stober G, Riederer P, Bengel D et al. Allelic variation of human serotonin transporter gene expression. J Neurochem 1996; 66: 2621–2624.

299. Schillani G, Era D, Cristante T, Mustacchi G, Richiardi M, Grassi L et al. 5-HTTLPR polymorphism and anxious preoccupation in early breast cancer patients. Radiol Oncol 2012; 46: 321–327.

300. Romanowicz M. Testing a diathesis-stress model: potential genetic risk factors for development of distress in context of acute leukemia diagnosis and transplant. Psychosomatics 2012; 53: 456–462.

301. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007 Sep 8;370(9590):851–8.

302. Howell D, Keshavarz H, Esplen MJ, Hack T, Hamel M, Howes J, et al. on behalf of the Cancer Journey Advisory Group of the Canadian Partnership Against Cancer. A Pan Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with Cancer, Toronto: Canadian Partnership Against Cancer (Cancer Journey Advisory Group) and the Canadian Association of Psychosocial Oncology, July 2015.

303. Andersen BL, DeRubeis RJ, Berman BS, Gruman J, Champion VL, Massie MJ, et al. American Society of Clinical Oncology.: screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. J Clin Oncol. 2014;32(15): 1605–19.

304. Rubin G, Berendsen A, Crawford SM, Dommett R, Earle C, Emery J, et al. The expanding role of primary care in cancer control. Lancet Oncol. 2015;16:1231–72.

305. Wein S, Sulkes A, Stemmer S. The oncologist's role inmanaging depression, anxiety, and demoralization with advanced cancer. Cancer J. 2010;16:493–9.