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UNIVERSITY OF SAN DIEGO
Hahn School of Nursing and Health Science
DOCTOR OF PHILOSOPHY IN NURSING

GENDER DIFFERENCES IN DEPRESSION AND IMMUNE RESPONSE IN
COLORECTAL CANCER

by

Barbara Anne Rose, MS, RN

A dissertation presented to the
FACULTY OF THE HAHN SCHOOL OF NURSING AND HEALTH SCIENCE
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In partial fulfillment of the
requirements for the degree
DOCTOR OF PHILOSOPHY IN NURSING

June, 2009

Dissertation Committee

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DEDICATION

Start by doing what's necessary; then do what's possible;

and suddenly you are doing the impossible.

St. Francis of Assisi, Founder of the Franciscan order, 1181-1226

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Abstract

The focus of this descriptive comparative study was to examine the relationship between gender and depression and immune system function in patients with colorectal cancer. The research questions were answered through secondary analysis, using data obtained from the answers of 117 men and women (71 men and 46 women) enrolled in a colorectal cancer study conducted between 1990 and 1991 in Pennsylvania. Descriptive statistics were used to characterize the sample, and general estimating equations were used to analyze depression and immune system function between men and women. Depression was measured by the Beck Depression Inventory, and immune system function was measured by natural killer cell levels. Results indicated that women reported higher levels of depression at all points in time, but the results were not statistically significant ($B=2.065, p=.151$). Age was statistically significant ($B=4.180, p=.041$). Women did not demonstrate statistically significantly lower NK cell levels than men ($B=.271, p=.603$) using GEE, although at all points in time, men's NK cell levels were higher than women's. Age was not a significant factor in the NK cell level differences ($B=3.667, p=.056$). The study was confounded by the relatively small sample size, and the high drop-out rate.

CHAPTER 1

INTRODUCTION

Cancer is the second most frequent cause of death in the United States, and colorectal cancer is the third most frequently diagnosed malignancy in both men and women (ACS, 2005). Although colorectal cancer rates have been steadily declining for the past 50 years, its five year survival is only 65% for white patients of both genders, and 55% for African-American men and women. According to the American Cancer Society, cancer will strike 679,510 women each year and of these women, 11% will be diagnosed with colorectal cancer, only slightly less than the number diagnosed with breast cancer (Society 2005)).

Statement of the Problem

Women have traditionally been underrepresented in medical studies, even though men and women have approximately the same lifetime risk (5.9% and 5.5% respectively) of being diagnosed with the disease. Colon cancer incidence rises with age; 91% of new cases are found in patients over the age of 50 (ACS, 2005). Compared to patients aged less than 40, there is a 50-fold increase in colon cancer in patients aged 60-79 (ACS, 2005). Colorectal cancer prognosis is directly related to the extent the tumor has entered

the bowel wall, the presence of lymph node involvement, and the presence of metastasis (National Cancer Institute, 2007).

Early diagnosis through screening beginning at age 50 is key to survival. Annual fecal occult blood testing (FOBT), primarily using rehydrated samples decreased mortality from colorectal cancer by 33% in study of 48,000 patients (Mandel, Bond et al., 1993). Screening sigmoidoscopy, using either a flexible or rigid sigmoidoscope, reduced the mortality risk by 70% -90% in two studies of screened patients compared to patients who were not screened (Selby, Friedman et al., 1992); (Newcomb, Norfleet et al., 1992). The American Cancer Society recommends that adults begin yearly FOBT screening at age 50, with sigmoidoscopy every five years (ACS 2005). Recurrent disease is found in up to 33% of patients (Safi, Link et al., 1993), leading to repeated treatment.

Patients with depression are less likely to continue in rigorous treatment and screening regimens. Depression has also been implicated in reduced functioning of the immune system, including the tumor surveillance function of the immune system. Yet little data exists about any differences between the immune systems of men and women, and depression in men and women who are diagnosed with colorectal cancer. A link between depression and immune system function can serve to identify those patients most at risk for complications, and those at risk of failing to continue treatment in follow-up care. Research is needed to examine the effects of colorectal cancer on men and women, and the differences, if any, in depressive symptoms and objective markers of immune function. The majority of completed studies did not include women, or did not analyze the women as a group separate from the men. Women are more likely to suffer from depression, and depression has been associated with reduced immune function. If women

with colorectal cancer are more depressed than men, one would expect that their immune function would suffer, leading to (potentially) more complications and poorer healing.

Purpose of the Study

Psychological state, particularly depression, has been implicated in reduced functioning of the immune system. Researchers have demonstrated diminished natural killer T-cell counts in patients reporting depression (Zorilla, Luborsky et al., 2001). In addition, numerous researchers have documented differences in levels of reported depression between men and women with cancer. Whether these differences are also reflected in patients' reports of depression over time has yet to be determined. Similarly, research has not established whether differences in depression translate into significant differences in immune system function between genders. The purpose of this study was to examine differences in levels of depression and immune function at three points in time of the colorectal cancer treatment trajectory.

The study consisted of a secondary analysis of data obtained from a study performed by Dr. Ruth McCorkle, from 1991 to 1992. The aim of the original study, supported by NIH grant P50 NR 02324, was to examine the physiological and psychological responses over time of patients with colorectal cancer. The McCorkle research team investigated whether outcome expectations and emotional distress changed over time, examined the interactions (if any) of outcome expectations and immune status, and whether outcome expectations and coping changed, or were related (Barsevick, Pasacrete et al., 1995; Orsi, McCorkle et al., 1996; Orsi, Tax et al., 1996). Orsi, McCorkle, Tax, and Barsevick (1996) examined the relationship between depression, depressive symptoms, and the immune system in patients with colorectal

cancer. Sixty-three patients were studied six months post diagnosis. Fourteen percent of patients reported depressive symptoms. Levels of NK cells were significantly lower in patients with more severe depressive symptoms both preoperatively and postoperatively. In addition, NK cell counts were lower than average in patients with more severe depressive symptoms. Preoperative depressive symptoms predicted NK counts and CD4/CD8 ratios (Orsi, McCorkle et al., 1996). Differences by gender were not examined, although women comprised between 32% and 39% of the sample, rather men and women were analyzed as one group. Findings indicated twice as many men as women in the sample reported no or minimal symptoms depressive symptoms at the first pre-operative visit, although women in general suffer from depression at roughly twice the rate of men. However, there was no separate analysis of the effect of gender on the interaction of depression and natural killer cell levels. This clearly requires further investigation.

Specific Aims

The specific aims of this study were to:

- 1) Determine if there were differences between reported depression levels in men and women diagnosed with colorectal cancer at four points in time (day of surgery, one week post surgery, three months post surgery, and six months post surgery).
- 2) Describe the differences, if any, in NK cell levels in men and women diagnosed with colorectal cancer at three points in time (day of surgery, three months post surgery, and six months post surgery).

Conceptual Framework

The conceptual framework of the study was based on the work of McCorkle integrating expectations about outcome of cancer treatment, depression, and immune response in person recovering from surgery for colorectal cancer (Figure 1.) (Orsi, McCorkle et al., 1996). The model posits that emotional distress, defined here as depression, leads to impaired immune responses (measured by NK cell level).

Figure 1.

Research Questions

1. Are women more likely to report more depressive symptoms than men in adult patients diagnosed with colorectal cancer at four points in time (pre-surgical, 1 week post-surgery, one month post-surgery, and three months post surgery)?

2. Do women demonstrate lower NK cell levels in adult patients diagnosed with colorectal cancer at three points in time (pre-surgical, one week post-surgery, and three months post surgery)?

Hypotheses

Based on gender differences in depression and reactions to the cancer diagnosis, and the already discovered interaction between NK cells and depression, the following hypotheses will be tested:

H1: Women will report a greater incidence of moderate to severe depressive symptoms.

H2: Women will demonstrate a more prolonged duration of depressive symptoms than men.

Significance to Nursing

The Healthy People 2010 Initiative (Office of Disease Prevention and Health Promotion, 2000) aimed to reduce deaths from colorectal cancer from 19.8 deaths per 100,000 persons between 2000 and 2003, to 13.9 deaths per 100,000 persons in the United States. Detecting and removing precancerous colorectal polyps and detecting and treating the disease in its earliest stages will reduce deaths from colorectal cancer (Office of Disease Prevention and Health Promotion, 2000). Detected at its earliest stages, colorectal cancer has a five year survival rate of 90%. However, only 38% of cases are diagnosed while the tumor is confined to the wall of the bowel (Ries, Eisner et al., 2002). Early detection is key to patient survival.

Healthy People 2010 lists depression as the most common disorder of mental illness (Office of Disease Prevention and Health Promotion, 2000), p. 36. Objective 18-9b aims to increase the proportion of adults with recognized depression who receive

treatment (p 36). Depression strikes twice as many women as men (Office of Disease Prevention and Health Promotion, 2000) p 37, and depression rates are higher in adults with coincident medical conditions. Some research has been conducted on the impact of a cancer diagnosis on state of mind. Stommel, Kurtz, Given, and Given (2004) studied 860 older patients for one year after a cancer diagnosis; they found that depression was predicted by cancer site and stage, co-morbidities, sociodemographic characteristics, and indicators of physical functioning(Stommel, Kurtz et al., 2004). Arndt, Merx, Stegmaier, Ziegler, and Brenner (2004) assessed quality of life in 439 patients in Germany one year after diagnosis with colorectal cancer(Arndt, Merx et al. 2004). Patients with colorectal cancer scored their physical, role, and cognitive, and global health functioning only slightly worse than the general population. However, patients described more severe limitations on the emotional and social functioning scales, as well as for physical symptoms and financial difficulties. Ramfelt, Severinsson, and Lutzen (2002) used a qualitative method to examine the emotional and interactional perspectives of the meaning of illness in 52 patients with colorectal cancer over the course of 12 months following diagnosis(Ramfelt, Severinsson et al., 2002). Using constant comparative analysis, the researchers described a process in which patients tried to find meaning in illness to achieve emotional coherence.

Klemm, Miller, and Fernsler (2000) examined the demands the illness of colorectal cancer placed on 121 patients over time. Ninety-three percent of participants thought about the value of life and how long they might live. Participants reported that colorectal cancer placed the greatest demands on them in the realm of personal meaning, and noted significant psychological and existential concerns (Klemm, Miller et al., 2000).

Galloway and Graydon (1996) examined the relationship between uncertainty, symptom distress, and discharge information needs in 40 patients after colon resection for cancer. Patients identified information about treatment, complications, and activities of daily living as highly important. Increased uncertainty was significantly associated with increased discharge information needs (Galloway & Graydon, 1996).

Course of Treatment

Treatment of colorectal cancer depends upon the stage of the disease at the time of diagnosis. Colorectal cancer is staged according to the TNM classification system by recommendation of the American Joint Committee on Cancer (Cancer 2003). The TNM system classifies tumors according to the tumor's invasion of the surrounding tissue, involvement of regional lymph nodes, and evidence of distant metastasis. As the tumor grows, it progressively invades the layers of the colon from the interior to the exterior; survival depends upon the degree of invasion of the colon and surrounding lymph nodes, and metastasis to distant structures. Treatment in all stages begins with local excision of the tumor, either polypectomy or laparoscopic or open surgical resection, with regional lymph node dissection. Because colorectal cancer spreads aggressively through the lymphatic system, it is recommended that at least 12 lymph nodes be examined to confirm the absence of nodal involvement by tumor (National Cancer Institute, 2003). In some cases, aggressive tumors which are too large to be excised are treated with debulking and adjuvant therapy such as chemotherapy and radiation therapy. Creation of a temporary or permanent colostomy is dependent on the size of the lesion and its location. In addition, patients may be referred for consideration for inclusion in clinical trials of biological or chemotherapy regimens.

Patients with extensive disease and metastases may face protracted courses of adjuvant therapy. How patients cope with the diagnosis and treatment of all types of cancer has been studied in both men and women, both qualitatively and quantitatively. Colorectal cancer places significant psychological, social, and physical demands on the patient, and all three domains have been studied. However, the impact of gender has not been studied.

Definition of Terms

Colorectal cancer: Cancer that develops in the colon (the longest part of the large intestine) and/or the rectum. Colorectal cancer encompasses a broad spectrum of neoplasms ranging from benign growths to invasive tumors. The predominant cancer is derived from the epithelial tissue of the colon and rectum. Lesions are classified into three groups: 1) non-neoplastic polyps; 2) neoplastic polyps; 3) cancers.

Natural killer cells: Natural killer (NK) cells are small subset of large, granular lymphocytes, but are neither B cell nor T cell lymphocytes. Natural killer cells possess spontaneous cytotoxic activity against a wide variety of cells such as tumor cells and cells infected with viruses. This activity occurs independently of any interaction with major histocompatibility complexes. In addition, NK cells influence lymphokine production, and regulate humoral and cytotoxic immune responses, as well as hematopoiesis. Natural killer cells activated by interleukin-2 (IL-2) serve to suppress tumor metastasis (Orsi, Tax et al., 1996).

CEA: Carcinoembryonic antigen. A substance that is sometimes found in an increased amount in the blood of people who have certain cancers, other diseases, or who smoke. It

is used as a tumor marker for colorectal cancer. Higher levels of CEA prior to treatment for colorectal cancer correlate with poor survival (Filella, Molina et al., 1992).

Chemotherapy: Treatment with drugs that kill cancer cells.

Polyp: A growth that protrudes from a mucous membrane.

Polypectomy: Surgery to remove a polyp.

Biological therapy: Treatment to stimulate or restore the ability of the immune system to fight cancer, infections, and other diseases. Also used to lessen certain side effects that may be caused by some cancer treatments. Also called immunotherapy, biotherapy, biological response modifier (BRM) therapy, and BRM therapy.

Radiation therapy: The use of high-energy radiation from x-rays, gamma rays, neutrons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy, implant radiation, or brachytherapy). Systemic radiation therapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that circulates throughout the body.

Assumptions

The assumptions on which this study was based include:

1. All information collected by the primary investigators is accurate, and reflects information about the course of treatment for colorectal cancer.
2. All patients were treated as similarly as possible according to their diagnostic stage and colorectal cancer treatment protocols.

3. All patients had economic access to equivalent levels of care for colorectal cancer treatment.

CHAPTER II

REVIEW OF THE LITERATURE

Colorectal Cancer Incidence and Course of Treatment

Although the incidence of colorectal cancer has declined since 1998, it continues to be the third most frequently diagnosed malignancy in men and women (Society 2005). Colorectal cancer is considered to be a disease of the elderly, with over 91% of new cases and 94% of deaths occurring in patients older than 50. The incidence of colorectal cancer is 50 times higher in patients aged 60-79 than in those under the age of 40 (ACS, 2005). Because of its high frequency in the aging population, colorectal cancer and patients' reactions to it have been studied extensively. In addition to physiological reactions to surgery and adjuvant therapies, much attention has been directed at how patients think and feel over the course of treatment.

Depression and Cancer

Psychological responses to both the cancer diagnosis and course of treatment have been studied since the 1970s. Wiesman and Worden (1976), Oberst and Scott (1984), Morris, Greer and White (1977), and Hughes (1982) examined the psychological responses of patients after various cancer diagnoses at various stages of diagnosis and treatment; emotional distress was common. Weisman and Worden (1976) used a sample of 120 patients with five different cancers (breast, lung, colon, Hodgkin's disease, and malignant melanoma) to examine the effect of expectations and emotional distress on

coping and health. Over the course of 100 days, patients were given the Minnesota Multiphasic Personality Inventory (MMPI), the Thematic Apperception Test (TAT), and the Profile of Mood States (POMS) in addition to scales on coping, resolution, predominant concerns, and vulnerability which were designed for the study. Patients were interviewed by social workers in an initial semi-structured interview and at four to six week intervals. Patients with high emotional distress attempted to cope by reducing their negative moods, such suppression, submission, and stoicism. While some relief was found through the use of these tactics, they did ultimately resolve the underlying problems. Patients with lower emotional distress used more functional strategies such as eliciting partnerships with others and problem-focused tactics to resolve problems. While they found that emotional distress and a pessimistic outlook were related, Weisman and Worden did not examine the interrelationships between coping and expectations, leading to a linear picture of cancer coping. Men and women were not analyzed separately. The majority of the women in the study had been diagnosed with breast cancer, although more women than men in the study had colon cancer(Weisman and Worden, 1976).

Oberst and Scott (1988) examined 40 patient-spouse dyads in which the patient had been diagnosed with colorectal or urinary cancer. Dyads were assessed at six points in the post-surgical period: pre-discharge, 10 days, 30 days, 60 days, 90 days, and 180 days post discharge; the Brief Symptom Inventory, the State-Trait Anxiety Inventory, the Vulnerability Scale, and an inventory of concerns and problems were used. Both ostomy and non-ostomy patients were used. Both spouses and patients reported similar numbers

of problems and concerns. Spouses reported more problems with their own physical states and with emotional difficulty and handling their own feelings. Spouses reported more lifestyle disruptions than patients. Spouses consistently reported more anxiety than patients did at 90 days, and prior to discharge. All dyads exhibited symptoms which had not resolved in the 180 day study period. The study was limited by its small sample size, and use of a relatively homogenous sample of middle to upper income families. No effort was made to distinguish between male and female patients in the analysis, and depression was not specifically addressed (Oberst & Scott, 1988).

Stommel, Kurtz, Given, and Given (2004) looked at depression in 860 older patients for one year after a cancer diagnosis, using the Center for Epidemiological Studies Depression Scale (CES-D). In the 393 patients who completed the full study, they found that depression was predicted by cancer site and stage, co-morbidities, education, gender, and a history of emotional problems. Overall depressive symptoms declined over the course of the investigation, especially depressive mood and somatic indicators. As might be expected, women exhibited higher depression scores than men, although education, history of emotional problems, and site of cancer in the lung had the highest association with depression. The study was limited to patients who could be accessed by telephone, lived in Michigan, and spoke English. Only patients aged 65 or older were recruited. The use of the CES-D also raises some concerns. The CES-D has been criticized for its questions about somatic symptoms; researchers have speculated that such questions might lead to exaggerations and over-reporting of depressive symptoms (Stommel, Kurtz et al., 2004).

Arndt, Merx, Stegmaier, Ziegler, and Brenner (2004) assessed quality of life in 439 patients in Germany one year after diagnosis with colorectal cancer using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life questionnaire (QLQ-C30). This 30-item self-report cancer-specific survey measures health-related quality of life, and consists of five functional scales (physical, emotional, role, cognitive, and social function). In addition, the questionnaire also evaluates somatic symptoms such as fatigue and nausea and vomiting, and financial difficulties. In the 309 patients who completed the full questionnaire, quality of life was most affected by fatigue and insomnia. Patients with colorectal cancer scored their physical, role, and cognitive, and global health functioning only slightly worse than the general population. No patterns related to gender were seen. However, patients described more severe limitations on the emotional and social functioning scales, as well as for physical symptoms and financial difficulties. The study was limited in that it did not specifically assess depression or depressive symptoms scores. Patients were studied at one point in time rather than over time with repeated measures, and were compared to the general population rather than to themselves. Those who responded to the request to participate in the study were better educated than nonresponders, and tended to be married. There was no data on those patients who died in the year between diagnosis and the request to participate, and whose quality of life might presumably be different from patients who survived for one year (Arndt, Merx et al., 2004).

Will (2002) used a constant comparative method to investigate the process by which patients learn to live with colorectal cancer. Using grounded theory, Will found that patients used a process of self-talk to work through the experience of colorectal

cancer. Patients experienced an 8 stage trajectory of living with colorectal cancer. Phases consisted of: (1) Knowing something is wrong; (2) seeking diagnosis; (3) receiving the diagnosis; (4) planning treatment; (5) being treated; (6) waiting and monitoring; (7) something is wrong again; (8) reflecting and moving on (Will, 2002).

Depression and Natural Killer Cells

Depression has long been known to have a significant effect on the immune system. Urch et al, (1988) compared the natural killer (NK) cell activity of in schizophrenics and patients with depression undergoing treatment with that of normal volunteers, and found that the schizophrenics had lower NK cell activity. Psychopharmacologic treatment led to increases in NK cell activity in the patients with schizophrenia, but not in those with depression. Urch et al concluded that the pituitary-adrenal axis was responsible for the difference, and that the decrease in NK cell activity might be responsible for failures in immunosurveillance (Urch, Muller et al., 1988). Unfortunately, while the study contained equal numbers of men and women (30 each), the influence of gender was not examined. Failures in immunosurveillance have been implicated in an increase in cancers in patients with depression (Shekelle, Raynor et al., 1981; Shavit, Lewis et al., 1984; Herberman & Ortaldo, 1981).

Irwin et al (1988) examined NK cell activity during significant life events as well as during bereavement, and documented reduced NK cell activity in women anticipating or undergoing bereavement. Irwin found that in 28 women who were either grieving, or anticipating the death of a spouse, NK levels fell. However, the decrease in NK cell levels was not mediated by changes in plasma cortisol levels; the adrenal cortex did not appear to influence the NK cell decline. The researchers did not, however, measure the

level of bereavement of the subjects, nor did they test for actual depression (Irwin, Daniels et al., 1988).

Irwin, Smith, and Gillin (1987) also examined NK cell levels and activity in a small group of men hospitalized for treatment with diagnosed major depression. Using a sample of 19 men matched with 19 nonhospitalized normal volunteers, Irwin et al found that the depressed patients had significantly lower NK cell activity. Depression was measured with the Hamilton Depression Rating Scale, which has been criticized for not discriminating between symptoms related to anxiety, and those related to depression. Regrettably, no women were included in the study, so any possible gender differences could not be investigated (Irwin, Smith et al., 1987).

In further work, Irwin et al (1987) explored the relationship between the effects of different life events on NK cells in women over a 3 month period. The Hamilton Rating Scale for Depression and the Social Readjustment Scale were used to quantify the women's states of mind. NK cell function was reduced in women with higher depression scores, as well as with higher scores on the Social Readjustment Rating Scale (Holmes & Rahe, 1967). Severity of depressive symptoms was accompanied by lower NK cell activity. However, the authors did not examine any differences between the effects of depression, and any effects of major life events (Irwin, Daniels et al., 1987).

Levy, Herberman, Lippman, and d'Angelo (1987) found an association between breast cancer, depression and fatigue, and lack of support at the time of diagnosis, and reduced NK cell activity at three months after diagnosis. Seventy-five women diagnosed with stage I or stage II breast cancer in a study comparing modified radical mastectomy to wide excision with radical radiotherapy were enrolled in a study to examine the

influence of fatigue, global adjustment to cancer, and social support on NK cell levels. Previous work had established that peripheral NK cell levels predicted the presence of cancer cells in axillary lymph nodes (Levy et al, 1985). Patients were interviewed between five and seven days after surgery (mastectomy plus axillary node dissection, or lumpectomy and lymph node dissection). In addition to an interview, patients filled out the Profile of Mood States (POMS) self-report form, and were rated by two observers for overall adjustment to their illness using the Global Adjustment to Illness Score (GAIS). Assays of NK cells were taken at the time of the interview, as well as during an outpatient visit three months later. Patients with lymph nodes positive for cancer demonstrated low NK cell activity at initial interview and at the three month check-up. In these patients, neither chemotherapy nor chemotherapy with radiation led to further decreases in NK cell activity. Fatigue and social support accounted for 30% of the NK cell activity decreases at three months. Patients reporting depressive, fatigue-like symptoms and who reported a lack of family support at the first interview tended to show a decrease in NK cell activity at the three-month follow-up (Levy, Herberman et al., 1987). Based on these results, it appears that depression and a perceived lack of social support at the time of initial surgery predicted NK cell activity three months later. The authors posited that a lack of NK cell activity would lead to reductions in cancer surveillance, and possibly an increase in the spread of the disease. However, no data were followed to substantiate that surmise. Patients in the study were young (mean age 52), and no socio-economic data were provided. In addition, no data were provided about race, co-morbidities, or family constellation.

Vines, Gupta, Whiteside, Dostal-Johnson, and Hummler-Davis (2003) measured natural killer (NK) cell counts and self-reports of depression in 24 patients with chronic pain. Pain perception was positively correlated with depression and NK cell percentage. Immune system function as measured by NK cell levels was significantly higher in patients without pain (Vines, Gupta et al., 2003).

Nunes et al (2002) measured immune function in 40 patients with depression, and compared them to the immune function of 34 matched non-depressed volunteers. Immune function as measured by acute phase proteins was significantly decreased in the depressed patients. However, NK cell levels were not tested. One notable strength of the study was the ratio of women to men in the depressed group (2.6:1), which mirrored the greater proportion of women diagnosed with depression. However, the lack of NK cell levels is not helpful (Nunes, Reiche et al., 2002).

The development or progression of colorectal cancer has been linked to immune function since the 1980s. Decreases in immune function, either by design or nature, have been found to be associated with either the development or metastasis of colorectal or other cancers. Talmadge, Meyers, Prieur, & Stanley (1980) found an association between NK cells and tumor growth in mice (Talmadge, Meyers et al., 1980). Letsou, Ballantyne, Zdon, Cambria, & Modlen, (1985) reported increases in renal cell carcinoma in patients after renal transplant associated with drug-induced immunosuppression (Letsou, Ballantyne et al., 1986). Weese, Gilbertson, Syrjala, Whitney, & Starling, (1985) were able to reduce the incidence of colon cancer metastasis in mice through immunostimulation (Weese, Gilbertson et al., 1985).

Immune System Function

The immune system discriminates between native and non-native cells within the body, and protects the body from invading pathogens. The immune system also carries out a significant internal surveillance function, designed to recognize cancer cells arising from errors in cell division, and eliminate them. Overly aggressive immune cells attacking the body's native cells have been implicated in the development of autoimmune disorders such as multiple sclerosis, insulin-dependent diabetes, rheumatic arthritis, and Crohn's disease, to name a few.

There are two arms in the immune system: the humoral-mediated immune system, and the cellular-mediated system. Humoral immune responses include the B-lymphocytes and their serological products, while the cellular-mediated system consists of the T-lymphocytes, the thymus, lymph nodes, blood vessels, and spleen. Both B-lymphocytes and T-lymphocytes arise from the bone marrow. T-lymphocytes migrate to the thymus gland in the neck, where they differentiate into several subtypes: cytotoxic T-lymphocytes, known as natural killer (NK) cells, T-helper lymphocytes, and T-suppressor lymphocytes. The T-lymphocytes then travel to the blood vessels, lymph nodes, and spleen to await activation by a pathogen. B-lymphocytes are responsible for the antibody-mediated response to pathogens or abnormal internal cells. All B-lymphocytes begin their life spans as secretors of immunoglobulin M (IgM).

When an invading organism or an abnormal cell is detected by the immune system, the macrophage mounts the first response. The macrophage cell surface engages the antigen with the major histocompatibility complex on the cell surface, leading to the secretion of interleukin-1 (IL-1). Interleukin-1 resets the hypothalamus to a higher normal set point, leading to the fever associated with infection; interleukin-1 also encourages the

proliferation of T-lymphocytes and B-lymphocytes. Both natural killer T-lymphocytes and helper T-lymphocytes respond to IL-1. Both natural killer and helper T-lymphocytes secrete immunoglobulins that modulate their adherence to major histocompatibility complexes formed by the interaction of macrophages and antigens. Natural killer T-lymphocytes possess specific binding sites on their cell surfaces that recognize and bind antigens as the antigens are presented to them by the macrophage. The NK cell then recognizes and responds to that specific antigen, leading to a faster T-lymphocyte response when the antigen is encountered again. Natural killer lymphocytes are evaluated with the CD-8 count, a measure of the expression of Cluster Determinant 8. T-helper lymphocytes are evaluated with the CD-4 count, a measure of the expression of Cluster Determinant 4. T-helper lymphocytes secrete interleukin-2, a cytokine, in response to antigens, and regulate the proliferation of T-lymphocytes in responses to antigens. When stimulated by T-helper lymphocytes secreting factors such as interleukin-2 and interleukin-4, B-lymphocytes change their antibody-secreting status and begin secreting other classes of antibodies (IgE, IgG, IgD) specific to the antigen presented to them by the T-helper cell. B-lymphocytes also proliferate at this stage, and maintain an antigen-specific response.

Natural killer cell number and activity serves as quick method of evaluating immune system function, and has received some attention in the era of acquired immune system diseases. However, in patients with human immunodeficiency virus (HIV) infection, the CD-4 count has been used as a marker of HIV infection in patients prior to seroconversion, because few diseases other than HIV infection so closely effect the CD-5 count.

Conclusion

The review of the literature supports the research design of this study, and the examination of the study variables in the conceptual framework. The review points to the extraordinary lack of attention paid to the experiences of women in the study of colorectal cancer, and the implications of colorectal for patients' psychological well-being. The majority of the studies did not include women, or did not analyze the women as a group separate from the men. Women are more likely to suffer from depression, and depression has been associated with reduced immune function. If women with colorectal cancer are more depressed than men, one would expect that their immune function would suffer, leading to (potentially) more complications and poorer healing.

In summary, the review of the literature indicates that further research is needed to examine the relationship between gender, depression, and immune function in patients with colorectal cancer. A secondary analysis of data which includes both men and women can be conducted to illuminate any relationships. The knowledge gained from this analysis could be used to formulate gender-specific treatment plans, and improve outcomes for patients with colorectal cancer.

CHAPTER III

METHOD

The purpose of this study was to examine gender differences in the relationship between depression, and immune function in patients with colorectal cancer over time. In this chapter the research design, sample and sample, procedures for data collection, measurement, as well as the data analysis techniques are described. The protection of human subjects is also discussed.

Design

A descriptive, correlational, repeated measures design using secondary data analysis was used for this study. Polit and Beck define secondary analysis as a form of research in which the data collected by one researcher are reanalyzed by another researcher to answer new research questions (Polit and Beck, 2004 p. 731). Although the database must be selected with care, there are numerous advantages to conducting a secondary analysis. Perhaps the greatest advantage lies in the money, time, and resources which are conserved by using data which have already been collected (Moriarty, Deatricks et al., 1999). In addition, the researcher does not need to impose upon the time and patience of the members in the database, nor invade their privacy once again. If the sample is large enough, the database may contain considerably more variables than could be obtained in a smaller sample. A secondary analysis may allow the researcher to reexamine data, and rethink previous conclusions. Finally, the researcher may be able to

use a secondary analysis to as a preliminary study to solicit additional funds for further research (Moriarty, Deatrck et al., 1999).

This study used a subsample of participants ($n = 117$) who participated in a larger study conducted by McCorkle and colleagues to examine the physiological and psychological responses over time of patients with colorectal cancer. The sample utilized in this study was selected for several reasons. The database consisted of unequal numbers of men and women. The unequal numbers may point to pre-existing differences between the groups in their willingness to participate, or to continue to participate once enrolled. The unequal numbers may reflect the overall demographic makeup of the population, or the tendency of women to request medical care later in an illness trajectory than men. Numerous other reasons may lie behind the unequal numbers, but the preponderance of men could make drawing conclusions problematic.

The data were collected prospectively, included data collection points throughout the illness trajectory, and standardized measures of depression and immune system function, in addition to demographic data. Finally, the data were made available by the researcher who collected them, who encouraged the secondary analysis.

McCorkle Study

A repeated measure prospective design was used to examine the physiological and psychological responses over time of patients with colorectal cancer.

Sample and Sampling

Patients diagnosed with colorectal cancer were identified by the surgical scheduling offices and then recruited from the four hospitals of the University of

Pennsylvania for three months during their recovery from surgery from 1990 to 1992. To achieve a power of .80 using three independent variables and 2 covariates, based on $R^2 = .10$ and $\alpha = .05$, 121 were required for the study (Cohen 1988; Orsi, Tax et al. 1996).

All subjects were selected on the basis of the following criteria:

1. Dukes Stage A or B (TNM stages I and II) carcinoma of the colon or rectum.
2. Scheduled for surgery for colon or rectal cancer.
3. Able to communicate in English.
4. Oriented to time, place, and person.

Two hundred eligible patients were invited to join. Thirty-four percent refused, either

due to fatigue or preoccupation, desire to avoid further blood draws, or family preference. After informed consent was obtained, participants were asked to complete a demographic survey, as well as an evaluation of the impact of their cancer on their state of mind, the Beck Depression Inventory. The Beck Depression Inventory (BDI) a 21 item self-report test measuring characteristic attitudes and symptoms of depression. Blood was drawn for lymphocyte assay, which was determined by flow cytometry measurements. The initial interview was conducted by a graduate student on the study team, and lasted between 30 and 45 minutes.

Data were collected prospectively at four points in time: 1) prior to surgery; 2) 1 week after surgery; 3) 1 month after surgery; 4) 3 months after surgery (Orsi, Tax et al. 1996). Each participant completed the Beck Depression Inventory each time. Blood samples were obtained for NK Cell Assay at the initial (pre-operative) visit, as well as at 1 week and 3 months.

Table 1. Data Collection Time points

Time Point	Prior to Surgery	1 Week Post-Op	1 Month Post-op	3 Months Post-op
Measure	Beck NK Cell Assay	Beck NK Cell Assay	Beck	Beck NK Cell Assay

The demographic make-up of the patients who began the study is presented below. Mean age of the participants was 62.4 years, with the mean age of the women equal to 62.0 years, and the mean age of the men 62.3 years. The participants were grouped according to their reports of depressive symptoms for the purposes of analysis (Orsi, McCorkle et al., 1996). Chi-square analyses were conducted to determine if there were any pre-existing differences between the demographics of the two groups. The groups were similar with the exception that those with no or minimal depressive symptoms were more likely to be married ($X^2 = 2.98, p = .05$) (Orsi, McCorkle et al., 1996). No differences were discerned with respect to age, employment, socioeconomic status, education, race, and presence or absence of an ostomy (Orsi, McCorkle et al., 1996). Twenty-seven percent of the subjects were mild to moderately depressed according to the criteria established by the Center for Cognitive Therapy (Beck, Ward et al., 1961).

Table 2.

Gender Breakdown by Sampling Time

	PreOp	1 week	30 Days	90 Days
Male n(%)	71 (61%)	60 (65%)	59 (68%)	58 (64%)
Female n(%)	46 (39%)	32 (35%)	28 (32%)	32 (36%)

Total n(%)	117 (100%)	92 (100%)	87 (100%)	90 (100%)
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The mean BDI score for those patients reporting more severe symptoms was 16.0 (± 7.5), indicating mild to moderate depressive symptoms (Orsi, McCorkle et al., 1996). The mean BDI score for the patients with no or minimal depressive symptoms was 3.3 (± 2.5).

The original investigators used t tests to look for differences in the preoperative lymphocyte phenotype measure based on the demographic and clinical characteristics. They reported no significant differences in the phenotype measures on any of the demographic and clinical characteristics. However, they did find a clear and significant difference in the relative lymphocyte levels between those patients reporting minimal or no depressive symptoms, and those with depressive symptoms. Patients with depressive symptoms prior to surgery had lower NK cell levels and CD8 levels, as well as lower T helper (CD4) counts. Not surprisingly, their ratios of CD4 to CD8 were lower. Patients with more depressive symptoms had significantly higher T helper counts (CD4), and higher CD4/CD8 ratios, and significantly lower NK cell counts. Postoperatively, patients with an ostomy had significantly lower CD4 counts, and patients receiving adjuvant therapy had significantly lower CD4 counts, CD4/CD8 ratios, and significantly higher CD8 counts. The mean BDI score post surgery for patients reporting more depressive symptoms was 17.6 (± 8.0), while the mean BDI score for patients with no or minimal depressive symptoms was 2.9 (± 2.7). This translates to a moderate level of depression. At 3 months, patients in both groups had a slight increase in NK cell counts, and a significant decrease in depression scores as measured by the BDI. Patient who reported

depressive symptoms preoperatively continued to show significantly lower NK cell counts at the 6 month evaluation.

The original team used stepwise multiple regressive analyses of the immune system to assess the impact of various factors on NK cell counts. The level of depressive symptoms reported, presence of an ostomy, occupation, and marital status predicted NK cell counts. The presence of more severe preoperative depressive symptoms explained a large amount of the variance in NK cell counts. Depression explained 7% of the variance in NK cell counts. Use of adjuvant therapy accounted for 10% of the variance in CD4/CD8 ratios at 6 months. The presence of an ostomy predicted 11% of the variance in CD4 counts after surgery.

Overall, 27% of patients reported mild to moderate depression as measured by the BDI (Orsi, McCorkle et al., 1996). The 24 women constitute a cohort whose psychological state can be linked to their immune system function. Postoperative depression was present at the 3 month evaluation, which demonstrates an extraordinary duration of suffering. What is not known about this group of depressed patients is whether the men and women had different trajectories of depression, and how this might affect their eventual outcomes.

Rose Study

For the study presented here, 117 patient records were available for analysis. Of these 117 cases, there were 71 men and 46 women at the initial sampling time, and the ratio of men to women who remained in the sample was consistent at each sampling point. Attrition was 25% for men between Time 1 and Time 2, 0 between Time 2 and Time 3, and 2% between Time 3 and Time 5. For women, the attrition was 37% between

Time 1 and Time 2, 3% between Time 2 and Time 3, and 0 between Time 3 and Time 4. Table 3 presents the number and percentage of men and women who participated in the study at each sampling point.

Table 3.

Gender Breakdown by Sampling Time

	Pre-operative	1 week	30 Days	90 Days
Male n (%)	71 (61%)	60 (65%)	59 (68%)	58 (64%)
Female n (%)	46 (39%)	32 (35%)	28 (32%)	32 (36%)
Total	117 (100%)	92 (79%)	87 (74%)	90 (77%)

Unfortunately, demographic data on the patients were not made available for the purposes of this analysis, thus necessitating the use of previously published data. (See page 314, Orsi, McCorkle, et. al. (1996)

Measurement

Beck Depression Inventory

Depression defined as a score of 21 was measured by the use of The Beck Depression Inventory (BDI) introduced by Beck, Ward, Mendelson, Mock, and Erbaugh in 1961, and revised in 1971. The Beck Depression Inventory is a 21 item self-report test measuring characteristic attitudes and symptoms of depression. It takes approximately 10 minutes to complete, and requires a fifth or sixth grade reading ability. A shorter, 13 item inventory is also available, but was not used in this study. Internal consistency ranges from 0.73 to 0.92, with a mean internal consistency of 0.86 (Beck, Steer et al., 1988). Cronbach's alpha is 0.93. Content validity was obtained by review by experts in the symptoms of depressed patients. Concurrent validity with clinical ratings of

depression ranges from 0.62 to 0.66; there are moderate correlations between the revised Beck Depression Inventory and other depression scales, including the Hamilton Psychiatric Rating Scale for Depression (0.73), the Zung Self-Reported Depression Scale (0.76), and the Minnesota Multiphasic Personality Inventory Depression Scale (0.76) (Groth-Marnat, 1990). Groth-Marnat also reported that the revised Beck Depression Inventory was able to discriminate between psychiatric patients and non-psychiatric patients, and yielded relatively higher scores for patients with major depressive disorders as compared to patients with dysthymic disorders. Scores on the Beck Depression inventory range from zero to 63 in patients diagnosed with depression. The test is scored differently for the general population, and those who have diagnosed with depression. In both groups, higher scores indicate greater depression. In the general population, a score of 21 or greater indicates depression. In those patients diagnosed with depression, mild to moderate depression levels begin at 10-18, moderate to severe depression scores range from 19 to 29, and severe depression scores range from 30 to 63. Groth-Marnat (1990) suggested that any score above 40 was indicative of possible exaggeration of depression, and might be found in histrionic patients or those with borderline personality disorders. Scores below 4 were deemed below usual scores in normal persons, and might represent faking or denial of depression. For this analysis, subjects were assigned to one of two groups: minimal or no depressive symptoms (scores less than 21), and more severe depressive symptoms (scores 21 or greater) (Orsi, McCorkle et al., 1996). Continuous variables were used for this analysis.

Flow Cytometry Evaluation

Flow cytometry was used to evaluate the numbers and types of immune cells. In flow cytometry, cells are measured by exposing them to fluorescent monoclonal antibodies that have been manufactured to react with the antigens present on each cell surface. After reacting with the fluorescent monoclonal antibodies, the resulting cell-antibody complexes produce different colors and degrees of fluorescence, and are counted in flow cytometry chamber. Flow cytometry measurements have been used in predicting responses to bone marrow and solid organ transplantation, the evaluation of immune system dysfunction (Tax, Orsi et al., 1994). The results can be obtained in as little as two hours, and are reliable and reproducible (Tax, Orsi et al., 1994). Monoclonal antibodies against specific surface antigens on the lymphocytes were purchased from Becton-Dickinson (Mountain View, California). These antibodies had been conjugated with one of two fluorescing solutions: fluorescein isothiocyanate (FITC), which can be detected by green emission in the flow cytometer, or phycoerythrin (PE), which can be detected by red emission in the flow cytometer. Using two different fluorescing stains allows the lymphocytes to be labeled with two different antibodies. Samples of ethylenediaminetetraacetate (EDTA)-anticoagulated blood were incubated with the monoclonal antibodies. A lysing solution was then added to remove the erythrocytes, leaving the lymphocytes and platelets. The remaining cells were sedimented in a centrifuge, washed, and fixed in a paraformaldehyde solution. A Becton-Dickinson FAC-Scan flow cytometer was used to perform the two-color flow cytometry analysis as described by Siegal et al (1989). A sum check on the values obtained from the flow cytometry analysis for each patient was performed ($Tcells + Bcells + NK\ cells = 100\%$) according to the Riechert method (Reichert, DeBruyere et al., 1991). Based on this

check, only 1 sample of the 95 obtained was eliminated from the analysis. The sum check for the remaining samples ranged from 95% to 105%, with a mean of 100%. Results from the flow cytometry analysis were expressed as percentages of lymphocyte phenotypes rather than absolute numbers of cells.

Data Analysis

The original investigator made Beck Depression Inventory and Natural Killer cell levels and gender available to this researcher. The data were entered by the researcher into a database of the Statistical Package for the Social Sciences (SPSS) version 16.0, Graduate Pack. Data entries were double-checked by the researcher and an associate, and no data entry errors were found. The study was approved by the Institutional Review Board for the protection of human subjects and the University of San Diego Institutional Review Board.

Descriptive statistics were used in this analysis. Prior to statistical analysis, missing data points were identified and analyzed by gender. The drop-out rate was extraordinarily high, perhaps because of the longitudinal nature of the investigation. Missing data for both depression scores and NK cell levels were imputed using the General Estimating Equation analysis.

Descriptive Statistics

Descriptive statistics for the sample were drawn from the published work of the original investigators and used to compare the samples according to depressive symptom reporting (Munro 2001) (Orsi, McCorkle et al. 1996) (Tax, Orsi et al. 1994).

Power Analysis

Power is influenced by the type of statistical test being performed, the size of the sample, the size of the effect being measured, and the level of error specified in the research. General estimating equation analysis was used to test for differences between the mean scores for depression and NK cell levels at four points in time for depression, and three points in time for NK cell levels, and between the two genders (Hanley, Negassa et al., 2003). General estimating equations (GEE) are of particular value when the data to be analyzed consist of longitudinal data, correlated data, in studies with considerable missing data points, or if the data are binary or counts (Hanley, Negassa et al., 2003). The GEE analysis is a regression analysis based on the General Linear Model (GLM), and develops a regression equation for each set of data points to impute missing data. The GEE method assumes that the model being tested is linear, and that any missing data are missing completely at random (Horton & Lipsitz, 1999; Norton, Bieler et al., 1996). General Estimating Equations are a synthesis of Feasible Generalized Least Squares approach and are of particular value in data sets with missing data. General Estimating Equations produce reasonably accurate standard errors, which produces confidence intervals with the correct coverage rates (Hanley, Negassa et al., 2003).

The size of the sample required to demonstrate an effect can be the limiting factor in an investigation. If the effect is small, the size of the sample may need to be extremely large, and prohibitively expensive. If the effect is large, a smaller sample size may be required. The power analysis used by the original investigators led them to recruit 200 participants. The size of the effect, in this case the sex of the participants, has been shown to be significant in other studies of depression as noted earlier, but not in studies of natural killer cells. The simplest approach to determine power in this analysis is to

estimate the effect size, or eta-squared (η^2). Eta-squared represents the proportion of the variance explained by the analysis (Polit & Beck, 2004) p.498). Finally, the level of error was set *a priori* at $p < 0.05$.

Table 4

Schedule of Tests for Men and Women Participants

	Prior to Surgery	1 Week Post-Op	1 Month Post-Op	3 Months Post-Op
Sex				
Men	BDI	BDI	BDI	BDI
	NK Cell Assay	NK Cell Assay		NK Cell Assay
Women	BDI	BDI	BDI	BDI
	NK Cell Assay	NK Cell Assay		NK Cell Assay

Limitations

There were several limitations to this study. While the overall number of participants was moderately sized, not all the data could be retrieved. The data were also drawn from the catchment area of a large metropolitan hospital in the northeastern corner of the United States, and included primarily elderly participants. Seventy-four percent of the participants were over the age of 56. Since 91% of new diagnoses of colorectal cancer occur in patients over the age of 50, it is likely that this sample underestimates the population mean for depressive scores and NK cell levels. The data were gathered in the 1990s. Since that time, colorectal cancer has received more publicity and more attention from the public, particularly since the death of newscaster Katie Couric's husband in 1998. After Couric underwent a televised colonoscopy in 2000, a study published in the Archives of Internal Medicine noted an increase in patients undergoing colonoscopy for

cancer screening. In addition, only 9 participants (10%) were African-American. African-Americans die from colorectal cancer at 40% higher rate than Caucasian men and women, and are more likely to be diagnosed at a more advanced stage of the disease (ACS, 2005).

Finally, the data are limited by the attrition rate. The treatment of the missing data has already been discussed. By the time of the first post-operative visit, one week after surgery, 15% of the men and 30% of the women had dropped out of the study or simply did not complete their depression score instruments. At one month, an additional 2% of men and 9% of women were lost to follow-up, and at three months, a total of 18% of men and 30% of women had dropped out of the investigation. At all data points, women were lost to follow-up at approximately twice the rate of men.

Similar results were found when the NK cell counts were analyzed. Results were available for 55 men and 34 women at the pre-operative visit. By the time of the post-operative interview at 1 week, 29% of men had opted out, and 38% of women. At three months, 36% of men and 42% of women dropped out of the study or their results could not be found. At all points, more women than men dropped out.

Human Subjects

To protect participants from risk or injury, the original investigators submitted the study proposal to the Committee on Studies Involving Human Beings at the University of Pennsylvania. For the secondary analysis, the proposal was submitted for approval by this investigator to the Institutional Review Board of the University of San Diego. Appendix B contains the approval letter from the University of San Diego. The original investigators hold the approval letter from the University of Pennsylvania.

The data collection tools were kept locked in a secure location by the original investigators, and made available to this researcher. All participants were coded by numbers rather than by names, and the original investigators kept the names separately from the coded data tools to maintain anonymity.

There were no potential physical, psychological, or social risks to the subjects in this secondary analysis. The findings will be used to assess the relationship, if any, between gender and depression and natural killer cell levels in patients with colorectal cancer.

Summary

The purpose of this study was to investigate the influence of gender on depression and natural killer cell levels in patients with colorectal cancer over a 3 month period. The data analysis is appropriate for the types of data collected, the purpose of the study, and the method used. It is hoped that the results of the data analysis provided information useful in the formulation of treatment plans for patients with colorectal cancer.

CHAPTER IV

RESULTS

The results of the analysis are presented in two sections. Section one describes the sample's demographics. Section two presents the analysis of the influence of gender on participants' reporting of depressive symptoms, and NK cell levels.

Description of the Sample

The demographic breakdown of the sample can be found in Table 5. The original investigators used t tests to look for differences in the preoperative lymphocyte phenotype measure based on the demographic and clinical characteristics. They reported no significant differences in the phenotype measures on any of the demographic and clinical characteristics. However, they did find a clear and significant difference in the relative lymphocyte levels between those patients reporting minimal or no depressive symptoms, and those with depressive symptoms. Patients with depressive symptoms prior to surgery had lower NK cell levels and CD8 levels, as well as lower T helper (CD4) counts. Not surprisingly, their ratios of CD4 to CD8 were lower. Patients with more depressive symptoms had significantly higher T helper counts (CD4), and higher CD4/CD8 ratios, and significantly lower NK cell counts. Postoperatively, patients with an ostomy had significantly lower CD4 counts, and patients receiving adjuvant therapy had significantly lower CD4 counts, CD4/CD8 ratios, and significantly higher CD8 counts. The mean BDI score post surgery for patients reporting more depressive

symptoms was 17.6 (± 8.0), while the mean BDI score for patients with no or minimal depressive symptoms was 2.9 (± 2.7). This translates to a moderate level of depression. At 3 months, patients in both groups evinced a slight increase in NK cell counts, and a significant decrease in depression scores as measured by the BDI. Patient who reported depressive symptoms preoperatively continued to show significantly lower NK cell counts at the 6 month evaluation.

The original team used stepwise multiple regressive analyses of the immune system to assess the impact of various factors on NK cell counts. The level of depressive symptoms reported, presence of an ostomy, occupation, and marital status predicted NK cell counts. The presence of more severe preoperative depressive symptoms explained a large amount of the variance in NK cell counts. Depression explained 7% of the variance in NK cell counts. The presence of an ostomy predicted 11% of the variance in CD4 counts after surgery.

Table 5

Subjects' Preoperative Demographic and Clinical Characteristics

Characteristics	Minimal or No Depressive Symptoms N = 46	Depressive Symptoms N = 17
Sex		
Male	31 (67%)	8 (47%)
Female	15 (33%)	9 (53%)
Age		
Range	64	59
Mean	37-63	30-87
Race		
Caucasian	41 (89%)	16 (94%)
African-America	5 (11%)	1 (6%)
Marital Status		
Married	40 (89%)	11 (65%)
Single	6 (13%)	6 (35%)

Education	26 (57%)	10 (59%)
Completed high school or more	20 (43%)	7 (41%)
Did not complete high school		
Occupation		
Professional	23 (50%)	4 (24%)
Non professional	23 (50%)	13 (4%)
Co-morbidity		
Yes	18 (39%)	7 (41%)
No	28 (61%)	10 (59%)
Ostomy		
Yes	19 (41%)	2 (12%)
No	27 (59%)	15 (88%)
Adjuvant Therapy		
Yes	23 (50%)	7 (41%)
No	23 (50%)	10 (59%)
Interfering substances and states		
Yes	9 (20%)	4 (24%)
No	37 (35%)	13 (76%)
Stage		
Early	30 (65%)	9 (24%)
Late	16 (35%)	8 (76%)

N=63

(Orsi, McCorkle et al., 1996)

In the sample available to this researcher, a descriptive analysis was performed for both depression scores and NK cell levels. Women exhibited higher depression scores as measured by the BDI at all points in time (pre-op, one week post-op, 1 month post-op, and three months post-op), but the results were not statistically significant $F(3,159) = 1.21, p = .303$ (partial $\eta = .022$), and Greenhouse-Geisser = .68. The small effect size and small sample size (21) require that results be interpreted with caution. Individual histograms of the depression scores at each sampling point revealed that the scores were not normally distributed. All were positively skewed, making statistical inferences more difficult. To this end, the Greenhouse-Geisser correction was employed

to make the analysis more robust. A logarithmic transformation was considered, but did not increase the analytic power, and so was discarded.

General estimating equation analysis was used to test for differences between the mean scores for depression and NK cell levels at three points in time across the illness trajectory, and between the two genders (Hanley, Negassa et al., 2003). General estimating equations (GEE) are of particular value when the data to be analyzed consist of longitudinal data, correlated data, in studies with considerable missing data points, or if the data are binary or counts (Hanley, Negassa et al., 2003). The GEE analysis is a regression analysis based on the General Linear Model (GLM), and develops a regression equation for each set of data points to impute missing data. The GEE method assumes that the model being tested is linear, and that any missing data are missing completely at random (Horton & Lipsitz, 1999; Norton, Bieler et al., 1996). General Estimating Equations are a synthesis of Feasible Generalized Least Squares approach and are of particular value in data sets with missing data. General Estimating Equations produce reasonably accurate standard errors, which produces confidence intervals with the correct coverage rates (Hanley, Negassa et al., 2003).

Table 6

Mean BDI Scores by Gender

	PreOp	1 Week	1 Month	3 Months
Male	6.0	7.9	6.5	5.3
Female	7.6	9.2	9.6	6.3

The analysis for time reveals that the largest depression scores on the BDI were reported at one week after surgery, and that depression scores progressively declined from that

peak to a low at three months for men. In women, the highest depression scores on the BDI were reported at one month after surgery, and the lowest at the three month mark. Both men and women reported lower depression scores at three months than preoperatively. No data were available on the mobilization of social and family supports for the participants after the diagnosis, but presumably this did occur. More than three quarters of the sample (77%) were married, and it is reasonable to assume that there was spousal support.

Table 7

Mean NK levels by Gender

	PreOp	1 Week	3 Months
Male	257	261	267
Female	254	251	238

Women in the sample available to this researcher exhibited lower NK cell levels preoperatively, at one week, and lower scores at 3 months than men. Individual histograms of the NK cell levels at each sampling point revealed that the levels were not normally distributed. All were positively skewed, making statistical inferences more difficult. The Greenhouse-Geisser correction was employed to make the analysis more robust. Logarithmic transformation did not increase the power of the analysis, and was not used.

Data Analysis Related to the Research Question

Research Question 1 Are women more likely to report more depressive symptoms than men in adult patients diagnosed with colorectal cancer at four points in time (pre-surgical, 1 week post-surgery, one month post-surgery, and three months post surgery)?

While women did report higher depression scores than men at all points in time, the results were not statistically significant ($B=2.065, p=.151$). Age was also statistically significant ($B=4.180, p=.041$).

Table 8 Beck Depression Scores and Gender:

2 (Group) by 4 (Time) General Estimating Equation and Multi-Level Modeling ($N=117$)

Variables (Range)	Men $\bar{X}$ (SD)	Women $\bar{X}$ (SD)	F Group	p	η^2
Beck Depression Score (0-63)			2.065	.151	.022
Time 1 (n=71)	5.96 (6.39)				
Time 2 (n=60)	7.93 (8.53)				
Time 3 (n=59)	6.54 (7.19)				
Time 4 (n=58)	5.34 (6.49)				
Beck Depression Score (0-63)					
Time 1 (n=46)		7.56 (5.86)			
Time 2 (n=32)		9.19 (6.48)			
Time 3 (n=28)		9.61 (5.86)			
Time 4 (n=32)		6.28 (6.20)			
Age (Men, 25-82)	62.6(12.8)		4.18	.041	
Age (Women,30-87)		62(12.8)			

^c Partial eta squared values are for the interactions only. Effect sizes: Small = .01, Medium = .06, Large = .1

Research Question 2 Do women demonstrate lower NK cell levels in adult patients diagnosed with colorectal cancer at three points in time (pre-surgical, one week post-surgery, and three months post surgery)?

Women did not demonstrate statistically significantly lower NK cell levels than men ($B=.271, p=.603$) using GEE, although at all points in time, men's NK cell levels were higher than women's. Age was not a significant factor in NK cell level differences ($B=3.667, p=.056$).

Table 9 Natural Killer Cell Levels and Gender:
2 (Group) by 3 (Time) General Estimating Equations ($N=117$)

Variables (Range)	Men X (SD)	Women X (SD)	F Group	p	η^2
Natural Killer Cell Levels (42-811)	257 (156)		.239	.625	.014
Time 1 (n=55)	261 (178)				
Time 2 (n=41)	267 (173)				
Time 4 (n=35)					
Natural Killer Cell Levels (42-811)		254 (155)			
Time 1 (n=34)		251 (138)			
Time 2 (n=21)		238 (120)			
Time 4 (n=20)					
Age (Men, 25-82)	62.6 (12.8)		2.977	.084	
Age (Women, 30-78)		62 (12.8)			

^aPartial eta squared values are for the interactions only. Effect sizes: Small = .01, Medium = .06, Large = .15

Summary

This chapter presented the data analysis results for the research questions in three sections. The first section described the sample. Section two discussed the analysis of the effect of sex on depression scores. Section three described the influence of sex on natural killer cell levels. An assessment of effect size was included in sections two and three. There was no statistically significant association between sex and depression scores, and no statistically significant association between sex and NK cell levels. Age was a statistically significant factor in depression scores using the GEE analysis and the multi-level model, but was not significant in either analysis for effects on NK cell levels.

CHAPTER V

SUMMARY, DISCUSSION, IMPLICATIONS, AND CONCLUSION

This chapter includes a summary of the research design and method, discussion of the research findings, implications for nursing practice, education, and research, and the conclusion of the research study.

Summary of the Research Design and Method

The purpose of this was to examine the relationship between gender, depression, and immune system status in individuals undergoing treatment for colorectal cancer at the University of Pennsylvania between 1990 and 1991. The conceptual framework for the study was based on McCorkle's work integrating expectations about outcome of cancer treatment, depression, and immune response in person recovering from surgery for colorectal cancer, and research asserting that women experience more depression than men when diagnosed with cancer. Depression was defined as the participant's score on the Beck Depression Inventory, and immune system status was defined as the participant's natural killer cell level. Depression was assessed at four points in time: preoperatively, one week, one month, and three months post-surgery. Immune system status was assessed at three points in time: preoperatively, one week, and one month post-surgery.

The following research questions were addressed:

1. Are women more likely to report more depressive symptoms than men in adult patients diagnosed with colorectal cancer at four points in time (pre-surgical, 1 week post-surgery, one month post-surgery, and three months post surgery)?
2. Do women demonstrate lower NK cell levels in adult patients diagnosed with colorectal cancer at three points in time (pre-surgical, one week post-surgery, and three months post surgery)?

Data provided by the original researcher, collected between 1990 and 1991, were analyzed using SPSS for Windows. Descriptive statistics were reported by the original researcher, and inferential statistics were used by this researcher to examine the relationships between the study variables of gender, depression, and immune system status. The results of the study did not support a link between gender and depression, or between gender and immune system status. However, the lack of power was a confounding factor. A discussion of the results of the study is presented in the next section of this chapter.

Discussion

Descriptive Characteristics of the Sample and Study Variables

Results for the two research questions on the effects of gender on Depression and the Immune System will be discussed separately due to differing numbers in each sample.

Research Question 1: Are women more likely to report more depressive symptoms than men in adult patients diagnosed with colorectal cancer at four points in time (pre-surgical, 1 week post-surgery, one month post-surgery, and three months post surgery)?

A total of 117 people with colorectal cancer participated in the study, but the drop out rate was high, and contributed to the lack of power. Of the 117, 55 completed the depression score inventories at three points: prior to surgery, one week post-surgery, one month post-surgery, and three months post-surgery. The sample consisted of 34 men (62%) and 21 women (38%). The sample was overwhelmingly Caucasian (90%) and married (77%). The majority of participants (57%) had completed college, and most worked or had worked as either skilled workers (50%) or as professionals (45%). Their ages ranged from 28 years to 88 years, with a mean of 63 years. According to the American Cancer Society(ACS, 2005), the incidence of colorectal cancer is more than 50 times higher in patients aged 60 years to 79 years than in those younger than in those aged less than 40 years old. In these respects, the study participants differ from the American Cancer Society's description of people with colorectal cancer. The sample included only 10% African-Americans, and the number of patients aged 60 years to 79 years with colorectal cancer was seven times greater than those aged less than 40 years. According to data released in 2005, 91% of new cases occur in patients older than 50 years, and the incidence is 35% higher in men than in women (ACS, 2005). Colorectal cancer incidence is approximately 15% higher in African-American men and women than in Caucasian men and women in the general population than in this sample. African-American patients are more likely to be diagnosed with colorectal cancer that has already metastasized than Caucasians, and are less likely to receive chemotherapy and adjuvant therapies than Caucasians (ACS, 2005). No data on chemotherapy and adjuvant therapies stratified by race were available, and the small number of African-American participants makes any conclusions risky. The sample consisted of 61% men and 39% women with

colorectal cancer. The men represent a 56% increase in the incidence of colorectal cancer, in contrast to the ACS statistics, which state that the incidence and mortality of colorectal cancer is more than 35% higher in men than women (ACS, 2005).

Women reported more depressive symptoms than men at every point in time, but the results were not statistically significant using both General Estimating Equations and Multi-level Modeling analyses. The small effect size and small sample size make the results difficult to trust. The lack of power made conclusions about the effect of gender difficult.

Analysis did reveal a significant main effect for age on depression scores. This result has been previously reported (Orsi, McCorkle et al., 1996). The analysis for time reveals that the largest depression scores on the BDI were reported at one week after surgery, and that depression scores progressively declined from that peak to low at three months. Both men and women reported lower depression scores at three months than preoperatively. Some of this change in depression scores can be attributed to the effects of being involved in an altruistic endeavor, the study itself. No data were available on the mobilization of social and family supports for the participants after the diagnosis, but presumably this did occur. More than three quarters of the sample (77%) were married, and it is reasonable to assume that there was spousal support.

There were not significant changes in the number of participants in the Depression Score portion of the study. In all probability, this is due to the nature of the instrument used, the Beck Depression Inventory. The BDI can be self-administered or the data can be collected in an interview. Neither method is particularly intrusive, and

there is no physical pain associated with the test, as is the case for the phlebotomy required to obtain NK cell results.

Research Question 2: Do women demonstrate lower NK cell levels in adult patients diagnosed with colorectal cancer at three points in time (pre-surgical, one week post-surgery, and three months post surgery)?

Women did demonstrate lower NK cell levels than men at all sample times (pre-operative, one week, and three months, but the results were not statistically significant. There was no significant effect for time, ignoring sex. The results were complicated again by the small sample size and the decreasing number of participants over time. The number of participants declined from 60 at the pre-operative sample to 51 at one week, and 45 at three months. Only 16 women were participating by the three month time frame.

The high attrition rate for women was especially troubling, since colorectal cancer strikes almost as many women as breast cancer. Yet data on women are lacking. No data were available from the original researchers regarding the reasons for the women dropping out of the study.

Implications for Nursing

Nursing Education

This study has implications for nursing education, in that little attention continues to be paid to the impact of disease states on women. The majority of the patients in this study were men, and a significant effect was found between time and depression. According to the World Health Organization (WHO), depression represents one of the most burdensome diseases facing the world (WHO, 2002). Depression occurs in up to 20

percent of patients with chronic medical illnesses such as diabetes and heart disease, and presumably, colorectal cancer. Depression is also associated with an approximately 50% increase in medical costs of chronic medical illness (Katon 2003).

Women are at greater risk for late-life depression, coinciding with the most likely years for a diagnosis of colorectal cancer. The prevalence of depression is higher in women across all age groups. Several factors may account for the disproportionate prevalence of depression in older women: greater susceptibility to depression, greater persistence of depression after its onset, and lower mortality (Barry, Allore et al., 2008). Although the gender gap in depression prevalence narrows with increasing age, women remain at higher risk (Kornstein, 1997). Women make up the majority of nurses and nursing students, yet nursing education focuses little to no attention on the psychological and physiological differences between men and women. The women in this admittedly small sample consistently reported more depressive symptoms, and demonstrated lower NK cell levels. While the results were not statistically significant, the potential implications should be considered in teaching. According to literature, women are much more likely to report depression than men, yet women are treated less often and less effectively. Nursing education needs to emphasize the special needs of women in recovering from major surgery such as colorectal surgery, and in the course of coping with a life-threatening disease. Social support may also influence depression and coping differently in women than in men. In 2005, Kristofferzon, Löfmark, and Carlsson, studied 74 women and 97 men diagnosed with myocardial infarction in Sweden. The women used more evasive and supportive coping, and rated psychological aspects of the heart disease as more problematic to manage. More women perceived available support from

friends and grandchildren, and more men perceived available support from their partner (Kristofferzon, Löfmark, & Carlsson, 2005). Manning-Walsh (2005) studied 100 women with breast cancer, and found that social support from friends and family members helped decrease the negative effects of symptoms on quality of life (Manning-Walsh, 2005). Considerable differences exist, moreover, between sources of social support in men and women. Gass, Weitzen, Clark, and Dizon studied 135 women diagnosed with breast cancer, 75% of whom were married or partnered. Asked to name their primary support, emergency contact, and health care proxy, more than 40% of women did not name the same person to these distinct roles. Even for women in relationships, almost 50% did not name their partner to all 3 support roles. (Gass, Weitzen, Clark, et. al., 2007). It would be particularly interesting to study the effects of non-spousal support on coping with cancer in married men and married women. In addition, comparing the sources of support in married and single women with cancer could provide insight into designing support systems for those women facing a diagnosis of cancer.

Nursing Research

This study presents a number of issues for nursing research. Women represent 46% of all patients diagnosed with colorectal cancer, yet this is the only longitudinal study to address the effects of the disease on their state of mind and their immune systems. A great deal of attention was paid to the Couric effect on colorectal cancer screening rates, but little attention has focused on the effects of the treatment course on women. Women have long been known to have an increased risk of depression, but there have been no intervention studies published which focus on how to treat depression in women with colorectal cancer.

The small number of women participating in this study makes additional research imperative. The sample also did not include significant numbers of African-American participants, yet this group has a 15% higher incidence of colorectal cancer, and a 40% higher mortality (ACS, 2005). Additional research on the impact of the disease and its treatment on depression and immune system status in the African-American population must be undertaken.

This study used NK cell levels as a marker of immune system function. It would be helpful to investigate immune system function, such as infection to determine if the NK cell levels are clinically significant.

Summary of recommendations for further study

Additional research is needed in women with colorectal cancer, and in African-Americans with colorectal cancer. Studies to determine the efficacy of interventions to combat depression in women and improve immune system status would be particularly helpful. Additional work is needed to determine if the depression levels and immune system changes are clinically significant.

Conclusion

This secondary analysis examined the influence of sex on depression and immune status in patients with colorectal cancer over a three month period. No significant effects were found, but the study was confounded by the small sample size. A significant main effect for time was found on depression in the entire sample, but not in separate sexes. Additional research is needed to examine the impact of sex on depression and immune status, and to look for clinically significant changes, if any, in this patient population.

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Appendix A

TNM Definitions

	Primary Tumor (T)	Regional Lymph Nodes	Distant Metastasis
Definitions	<p>TX: Primary tumor cannot be assessed</p> <p>T0: No evidence of primary tumor</p> <p>Tis: Carcinoma in situ: intraepithelial or invasion of the lamina propria.</p> <p>T1: Tumor invades submucosa</p> <p>T2: Tumor invades muscularis propria</p> <p>T3: Tumor invades through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissues</p> <p>T4: Tumor directly invades other organs or structures and/or perforates visceral peritoneum</p>	<p>NX: Regional nodes cannot be assessed</p> <p>N0: No regional lymph node metastasis</p> <p>N1: Metastasis in 1 to 3 regional lymph nodes</p> <p>N2: Metastasis in 4 or more regional lymph nodes</p>	<p>MX: Distant metastasis cannot be assessed</p> <p>M0: No distant metastasis</p> <p>M1: Distant metastasis</p>

Colon Cancer and Rectal Cancer TNM Stages

Stage	Tumor/Node/Metastasis	Treatment	Prognosis
0 Cancer <i>in situ</i>	Tis, N0, M0	Local excision or polypectomy	
I Cancer in the mucosa	T1, N0, M0 T2, N0, M0	Open surgical resection and anastomosis	
II A	T3, N0, M0	Open surgical resection with or without anastomosis, chemotherapy, radiation therapy, biologic therapy	
II B	T4, N0, M0	Open surgical resection with or without anastomosis, chemotherapy, radiation therapy, biologic therapy	
III A	T1, N1, M0 T2, N1, M0	Open surgical resection with or without anastomosis, chemotherapy, radiation therapy, biologic therapy	
III B	T3, N1, M0 T4, N1, M0	Open surgical resection with or without anastomosis, chemotherapy, radiation therapy, biologic therapy	
III C	Any T, N2, M0	Open surgical resection with or without anastomosis, chemotherapy,	

		radiation therapy, biologic therapy	
IV	Any T, Any N, M1	Open surgical resection with or without anastomosis, chemotherapy, radiation therapy, biologic therapy	

In the past, colorectal cancer was staged primarily according to the Duke's classification system. The Duke's system sorted tumors into four categories (A, B, C, D) according to the extent of tumor penetration into the colon, surrounding tissue, and distant sites.

Dukes Stages of Colon Cancer

Stage	TNM Classification	Extent of Tumor	Prognosis
A	I	Cancer has spread beyond the innermost lining of the colon and/or rectum to the second and third layers and involves the inside wall of the colon and/or rectum, but it has not spread to the outer wall or outside the colon and/or rectum.	97% 5 year survival
B	II	Cancer has spread outside the colon and/or rectum to nearby tissue, but it has not gone into the lymph nodes	80% 5 year survival; if locally-invasive, dramatically worse prognosis
C	III	Tumor cells have spread to organs and lymph nodes near the colon/rectum	C1: only a few nodes are involved near the primary growth and the proximal nodes are free from metastases, 65% 5 year survival. C2: proximal nodes are involved, 35% 5 year survival
D	IV	Cancer may have spread to nearby lymph nodes and has	less than 5% 5 year

		spread to other parts of the body, such as the liver or lungs.	survival
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