Fat Intake, Diet Quality, Depressive Symptoms, and Cancer

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Masters of Science in
the Graduate School of The Ohio State University

By
Anne Elizabeth Campbell, B.S.
Graduate Program in Allied Medicine

The Ohio State University
2013

Thesis Committee:
Diane L. Habash, PhD, MS, RD, LD, Advisor
Colleen K. Spees, PhD, MEd, RD, LD
Christopher A. Taylor, PhD, RD, LD
Abstract

Fats are important in the body for many physiological functions. Unsaturated fats, specifically omega-3 fatty acids, have been shown to have an anti-inflammatory effect in the body (1). It has been shown that depression promotes chronic inflammation, and that altered omega-3 fatty acid status may be associated with increased stress and mood disorders, such as depression (1). A variety of studies have examined the relationships between diet quality and cancer outcomes (13,22,23,24), cancer and depression (1,4,25,27,28), diets and depression (15,16,17,35) and fat intake and depression (5,6,7,10,11,12). This study examined the relationships between total intake of fat, specifically omega 3 fatty acids, omega 6:3 ratio, and diet quality with depressive symptoms in cancer survivors. We hypothesized that high intakes of omega-3 fatty acids (0.3-3.0 g/day) in the diet are associated with decreased depressive symptoms, and that lower intakes (0-0.3 g/day), with poor diet quality as assessed by Alternative Healthy Eating Index (AHEI) could be associated with increased depressive symptoms. Also, that a high omega 6:3 ratio and high total fats in the diet are associated with increased depressive symptoms. Measurements of depressive symptoms were completed using a standardized, validated tool, Center for Epidemiological Studies – Depression Scale (CES-D) during clinic visits at baseline before any cancer treatment, and at six and 18 months after cancer treatments. Daily dietary intake was collected during six and 18-month clinic visits using a 24-hour recall. Dietary data and CES-D scores were analyzed.
as an average of the two visits for each participant. Participants were split into two groups based on CES-D scores. CES-D scores were grouped as “Low Depressive Symptoms” if the subject had a CES-D score less than 16. The “Depressive Symptoms” group was identified as a CES-D score equal to or greater than 16. There were no relationships found with total fat intake and depression scores, or with omega 6:3 ratios and depression scores among participants. The low depressive symptoms group had higher intakes of omega-3 fatty acids (1.8±1.0 grams/day) when compared to the depressive symptoms group (1.3±0.9 grams/day) though not statistically different among participants. When AHEI was compared with CES-D scores for individual participants, there was a significant inverse relationship (R=−0.378) with CES-D scores (P<0.001). In conclusion, while the cancer survivors in our study portrayed depressive symptoms in dichotomous groups (low depressive versus depressive symptoms), we did not find that specific nutrients were associated with these scores. However when we evaluated overall diet quality using the AHEI, which includes specific components of high total PUFA and low total fat, we found that consumption of a diet with a high AHEI score was associated with low depressive symptoms. Future research to understand the impact of diet in health and disease recovery especially relative to depressive symptoms is warranted.
Dedication

Dedicated to the students at The Ohio State University
Acknowledgments

I would like to thank Dr. Janice Kiecolt-Glaser in correspondence with the THRIVE study. I would also like to thank my advisor, Dr. Diane Habash, my thesis committee, and the rest of the staff from The Clinical Research Center at The Ohio State University for all of your assistance.
Vita

2007………………………………………………St. Clairsville High School

2011…………………………………B.S. Dietetics, The Ohio State University

Fields of Study

Major Field: Allied Medicine
# Table of Contents

Abstract.................................................................ii-iii
Dedication.................................................................iv
Acknowledgements....................................................v
Vita..............................................................................vi
Table of Contents........................................................vii
List of Tables....................................................................viii
List of Figures....................................................................ix
Chapter 1.................................................................1-4
Chapter 2.................................................................5-15
Chapter 3.................................................................16-21
Chapter 4.................................................................22-35
Chapter 5.................................................................36-58
References.................................................................59-63
Appendix A: Center for Epidemiological Studies on Depression Scale (CES-D) ....64
Appendix B: Multiple Pass Approach (MPA)....................................................65
List of Tables

Table 1. Characteristics of Participants ..............................................................................22
Table 2. Depressive Symptom Scores for Total Population at Each Visit .......................24
Table 3. Mean and Standard Deviation of Nutrient Intake and Diet Quality Index for
Total Cancer Survivors and for Cancer Survivors Grouped by Depressive
Symptom Scores ..................................................................................................................26
Table 4. Correlations Between Nutrient Intake and Depressive Symptom Score ..........28
Table 5. Relationships Between Specific Nutrients of Interest, Depressive Symptom
Scores, and the Diet Quality Indicator ................................................................................30
Table 6. Characteristics of Participants ..............................................................................45
Table 7. Depressive Symptom Scores for Total Population at Each Visit .......................47
Table 8. Mean and Standard Deviation of Nutrient Intake and Diet Quality Index for
Total Cancer Survivors and for Cancer Survivors Grouped by Depressive
Symptom Scores ..................................................................................................................49
Table 9. Correlations Between Nutrient Intake and Depressive Symptom Score ..........51
Table 10. Relationships Between Specific Nutrients of Interest, Depressive Symptom
Scores, and the Diet Quality Indicator ..............................................................................63
List of Figures

Figure 1. Baseline Depressive Symptom Scores .................................................................23
Figure 2. Graphic Representation of Trends in Depressive Symptom Scores From All
Participants for All Visits..................................................................................................25
Figure 3. Variability of Mean Omega 6:3 Ratio Among All Participants .......................29
Figure 4. Baseline Depressive Symptom Scores .................................................................46
Figure 5. Graphic Representation of Trends in Depressive Symptom Scores From All
Participants for All Visits..................................................................................................48
Figure 6. Variability of Mean Omega 6:3 Ratio Among All Participants .......................52
Chapter 1: Introduction

Cancer is currently the second leading cause of death among all Americans, (1) and those who survive often face a battle with depression (1). As cancer often decreases one’s overall quality of life, syndromal depression has been shown to have biologic effects on the body by compromising the immune system, leaving the patient more vulnerable to additional health issues (1, 25). Psychosocial stress and depression contribute to a greater risk for infection, prolonged infectious episodes, and delayed wound healing—all processes that can fuel proinflammatory cytokine production (1,2,26,29,30). Stressed individuals often have appetite disturbances that can manifest by eating less often, or eating meals of lower nutritional quality (1, 27). Poor nutrition is associated with a variety of immunological dysfunction, including inefficient cell-mediated immunity, impaired phagocyte function, and decreased mucosal immunity (1,27).

Dietary strategies clearly influence inflammation, as documented through both prospective observational studies as well as randomized, controlled, feeding trials in which participants agree to eat only the food provided to them (2,27). Diets that promote inflammation are often high in refined starches, sugar, saturated and trans fats, and low in omega-3 fatty acids, natural antioxidants, and fiber from fruits, vegetables, and whole grains (28). High levels of omega-3 fatty acids as well as lower omega 6:3 ratios are
associated with lower proinflammatory cytokine production (2,31,32,33,34). The aim of this study is to determine the relationships between depressive symptoms and overall diet quality, omega-3 fatty acid intake, total fat intake, omega 6:3 ratio in the cancer survivor population. We hypothesized that depressive symptoms would be directly related to total fat intake and omega 6:3 ratio, but inversely related to omega-3 intake and to overall healthy diet quality as classified by Alternative Healthy Eating Index (AHEI). In a depressed population, such as cancer patients (4), evidence from this study may advocate a dietary approach in managing depression.
List of Key Terms

**Essential Polyunsaturated Fatty Acids (PUFA)** – Essential for human function, however not made in the human body and must come from dietary sources. (10) Essential PUFAs include linoleic acid (LA: 18:2n6) and linolenic acid (LNA: 18:3n3), which are the precursors of the omega 6 and omega 3 families of fatty acids. (10). Essential fatty acids make up 45% of the fatty acids in synaptic membranes and play an active role in neuronal membrane function. (20)

**Omega 3 Fatty Acids (n-3)** – Essential Polyunsaturated Fatty Acids, which include docosahexaenoic acid and eicosapentaenoic acid. They control the membrane fluidity, enzymatic activities, binding between molecules and receptors, biochemical interactions, and movement of nutrients. (11)

**Docosahexaenoic Acid (DHA)** – An omega-3 fatty acid required for brain function, and accumulates in neuronal membrane phospholipids. (11) Hypothesized to protect against depression, hostility, and aggressiveness. (20)

**Eicosapentaenoic Acid (EPA)** – An omega-3 fatty acid hypothesized to have a specific function in the adrenal cortex, and is the precursor for the complex series of eicosanoids formed via cyclooxygenase and lipooxygenase. (11)

**Major Depressive Disorder (MDD)** – One of the most common forms of depression among cancer patients. (4) Diagnosed using Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria (4), and entail core symptoms including
feelings of unhappiness, loss of energy and interest, fatigue, poor concentration, altered appetite, sleep disturbances, diminished cognitive function, weight gain/loss, anxiety, agitation or irritability, and chronic indecisiveness (5).

**Center for Epidemiologic Study Depression Scale** – Developed and validated by the Center for Epidemiologic Studies, National Institute of Mental Health (NIMH). (18) The CES-D was designed to be a short self-reporting instrument used for measuring depressive symptomology in the general population and clinical patients. (18) The scale ranges from 1-60, and scores ranging from 16-60 have been interpreted to mean high levels of endorsement depressive symptomatology.

**Alternative Healthy Eating Index** – Designed to measure adherence to dietary guidelines for Americans with the specific intention to combat major chronic diseases (35). High scores on this index have been shown to be associated with decreased risk of CVD and type 2 diabetes (35). The AHEI also provides quantitative scoring for qualitative dietary guidance (eg, choose more fish, poultry, and whole grains, and if you drink alcohol, do so in moderation). AHEI variables were chosen and scoring decisions were made a priori, on the basis of discussions with nutrition researchers (35).
Cancer and Depression

Every year, according to the US Census Bureau of Demographics and United States Department of Health and Human Services, depression affects more than 19 million Americans over the age of 18, thereby making it one of the most widespread mental disorders in the United States (3,5,21). The core symptoms of depression include feelings of unhappiness, loss of energy and interest, fatigue, poor concentration, altered appetite, sleep disturbances, diminished cognitive function, weight gain/loss, anxiety, agitation or irritability, and chronic indecisiveness (5). Yet, the exact biological cause of depression remains unclear (5).

To further estimate the prevalence, severity, and co-morbidity of depression, a 12-month household survey study was conducted. (3) The World Health Organization World Mental Health Survey Initiative of the Composite International Diagnostic Interview was used in this survey (3). Out of 9282 respondents 18 and older, this study showed that more than one third of cases were classified as mild depression, and the prevalence of moderate and serious depression cases combined was substantial (14.0% of the population studied) (3).

Rates of major depressive disorder (MDD) and depressive symptoms comorbid with cancer vary, and range between 10-25% according to an evidence-based meta-analysis of more than 350 studies published from 1966-2001, (4). The National Library
of Medicine completed the literature search used in this analysis. An initial search was conducted with the subject headings “neoplasms” combined with “depression,” “depressive disorder,” or “antidepressant agents,” using the search engines of PubMed, PsycInfo, CINAHL, and Biosis. This initial search found more than 3000 abstracts related to depression and cancer (4). A second search limited to citations that contained the term “depression” as a key word search in the title yielded about 1000 articles. Review articles, letters, news, and editorial citations were eliminated (4). Abstracts were screened for relevance according to the three topic areas, and pertinent articles were retrieved. Data from the articles were extracted and summarized (4).

As shown by this literature review, “Depression” in comparison to other symptoms associated with cancer, such as pain or fatigue, is described as a set of symptoms as well as clinical syndromes (4). The most common forms of depression in cancer patients are major depressive disorder (MDD), adjustment disorder, and depression secondary to a medical condition (4). Eleven studies used the diagnostic and statistical manual of mental disorders to diagnose MDD. After evaluation of these studies, the majority of the rates for MDD fell between 10% and 25% of patients, with 25% of studies reporting rates below and 17% reporting rates above this range. One of these studies examined the rate of MDD in long-term head and neck cancer survivors, and this sample had one of the highest rates of depression, at 39.6% (4).

**Depression and fats**

In a meta-analysis of 116 publications, direct measures red blood cell membranes and plasma essential fatty acid composition of depressed patients have supported the hypothesis that omega-3 fatty acids protect against depression (5). Evidence suggests that
an imbalance in the ratio of the essential fatty acids, namely the omega-6 and omega-3 fatty acids, and/or a deficiency in omega-3 fatty acids, may be responsible for the heightened depressive symptoms (5,6,7,10,11,12).

Adams et al. (7) reported a strong inverse relationship between plasma EPA and the severity of the depression. In this cross-sectional study, 20 patients who were moderately to severely depressed as defined by the Hamilton Depression Scale (HRS) were selected from those referred for routine psychiatric treatment who were either inpatients or outpatients of the participating psychiatrists. All patients completed a dietary assessment of lipids over a three-month period using a food frequency questionnaire (From Deakin University Geelong, Australia) in addition to a food diary kept the week prior to the referral. A 10 ml blood sample was also taken from each patient post overnight fast in the beginning of the study to examine erythrocyte plasma lipid (PL) content (7).

There was a significant correlation found between the ratio of erythrocyte plasma lipid arachidonic acid (AA) to eicosapentaenoic acid (EPA) and severity of depression as rated by the HRS (P < 0.05) and the Linear Regression Scale (LRS) for depression (P < 0.01). There was also a significant negative correlation between erythrocyte EPA and the LRS (P < 0.05). The AA/EPA ratio in plasma PL and the ratio of erythrocyte omega 6:3 ratio were also significantly correlated with the LRS (P < 0.05) (7).

The authors concluded their findings by showing a relationship between severity of depression and the plasma and erythrocyte AA/EPA ratio. They suggested these findings provide a basis for studying the effect of nutritional supplementation of
depressed subjects aimed at reducing the AA/EPA ratio in tissues and the severity of depression (7).

Edwards et al (8) demonstrated that total omega-3 fatty acids (EPA and DHA) levels were significantly lower in red blood cell (RBC) membranes of depressed participants when compared with those of the control group and were strongly inversely correlated with the Beck Depression Inventory scores. The aim of this cross-sectional, controlled study was to measure RBC membrane fatty acids in a group of depressed patients relative to a well-matched healthy control group (8).

RBC membrane levels and dietary PUFA intake were measured in 10 patients with MDD (as diagnosed by DSM IV criteria) and 14 matched healthy control subjects. Depression was measured using the Beck Depression Inventory score. Diet was also analyzed and collected using a 7-day weighed intake method (8).

The results of this study showed a significant (P<0.001) depletion of RBC membrane omega-3 fatty acids in the depressed subjects. Severity of depression was negatively correlated with RBC membrane levels and with dietary intake of omega-3 fatty acids. These authors concluded that lower RBC membrane omega-3 fatty acids are associated with the severity of depression, and raise the possibility that depressive symptoms may be alleviated by n-3 PUFA supplementation (8).

Maes et al (9) documented a deficiency of omega-3 fatty acids in cholesterol esters and a compensatory increase in monounsaturated fatty acids (MUFAs) and omega-6 fatty acids in serum phospholipids in depressed patients. The objectives of this study were to examine: (i) serum phospholipid and cholesteryl ester compositions of individual saturated fatty acids (SFAs), monounsaturated FAs (MUFAs) and polyunsaturated FAs
(PUFAs) in major depressed patients vs. healthy volunteers; (ii) the relationships between the above FAs and lowered serum zinc (Zn), a marker of the inflammatory response in depression; and (iii) the effects of subchronic treatment with antidepressants on FAs in depression (9).

In this cross-sectional, controlled study, 34 major depressed inpatients were compared to 14 healthy individuals. Severity of depression was measured by the Hamilton Depression Rating Scale, 17-item version. In patients and healthy volunteers, serum for the assay of serum phospholipids and cholesteryl esters and Zn was sampled after an overnight fast. In both patients and healthy volunteers, blood was collected after an overnight fast (9). The results showed that in patients with major depression, there was a deficiency of omega-3 fatty acids and actually a compensatory increase in MUFAs and PUFAs in phospholipids. Serum Zn was significantly (P<0.0001) lower in major depressed patients than in healthy volunteers. There was no significant effect of antidepressive treatment on any of the FAs (9).

The authors suggest that there is an abnormal metabolism of omega-3 fatty acids in patients with depression, and that FA alterations in depression are related to the inflammatory response in that illness and the disorders may persist despite successful antidepressant treatment. Thus, they suggested that foods or supplements rich in omega-3 fatty acids may reduce the vulnerability to depression (9).

The researchers of the aforementioned studies suggest that the fatty acid alterations seen with depression may be due to an abnormal metabolism of omega-3 fatty acids in depression and/or the inflammatory response of the body (5).
**Essential Fatty Acids**

Essential polyunsaturated fatty acids (PUFAs), linoleic acid (LA: 18:2n6) and linolenic acid (LNA: 18:3n3), are the precursors of the n-6 and n-3 families of fatty acids. Since these essential fatty acids cannot be produced in humans, a dietary source of these fatty acids is necessary (10). The 2010 Dietary Guidelines for Americans outright recommend that monounsaturated and polyunsaturated fats (PUFA) be substituted for saturated fats in diets (2).

Essential fatty acids make up 45% of the fatty acids in synaptic membranes and play an active role in neuronal membrane function (20). In particular, omega-3 fatty acids accumulate in membrane phospholipids primarily as DHA. It is well established that DHA is required for brain function and that the incorporation and selectivity of biomembranes for DHA are extremely efficient (11). It has been argued that DHA, may protect against depression, hostility, and aggressiveness (20). EPA is hypothesized to have a specific function in the adrenal cortex, and is the precursor for the complex series of eicosanoids formed via cyclooxygenase and lipooxygenase (11). The omega-3 fatty acids control the membrane fluidity, enzymatic activities, binding between molecules and receptors, biochemical interactions, and movement of nutrients (12). They are hypothesized to have anti-inflammatory properties within the body (12). In addition, a comprehensive review suggests high levels of omega-3 fatty acids as well as lower omega 6:3 ratios are associated with lower proinflammatory cytokine production (2).
Cancer and Diets

Improved diet and weight management in survivors can prevent cancer recurrence and other co-morbidities (13, 22, 23, 24). Dietary patterns should be considered when designing a health plan for cancer survivors (13). In this study, dietary patterns of urban and rural cancer survivors (n=729) were compared, and associations of dietary patterns with body mass index (BMI) were also examined (13). Dietary intake data were collected during two telephone surveys by 24-hour dietary recalls using the interactive Nutrition Data System for Research software. Nutrition Data System for Research software version 2005 was developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN (13).

This study found three primary dietary patterns among rural dwellers (high sweets and starches, high reduced-fat dairy, cereal, nuts, and fruits, and mixed) and three among urban dwellers (high fruits and vegetables, high meat and refined grains, and high sugar-sweetened beverages) (13). Among rural survivors, greater adherence to the high reduced-fat dairy, cereal, nuts, and fruits pattern was positively associated with lower BMI (P trend <0.05), whereas higher scores on the mixed pattern was associated with greater BMI (P trend <0.05) (13). Greater adherence to the high fruits and vegetables pattern among urban survivors was inversely associated with BMI (P trend <0.05) (13). This study shows that a reduction in total dietary fat consumption has been promoted in cancer prevention, as well as urban and rural differences in dietary intake behavior should be considered in designing public health interventions among the increasing population of older cancer survivors (13).
Alternative Healthy Eating Index (AHEI) and Depression

The Alternative Healthy Eating Index was originally designed to measure adherence to dietary guidelines for Americans with the specific intention to combat major chronic diseases (35). High scores on this index have been shown to be associated with decreased risk of CVD and type 2 diabetes (35). The AHEI incorporates some components correspond to existing dietary guidelines (eg, to increase fruit and vegetable intakes). The AHEI also provides quantitative scoring for qualitative dietary guidance (eg, choose more fish, poultry, and whole grains, and if you drink alcohol, do so in moderation). AHEI variables were chosen and scoring decisions were made a priori, on the basis of discussions with nutrition researchers (35).

In Tasnime 2009, a prospective cohort study was carried out to examine the association between dietary patterns and depression using an overall diet approach. The target population for the Whitehall II study was all London-based office staff, aged 35–55 years with good health status, working in 20 civil service departments. Analysis was done with 3486 participants from the Whitehall II prospective cohort in which two dietary patterns were identified. Factor loadings used in this study represent correlation coefficients between the food groups and the dietary pattern. The first pattern was heavily loaded by high intake of vegetables, fruits and fish, labeled the ‘whole food’ pattern. The second pattern, labeled ‘processed food’, was heavily loaded by high consumption of sweetened desserts, chocolates, fried food, processed meat, pies, refined grains, high-fat dairy products and condiments (15).
According to nutrient profile and culinary use of food items, the 127 items of the FFQ were grouped into 37 predefined food groups by adding food items within each group. Dietary patterns were identified using principal component analysis of these 37 groups. A machine-readable Food Frequency Questionnaire (FFQ), based on the one used in the US Nurses Health Study, was sent to the participants. The food list (127 items) from the original questionnaire was adjusted, and foods commonly eaten in the UK were added (15).

Self-reported depression was assessed 5 years later using the Center for Epidemiologic Studies – Depression (CES–D) scale. Participants scoring more than 15 were categorized as cases of CES–D depression (15).

The authors suggest that consumption of fruits, vegetables and fish affords protection against the onset of depressive symptoms, whereas a diet rich in processed meat, chocolates, sweet desserts, fried food, refined cereals and high-fat dairy products increases vulnerability. These findings suggest that existing healthy eating policies will generate additional benefits to health and well-being, and that diet should be considered as a potential target for the prevention of depressive disorders (15).

A similar study was conducted by Kuczmarski et al in 2010. Participants included 1,118 African American and white adults, aged 30–64 years, living in Baltimore, MD and represented a sub-sample of the initial examination and recruitment phase of the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study (16).

Nutrition data were based on two 24-hour dietary recalls collected by trained interviewers using the United States Department of Agriculture (USDA) Automated Multiple Pass Method (AMPM). Diet quality was calculated using the USDA's Healthy
Eating Index (HEI)-2005. Depressive symptoms were assessed by a trained interviewer using the Center for Epidemiologic Studies Depression (CES-D) scale (16). Both linear and logistic regression analyses were used to examine whether diet quality was associated with depressive symptoms. The dependent variable was depressive symptoms and independent variables included HEI-2005, race, sex, age, education, income, and food assistance program participation. Mean HEI-2005 score (± SEM) was 52.17 ± 0.40 (out of 100). Mean CES-D score was 11.64 ± 0.25 (out of 40). Diet quality was significantly (P<0.0001) associated with reported symptoms of depression (16).

A third study, Sontrop 2008, examined the relationship between depression and fish consumption in relation to omega-3 fatty acid intake in 2394 healthy pregnant women. Women interviewed between 10 and 22 weeks’ gestation in London, Ontario, 2002-05. Intake of fish and EPA+DHA were measured using a 106-item validated food-frequency questionnaire (FFQ). The FFQ was modified to reflect the dietary patterns of the Canadian Nutrient File. Many of the foods included on this FFQ were based on one developed for an American study of pregnant women. Sequential multiple regression was used to examine associations of depressive symptoms with intake of fish and EPA+DHA, respectively, while controlling for sociodemographic, health and lifestyle variables (17).

The mean CES-D score was 9.9 (SD 8.0). Intake of EPA+DHA was dichotomized at the median value of 85 mg/day. Fish consumption and intake of EPA+DHA were not associated with prenatal depressive symptoms after adjustment for confounders; however, depressive symptoms were significantly (P < 0.001) higher for women with lower intakes (<85 mg/day) of EPA+DHA among current smokers and women of
single/separated/divorced marital status. No associations were statistically significant when intake of EPA+DHA was dichotomized at 300 mg/day (17).

**Depression and CES-D**

The CES-D was developed and validated by the Center for Epidemiologic Studies, National Institute of Mental Health (NIMH). The questions of the CES-D scale positively correlated (correlation coefficient=0.71) with the Depressed Mood Subscale of the General Well-Being Scale when used during NHANES 1 (18).

The CES-D was designed to be a short self-reporting instrument useful for measuring depressive symptomology in the general population and clinical patients. It has been tested in household interviews and in psychiatric settings and was found to have very high internal consistency and adequate test-retest repeatability. The validity of the instrument has been established by obtaining other correlations with clinical ratings of depression. This instrument can also detect changes in clinical status over time, which can be extremely valuable when studying how depressive symptomatology changes with physiological well-being (18).

CES-D scores of 16-60 have been interpreted to mean high levels of endorsement depressive symptomatology as they represented the upper quintile of test scores when the instrument was used by the National Institute of Mental Health. The factor structure of the CES-D and its reliability and validity has been found to hold true across a variety of demographic characteristics in samples of the general population tested, as well as those who have endured “life events” such as alcohol problems, social functioning, physical illness, use of medications (19, 18). CES-D is not to be used as a diagnostic tool, but to be used for understanding the correlations of depressive symptoms and associations (19).
Chapter 3: Methods

In this study, 489 participants from the THRIVE: Total Health: Research on Inflammation, Vigor, and Energy Study volunteered to be enrolled. The THRIVE Study had three main objectives. First, the THRIVE study aimed to assess the association between inflammation and fatigue. Second, the study wanted to assess relationships between past or current syndromal depression and/or depressive symptoms with inflammatory markers. Third, the study aimed to appraise the relative impact of health-related behaviors (sleep, pain, physical activity, dietary omega 6:3 fatty acid ratio, central adiposity, and chronic health conditions) as correlates and predictors of syndromal depression and depressive symptoms, inflammatory markers, and fatigue (37). The present study is nested within the THRIVE study, and examined the relationships between fat intake, including total fat, specifically omega-3 fatty acids, omega-6 fatty acids, omega 6:3 ratio and depressive symptoms in cancer survivors enrolled in the THRIVE study after cancer treatments had been completed among participants.

Those who participated in the THRIVE study were breast cancer survivors (Stage I-IIIA), colorectal cancer survivors (Stage I-IIIC), both male and female. Mean age of participants was 58 years of age with a range of 30-89 years of age. Depressive symptoms were measured using the Center for Epidemiological Studies – Depression Scale.
(CES-D) scale where according to the 60-point scale, measurements greater than or equal to 16 indicate clinical depressive symptomatology (18,19). Depressive symptom measurements using the CES-D were obtained at clinic visits at three separate time points, 1) baseline, just after diagnosis, before the patients had any cancer treatment or surgery, 2) at six months post-cancer treatment, and 3) at 18 months post-cancer treatment. During the course of the THRIVE study, at six months and 18 months after cancer treatments were completed, THRIVE study personnel trained by nutrition researchers from the Clinical Research Center used the validated Multiple Pass Approach (MPA) (45) to obtain 24-hour food recalls from the study participants.

Dietary intakes obtained from the MPA were entered into the Nutrition Data Systems for Research (NDSR v. 2009) by trained THRIVE study personnel, which estimates approximately 140 nutrients and food components using underlying nutrient database from NDSR (USDA Ref 24 and FNDDS databases) (36). NDSR software version 2009 was developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN (36). Omega-6 fat intake was determined from NDSR data by subtracting the difference of total omega-3 fatty acids from total PUFA for each visit. The omega 6:3 ratio was determined by dividing the amount of omega-6 fatty acids for each visit by the total intake of omega-3 fatty acids for each visit.

The overall quality of diet was further assessed with the Alternative Healthy Eating Index (AHEI). The AHEI was developed in 2002 and adapted from the original Healthy Eating Index based on the evaluation of compliance of 1992 U.S. Food guide pyramid for Americans and the 1995 Dietary Guidelines for Americans (35). Increased AHEI scores are associated with decreased cardiovascular disease risk and include a diet
pattern that consists of high intakes of fruits and vegetables, nuts and vegetable protein, poultry or fish, whole grains, fiber, low trans fats, and low total fats (35). There are many elements of high AHEI diets that are also associated with decreased levels of inflammation as measured by pro-inflammatory cytokines, such as greater intakes of fish, omega 3 fatty acids, high intakes of fruits and vegetables, fiber, and whole grains (28).

Due to the previous results from literature regarding AHEI and its relationship with inflammation and chronic disease risk, we elected to use this diet quality assessment technique for this study (35).

The original AHEI includes nine components, each of which provide zero to ten points towards the total score. A score of ten in each component indicates that the recommendations were fully met for that component, whereas a score of zero represents recommendations were not fully met. Intermediate intakes were scored proportionately between zero and ten. The AHEI we used was modified for this analysis by omitting the use of a multivitamin and also total fiber was used in place of cereal fiber. This was due to the fact that NDSR does not calculate a value for cereal fiber, and use of a multivitamin was not collected during the 24-hour food recalls. This left eight categories to be scored from zero to ten for a maximum score of eighty. The eight categories included vegetable, fruit, nuts and soy protein intake, ratio of red to white meat, total fiber, trans fat, ratio of PUFA to saturated fat, and alcohol consumption. Criteria for scoring the modified AHEI were as follows: higher scores were given for a greater intake of vegetables (ten points for five or more servings per day; zero points for no servings per day), fruits (ten points for four or more servings per day; zero points for no servings per day), total fiber (ten points for a total of 25 grams per day; zero points for no servings per
day). The ratio of white to red meat was calculated as ten points for a ratio of 4:1; zero points for a ratio of zero. The PUFA to saturated fat ratio was calculated to capture higher intakes of unsaturated oils. Ten points were given for a ratio greater than or equal to one; no points were given for a ratio less than one tenth. A low trans fat intake received higher scores, ten points for less than 0.5% of calories and zero points for greater than or equal to 4% of calories. Moderate alcohol consumption contributed to higher points (ten points for 1 1/2 - 2 1/2 servings per day for men and 1/2 – 1 1/2 for women; zero points for either no consumption or greater than 3 1/2 servings per day for men and greater than 2 1/2 servings per day by women). Since this study was not aimed towards relationships with cardiovascular disease, and also use of alcohol is rarely captured by 24-hour food recalls, AHEI scores were provided both with and without the inclusion of alcohol consumption. In total, the maximum score of eighty would be earned by a score of ten in each of the eight components signifying that all the daily intake recommendations in the AHEI were met. These scoring metrics were programmed into an Excel spreadsheet by the bionutrition staff at the OSU Clinical Research Center. Dietary Data exported from NDSR was then put into this spreadsheet to evaluate participants’ AHEI scores. Each component is calculated based on the foods or nutrients consumed for that category based on NDSR data (44).

We evaluated the relationships between dietary measures (total intake of fat, omega-3 fatty acids, omega-6:3 ratio, diet quality via AHEI scores) and depressive symptom measures (CES-D scores). Carroll et al. demonstrated the gold-standard in dietary assessment measures to be the combination use of four to six 24 hour food recalls and a Food Frequency Questionnaire (38). There were only two separate 24-hour food
recalls collected for each participant, (six and 18 month visits) during the THRIVE study. In order for our dietary data to be more sensitive for collection of participant’s consumption of specific nutrients, we combined the dietary data from both visits and averaged it into one dataset to strengthen the dietary measures of participants’ intakes for the two days. We were not interested in participants’ 24 hour food recall dietary measures at a single point in time as this would not likely accurately capture sporadically consumed nutrients of interest, such as PUFAs (38). Also, literature demonstrating the relationships of specific PUFAs (900 mg DHA + 180 mg EPA) and depressive symptoms show significant relationships starting at 34-46 weeks of consumption (43); therefore, analyzing one day of dietary intake would not have an expected relationship with depressive symptoms. We were also not interested in analyzing how diet may have changed over the two time points, but the overall relationships with depressive symptoms. Head et al. demonstrated the validity of self-administered instruments, including CES-D, to assess psychiatric disorders (41). CES-D measurements were found to measure the presence or absence of depressive symptoms at a given time point with high reliability and validity (19, 41). CES-D scores were averaged from six and 18 month visits into one dataset to compare with the averaged dietary dataset for each participant.

Due to the validity of CES-D detection of depressive symptoms at each time point, CES-D scores were also analyzed separately from each time point to compare how depressive symptoms changed over time post-treatment in no relation to diet data to further describe characteristics of the population at each time point.

Data was analyzed as an average of the two visits. Using bivariate correlation with SPSS Statistics Version 19, IBM SPSS, Chicago, IL, relationships were explored
between dietary intake and CES-D scores from six and 18 month visits among participants. Means and standard deviations were used for descriptive statistics. Variables controlled during the analysis included participant use of omega-3 fatty acid supplements, baseline CES-D scores, and use of anti-depressants. We intended to control for cancer stage and treatment, however the data was incomplete for these variables and was only collected for 46% of the population. Since all dietary measurements were taken post-cancer treatment and little was known about specific type and duration of treatments for each participant, type of cancer treatment was not controlled. The control of other variables included MET exercise levels, age, gender, and BMI were considered but later found to have no effect on the results.

Participants were split into two groups based on their average CES-D scores. Participants were grouped as “Low Depressive Symptoms” if the participant had a CES-D score less than 16. The “Depressive Symptoms” group was identified as a CES-D score greater than or equal to 16.
Chapter 4: Results, Discussion, and Conclusions

Descriptive data for participants is located in Table 1. One hundred fifty seven participants were eligible for this study who attended two clinic visits consecutively and thereby had completed two food recalls. Participant data was excluded from analysis for those participants whose energy consumption was not within 3 standard deviations (95th percentile) of the average energy intake average (a range between 499 and 3900 kilocalories) for the dataset. In total, 10 participants were eliminated and considered outliers, and a total of 147 participants remained. Of these participants, 99 were breast cancer survivors, 48 were colorectal cancer survivors, with 131 females and 16 males. 94 participants were categorized in the “Low Depressive Symptoms” group and 53 in the “Depressive Symptoms” group (Table 1).

<table>
<thead>
<tr>
<th>Breast Cancer Survivor</th>
<th>Colorectal Cancer Survivor</th>
<th>Female</th>
<th>Male</th>
<th>Low Depressive symptoms</th>
<th>Depressive Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>99 participants</td>
<td>48 participants</td>
<td>131 participants</td>
<td>16 participants</td>
<td>94 participants</td>
<td>53 participants</td>
</tr>
</tbody>
</table>

Depressive Symptoms: mean CES-D equal to or greater than 16
Total Sample: N=147, both breast and colorectal cancer survivors.
Low Depressive Symptoms: mean CES-D score less than 16

Table 1: Characteristics of Participants
Depressive symptoms were measured by Center for Epidemiologic Studies – Depression (CES–D) scale. Baseline CES-D Scores were measured prior to cancer treatment. Each bar on this graph represents an individual participant’s CES-D score. Scores are listed in ascending order. CES-D scores equal to or greater than 16 (solid line) indicate presence of depressive symptoms.

Figure 1. Baseline Depressive Symptom Scores

Figure 1 illustrates individual participant depressive symptoms scores assessed with the Center for Epidemiologic Studies – Depression (CES–D) scale at baseline after cancer diagnosis and prior to any cancer treatment. The mean baseline CES-D score for the population was 13.3 ± 11.8. At baseline, 60.5% of the population had a CES-D score less than 16, and 39.5% of the population had a CES-D score equal to or greater than 16.
CES-D scores were measured from baseline to six and 18-month visits post-treatment. Table 2 portrays the percent and frequency of participants’ CES-D scores during each clinic visit. At six months post-cancer treatment, 64.6% of the population had a CES-D score less than 16, and 34.4% of the population had a CES-D score greater than or equal to 16. At 18 months post-cancer treatment, 73.5% of the population had a CES-D score less than 16 and 26.5% of the population had a CES-D score greater than or equal to 16. The mean CES-D score at the six month visit was 13.0±11.6 and the mean CES-D score at 18-months was 11.7±11.65 (Figure 2).

<table>
<thead>
<tr>
<th>CES-D Scores</th>
<th>Participants at Baseline (n=147)</th>
<th>Participants at Six Month Visit (n=145)*</th>
<th>Participants at 18 Month Visit (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percent of population</td>
<td>Frequency</td>
</tr>
<tr>
<td>Low Depressive Symptoms</td>
<td>89</td>
<td>60.5</td>
<td>95</td>
</tr>
<tr>
<td>Depressive Symptoms</td>
<td>58</td>
<td>39.5</td>
<td>50</td>
</tr>
</tbody>
</table>

Baseline depressive symptoms scores were measured by Center for Epidemiologic Studies – Depression (CES–D) scale prior to cancer treatment. CES-D Scores were also completed at six-months post-cancer treatment and at 18-months post-cancer treatment. Participants with Low Depressive Symptoms were characterized by a CES-D score less than 16 and participants with Depressive Symptoms were characterized by a CES-D score equal to or greater than 16. *Two participants did not complete CES-D at the 6-month visit.

Table 2. Depressive Symptom Scores for Total Population at Each Visit
Each bar on this graph represents an individual participants’ depressive symptoms scores as measured by Center for Epidemiologic Studies – Depression (CES-D) scale; participants are listed in ascending order by CES-D scores at baseline represented by blue bars. CES-D scores are overlayed for each subsequent visit for each individual participant

CESdepress.1 = Participant’s CES-D Score at Baseline (blue)
CESdepress.2 = Participant’s CES-D Score at 6-months post-cancer treatment (red)
CESdepress.3 = Participant’s CES-D Score at 18-months post-cancer treatment (green)

Figure 2. Graphic Representation of Trends in Depressive Symptom Scores From All Participants for All Visits
Table 3 provides the average daily intake for nutrients of interest and AHEI for the total population and subgroups of individuals when grouped by their CES-D scores. The average daily intake of total fat for the total population was 71.4 ± 30.8 grams. When separated by depressive symptom scores, the low depressive symptoms group had an average total fat intake of 72± 30.7 grams. For the depressive symptoms group, the average total fat intake was 70.2 ± 31.2 grams.

The average daily intake of omega-3 fatty acids for the population was 1.7±1.0 grams. When the population was separated by depressive symptoms score, the low depressive symptoms group had higher average intakes of omega-3 fatty acids (1.8±1.0 grams).
grams/day) compared to the depressive symptoms group (1.3±0.9 grams/day) but this difference was not statistically significant.

The average omega 6:3 ratio for the population was 8.9±3.0. When the population was separated by depressive symptoms, the low depressive symptoms group had a mean ratio was 9.0±3.6, and the depressive symptoms group had a mean omega 6:3 ratio of 8.8±2.7. As shown in Figure 3, there was a wide range in the variability of omega 6:3 ratios consumed among the population, with a maximum value of 19 and minimum value of 2.

The quality of the dietary intake is shown as an average AHEI score for the population which was 34.5±11.0. When alcohol consumption was not included as a factor in the diet quality score, the overall AHEI for the population was very similar at 33.5 ±10.3. When groups were separated by depressive symptoms, the low depressive symptoms group had a mean AHEI of 37.0±10.8 and the mean for the depressive symptom group was 30.1 ±10.1.
Depressive Symptoms were measured by Center for Epidemiologic Studies – Depression (CES-D) scores. Nutrients were calculated from NDSR nutrient data as an average of two separate 24-hour food recalls at six and 18 month visits for each individual participant. The Correlation Statistics for Baseline CES-D score was measured before cancer treatments for each individual participant. The Correlation Statistics for Average CES-D score was calculated from an average of CES-D scores from six and 18 month visits post cancer treatment for each individual participant. A priori was set at p=0.05.

Table 4 provides data showing the relationships between nutrients of interest and depressive symptoms scores at baseline or as an averaged CES-D score. Although the relationships have negative trends, there were no significant relationships found between individual nutrient intake and depressive symptoms score.
Each data point shown represents an individual participant (n=147). The data point per individual is the average across two days of dietary intake calculated from NDSR nutrient analysis.

Figure 3. Variability of Omega 6:3 Ratio Among All Participants
Table 5 provides the correlation statistics for the relationship between overall diet quality, as assessed with the AHEI, and both the individual nutrients and the depressive symptoms score, assessed by CES-D scores. As expected, since total PUFA's are a component of the AHEI, there are significant relationships (see bolded nutrients and p values). There was a statistically significant (P<0.001) inverse relationship (R=-0.378), between AHEI and CES-D score among individual participants. These relationships remain regardless of whether or not the AHEI included alcohol consumption.
Discussion

Our results suggest a potential inverse association between dietary intake of omega-3 fatty acids and depressive symptoms, though they did not reach statistical significance. Maes et al. (8) evaluated the relationships between serum phospholipid PUFA and depression in a sample of individuals with Major Depressive Disorder (MDD) versus a control group of healthy volunteers. Similarly, Edwards et al. evaluated the relationships between red blood cell membrane PUFA and depression in a sample of depressed patients versus a healthy control group. (9) The measurements of total PUFA in each cell membrane from both studies were completed in order to obtain a measure of dietary consumption and absorption of fatty acids for the individuals in both studies. Both studies specifically found that lower omega-3 fatty acid values measured from corresponding cell membranes were directly associated with the severity of depression. While our study did not evaluate serum phospholipid PUFA or red blood cell PUFA, the results from our study aligned with this relationship by demonstrating an inverse relationship between dietary measures of omega 3 fatty acid intake and depressive symptom scores, though it did not reach statistical significance. Such findings from our study and other literature raise the possibility that depressive symptoms may be alleviated by foods rich in omega-3 fatty acids or omega-3 fatty acid supplementation, however more research is needed in this area (8,9).

McCullough et al. (35) began demonstration that lower AHEI was associated with chronic disease risk, primarily a strong association with cardiovascular disease and type 2 diabetes (35). Our data demonstrated that high AHEI is associated with lower depressive
symptoms, suggesting that the AHEI may not only useful for indication of a heart healthy diet, but also that increasing AHEI is associated with lower depressive symptoms. Kuczmarski et al. (16) evaluated the relationships between diet quality as measured by HEI-2005 and depressive symptoms measured by CES-D for participants in the aging population. Daily dietary intakes were collected by 24-hour food recalls. The HEI-2005 was created in 1995 by the Center for Nutrition Policy and Promotion and consisted of 12 dietary components. This study found that diet quality was significantly associated with reported symptoms of depression as measured by CES-D scores. Tasnime et al. (15) evaluated relationships with depressive symptoms as measured by CES-D and dietary quality in a middle-aged population. Dietary data was determined from FFQ measurements, and quality was determined by grouping participants to either “whole food” category (high in consumption of fruits, vegetables and fish) or “processed food” category (high in processed meat, chocolates, sweet desserts, fried food, refined cereals and high-fat dairy products) based on their FFQ data. This study found that diets high in consumption of fruits, vegetables and fish affords protection against the onset of depressive symptoms, whereas a diet rich in processed meat, chocolates, sweet desserts, fried food, refined cereals and high-fat dairy products increases vulnerability towards depressive symptoms as measured by CES-D scores (15). We did not find any significant relationships with individual specific nutrients (i.e. omega 3 fatty acids, omega 6:3 ratio, or total fat) and depressive symptoms. However, we elected to use AHEI to evaluate diet quality, an index that scored diet quality from 24-hour food recall data based on a combination of eight different dietary components and their associations with chronic disease risk. When the AHEI for each participant was compared with reported depressive
symptoms as measured by CES-D, significant inverse relationships were found among all participants, indicating that better diet quality is associated with lower depressive symptoms. Such findings align with results from previous literature, and suggest that existing healthy eating guidelines as measured by the AHEI may generate additional benefits to health and well-being, such as the prevention or treatment of depressive disorders (15, 16).

As our sample was made up primarily of females with a history of breast cancer, our study also supported other findings in literature regarding depression upon breast cancer survivorship. One cohort study of 222 women with breast cancer found that nearly 50% of the women with early breast cancer had depression, anxiety, or both in the year after diagnosis, 25% in the second, third, and fourth years, and 15% in the fifth year (42). Interestingly, clinical factors were not associated with depression and anxiety, at any time (42). Our study was aligned with these findings by demonstrating a decrease in depressive symptoms for the total population studied upon cancer diagnosis as evidenced by CES-D scores over each visit from baseline, six months, and 18-months, regardless of dietary measures. CES-D scores began with 39.5% of the population having depressive symptoms as measured by the CES-D at baseline. At six months post cancer treatment, the percentage of the population decreased to 34.4% having depressive symptoms as measured by CES-D, and at 18-months post cancer treatment, the incidence further decreased to 26.5% of the population having depressive symptoms.

Limitations of this study included the use of 24-hour food recalls at only two separate time points and without combination use of a food frequency questionnaire. Carroll et al. (38) reviewed the precision, power, and sample size for various dietary
collection instruments. This study found that the gold standard for dietary collection techniques is administration of four to six 24-hour food recalls to optimally capture most nutrients and food groups, and that a combined use of a food frequency questionnaire (FFQ) with a 24-hour recall was superior to use of either method alone, especially to capture foods that are not regularly consumed (38). The number of repeat administrations of 24-hour food recalls needed to capture intake of sporadically consumed foods or nutrients (i.e., those that are not consumed every day by most people, such as omega-3 fatty acids which were of interest in this study) may be impractical due to the respondent burden and cost. The FFQ, despite its imprecision and cognitive difficulty, has the strength of querying about long-term intake, thereby aiming to obtain data on usual intake with a single administration (38). Our study intended to accurately capture intakes of fats and other sporadically consumed nutrients, specifically PUFAs. According to Carroll et al. (38) and Freedman et al. (40), these specific nutrients could have been better obtained with a combination use of a FFQ during each visit of dietary intake collection in addition to at least two more 24-hour food recalls during the course of the THRIVE study to achieve the gold standard for dietary collection (38,40).

Although the use of an omega-3 fatty acid supplement was controlled in this analysis, the quantity and source of omega-3 fatty acids in the supplements was not obtained by the THRIVE research team. The quantity of omega-3 fatty acids from supplements could possibly have had an effect on participants’ depressive symptoms. This warrants future research that evaluates both the source and quantity of omega-3 fatty acid intake, as well as their resulting blood values of omega-3 fatty acids for more quantifiable results.
The sample of participants enrolled in this study who had attended both consecutive clinic visits where dietary intakes were collected by 24-hour food recalls also provided some limitations. The exclusion of participants who had not gone to the two clinic visits of interest during the THRIVE study left a remaining sample for our study that was unevenly distributed between males and females, and also between breast and colorectal cancers, in which females with a history of breast cancer dominated the sample. Since controlling for gender or cancer type did not change results for the hypotheses being tested, the sample accounted for both genders.

Conclusions

We hypothesized that high intakes of omega-3 fatty acids (0.3-3.0 g/day) with healthy diet quality is associated with decreased depressive symptoms, and that low intakes of omega 3 fatty acids (<0.3 g/day), with poor diet quality including consumption of a high omega 6:3 ratio and total fat is associated with increased depressive symptoms. We found evidence that healthy diets as evidenced by AHEI are associated with low depressive symptoms. Our study is unique in expanding the focus from associations with single nutrients to overall diet quality measured from a combination of nutrients. In conclusion, while the cancer survivors in our study portrayed depressive symptoms in dichotomous groups (low depressive versus depressive symptoms), we did not find that specific nutrients were associated with depressive symptoms. However, when we evaluated overall diet quality using the AHEI, which includes specific components of high total PUFA and low total fat, we found that consumption a diet with a high AHEI score was associated with low depressive symptoms. Future research to understand the impact of diet in health and recovery of depressive symptoms is warranted.
Chapter 5: Manuscript

Abstract

Fats are important in the body for many physiological functions. Unsaturated fats, specifically omega-3 fatty acids, have been shown to have an anti-inflammatory effect in the body (1). It has been shown that depression promotes chronic inflammation, and that altered omega-3 fatty acid status may be associated with increased stress and mood disorders, such as depression (1). A variety of studies have examined the relationships between diet quality and cancer outcomes (13,22,23,24), cancer and depression (1,4,25,27,28), diets and depression (15,16,17,35) and fat intake and depression (5,6,7,10,11,12). This study examined the relationship between total intake of fat, specifically omega 3 fatty acids, omega 6:3 ratio, and diet quality with depressive symptoms in cancer survivors. We hypothesized that high intakes of omega-3 fatty acids (0.3-3.0 g/day) in the diet are associated with decreased depressive symptoms, and that lower intakes (0-0.3 g/day), with poor diet quality as assessed by Alternative Healthy Eating Index (AHEI) could be associated with increased depressive symptoms. Also, that a high omega 6:3 ratio and high total fats in the diet are associated with increased depressive symptoms. Measurements of depressive symptoms were completed using a standardized, validated tool, Center for Epidemiological Studies – Depression Scale (CES-D) during clinic visits at baseline before any cancer treatment, and at six and 18 months after cancer treatments. Daily dietary intake was collected during six and 18-
month clinic visits using a 24-hour recall. Dietary data and CES-D scores were analyzed as an average of the two visits for each participant. Participants were split into two groups based on CES-D scores. CES-D scores were grouped as “Low Depressive Symptoms” if the subject had a CES-D score less than 16. The “Depressive Symptoms” group was identified as a CES-D score equal to or greater than 16. There were no relationships found with total fat intake and depression scores, or with omega 6:3 ratios and depression scores among participants. The low depressive symptoms group had higher intakes of omega-3 fatty acids (1.8±1.0 grams/day) when compared to the depressive symptoms group (1.3±0.9 grams/day) though not statistically different among participants. When AHEI was compared with CES-D scores for individual participants, there was a significant inverse relationship (R=−0.378) with CES-D scores (P<0.001). In conclusion, while the cancer survivors in our study portrayed depressive symptoms in dichotomous groups (low depressive versus depressive symptoms), we did not find that specific fat-related nutrients were associated with these scores. However when we evaluated overall diet quality using the AHEI, which includes specific components of high total PUFA and low total fat, we found that consumption of a diet with a high AHEI score was associated with low depressive symptoms. Future research to understand the impact of diet in health and disease recovery especially relative to depressive symptoms is warranted.
Introduction

Cancer is currently the second leading cause of death among all Americans, (1) and those who survive often face a battle with depression (1). As cancer often decreases one’s overall quality of life, syndromal depression has been shown to have biologic effects on the body by compromising the immune system, leaving the patient more vulnerable to additional health issues (1, 25). Psychosocial stress and depression contribute to a greater risk for infection, prolonged infectious episodes, and delayed wound healing—all processes that can fuel proinflammatory cytokine production (1,2,26,29,30). Stressed individuals often have appetite disturbances that can manifest by eating less often, or eating meals of lower nutritional quality (1,27). Poor nutrition is associated with a variety of immunological dysfunction, including inefficient cell-mediated immunity, impaired phagocyte function, and decreased mucosal immunity (1,27).

Dietary strategies clearly influence inflammation, as documented through both prospective observational studies as well as randomized, controlled, feeding trials in which participants agree to eat only the food provided to them (2,27). Diets that promote inflammation are often high in refined starches, sugar, saturated and transfats, and low in omega-3 fatty acids, natural antioxidants, and fiber from fruits, vegetables, and whole grains (28). High levels of omega-3 fatty acids as well as lower omega 6:3 ratios are associated with lower proinflammatory cytokine production (2,31,32,33,34). The aim of this study is to determine the relationships between depressive symptoms and overall diet quality, omega-3 fatty acid intake, total fat intake, omega 6:3 ratio in the cancer survivor
population. We hypothesized that depressive symptoms would be directly related to total fat intake and omega 6:3 ratio, but inversely related to omega-3 intake and to overall healthy diet quality as classified by Alternative Healthy Eating Index (AHEI). In a depressed population, such as cancer patients (4), evidence from this study may advocate a dietary approach in managing depression.

Methods

In this study, 489 participants from the THRIVE: Total Health: Research on Inflammation, Vigor, and Energy Study volunteered to be enrolled. The THRIVE Study had three main objectives. First, the THRIVE study aimed to assess the association between inflammation and fatigue. Second, the study wanted to assess relationships between past or current syndromal depression and/or depressive symptoms with inflammatory markers. Third, the study aimed to appraise the relative impact of health-related behaviors (sleep, pain, physical activity, dietary omega 6:3 fatty acid ratio, central adiposity, and chronic health conditions) as correlates and predictors of syndromal depression and depressive symptoms, inflammatory markers, and fatigue (37). The present study is nested within the THRIVE study, and examined the relationships between fat intake, including total fat, specifically omega-3 fatty acids, omega-6 fatty acids, omega 6:3 ratio and depressive symptoms in cancer survivors enrolled in the THRIVE study after cancer treatments had been completed among participants.

Those who participated in the THRIVE study were breast cancer survivors (Stage I-IIIA), colorectal cancer survivors (Stage I-IIIC), both male and female. Mean age of participants was 58 years of age with a range of 30-89 years of age. Depressive symptoms were measured using the Center for Epidemiological Studies – Depression
(CES-D) scale where according to the 60-point scale, measurements greater than or equal to 16 indicate clinical depressive symptomatology \((18,19)\). Depressive symptom measurements using the CES-D were obtained at clinic visits at three separate time points, 1) baseline, just after diagnosis, before the patients had any cancer treatment or surgery, 2) at six months post-cancer treatment, and 3) at 18 months post-cancer treatment. During the course of the THRIVE study, at six months and 18 months after cancer treatments were completed, THRIVE study personnel trained by nutrition researchers from the Clinical Research Center used the validated Multiple Pass Approach (MPA) \((45)\) to obtain 24-hour food recalls from the study participants.

Dietary intakes obtained from the MPA were entered into the Nutrition Data Systems for Research (NDSR v. 2009) by trained THRIVE study personnel, which estimates approximately 160 nutrients and food components using underlying nutrient database from NDSR (USDA Ref 24 and FNDDS databases) \((36)\). NDSR software version 2009 was developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN \((36)\). Omega-6 fat intake was determined from NDSR data by subtracting the difference of total omega-3 fatty acids from total PUFA for each visit. The omega 6:3 ratio was determined by dividing the amount of omega-6 fatty acids for each visit by the total intake of omega-3 fatty acids for each visit.

The overall quality of diet was further assessed with the Alternative Healthy Eating Index (AHEI). The AHEI was developed in 2002 and adapted from the original Healthy Eating Index based on the evaluation of compliance of 1992 U.S. Food guide pyramid for Americans and the 1995 Dietary Guidelines for Americans \((35)\). Increased AHEI scores are associated with decreased cardiovascular disease risk and include a diet
pattern that consists of high intakes of fruits and vegetables, nuts and vegetable protein, poultry or fish, whole grains, fiber, low trans fats, and low total fats (35). There are many elements of high AHEI diets that are also associated with decreased levels of inflammation as measured by pro-inflammatory cytokines, such as greater intakes of fish, omega 3 fatty acids, high intakes of fruits and vegetables, fiber, and whole grains (28). Due to the previous results from literature regarding AHEI and its relationship with inflammation and chronic disease risk, we elected to use this diet quality assessment technique for this study (35).

The original AHEI includes nine components, each of which provide zero to ten points towards the total score. A score of ten in each component indicates that the recommendations were fully met for that component, whereas a score of zero represents recommendations were not fully met. Intermediate intakes were scored proportionately between zero and ten. The AHEI we used was modified for this analysis by omitting the use of a multivitamin and also total fiber was used in place of cereal fiber. This was due to the fact that NDSR does not calculate a value for cereal fiber, and use of a multivitamin was not collected during the 24-hour food recalls. This left eight categories to be scored from zero to ten for a maximum score of eighty. The eight categories included vegetable, fruit, nuts and soy protein intake, ratio of red to white meat, total fiber, trans fat, ratio of PUFA to saturated fat, and alcohol consumption. Criteria for scoring the modified AHEI were as follows: higher scores were given for a greater intake of vegetables (ten points for five or more servings per day; zero points for no servings per day), fruits (ten points for four or more servings per day; zero points for no servings per day), total fiber (ten points for a total of 25 grams per day; zero points for no servings per
day). The ratio of white to red meat was calculated as ten points for a ratio of 4:1; zero points for a ratio of zero. The PUFA to saturated fat ratio was calculated to capture higher intakes of unsaturated oils. Ten points were given for a ratio greater than or equal to one; no points were given for a ratio less than one tenth. A low trans fat intake received higher scores, ten points for less than 0.5% of calories and zero points for greater than or equal to 4% of calories. Moderate alcohol consumption contributed to higher points (ten points for 1 ½ - 2 ½ servings per day for men and 1/2 – 1 ½ for women; zero points for either no consumption or greater than 3 ½ servings per day for men and greater than 2 ½ servings per day by women). Since this study was not aimed towards relationships with cardiovascular disease, and also use of alcohol is rarely captured by 24-hour food recalls, AHEI scores were provided both with and without the inclusion of alcohol consumption. In total, the maximum score of eighty would be earned by a score of ten in each of the eight components signifying that all the daily intake recommendations in the study were met. These scoring metrics were programmed into an Excel spreadsheet by the bionutrition staff at the OSU Clinical Research Center. Dietary Data exported from NDSR was then put into this spreadsheet to evaluate participants’ AHEI scores. Each component is calculated based on the foods or nutrients consumed for that category based on NDSR data (44).

We evaluated the relationships between dietary measures (total intake of fat, omega-3 fatty acids, omega-6:3 ratio, diet quality via AHEI scores) and depressive symptom measures (CES-D scores). Carroll et al. demonstrated the gold-standard in dietary assessment measures to be the combination use of four to six 24-hour food recalls and a Food Frequency Questionnaire (38). There were only two separate 24-hour food
recalls collected for each participant, (six and 18 month visits) during the THRIVE study. In order for our dietary data to be more sensitive for collection of participant’s consumption of specific nutrients, we combined the dietary data from both visits and averaged it into one dataset to strengthen the dietary measures of participants’ intakes for the two days. We were not interested in participants’ 24 hour food recall dietary measures at a single point in time as this would not likely accurately capture sporadically consumed nutrients of interest, such as PUFAs (38). Also, literature demonstrating the relationships of specific PUFAs (900 mg DHA + 180 mg EPA) and depressive symptoms show significant relationships starting at 34-46 weeks of consumption (43); therefore, analyzing one day of dietary intake would not have an expected relationship with depressive symptoms. We were also not interested in analyzing how diet may have changed over the two time points, but the overall relationships with depressive symptoms. Head et al. demonstrated the validity of self-administered instruments, including CES-D, to assess psychiatric disorders (41). CES-D measurements were found to measure the presence or absence of depressive symptoms at a given time point with high reliability and validity (19, 41). CES-D scores were averaged from six and 18 month visits into one dataset to compare with the averaged dietary dataset for each participant. Due to the validity of CES-D detection of depressive symptoms at each time point, CES-D scores were also analyzed separately from each time point to compare how depressive symptoms changed over time post-treatment in no relation to diet data to further describe characteristics of the population.

Data was analyzed as an average of the two visits. Using bivariate correlation with SPSS Statistics Version 19, IBM SPSS, Chicago, IL, relationships were explored
between dietary intake and CES-D scores from six and 18 month visits among participants. Means and standard deviations were used for descriptive statistics. Variables controlled during the analysis included participant use of omega-3 fatty acid supplements, baseline CES-D scores, and use of anti-depressants. We intended to control for cancer stage and treatment, however the data was incomplete for these variables and was only collected for 46% of the population. Since all dietary measurements were taken post-cancer treatment and little was known about specific type and duration of treatments for each participant, type of cancer treatment was not controlled. The control of other variables included MET exercise levels, age, gender, and BMI were considered but later found to have no effect on the results.

Participants were split into two groups based on CES-D scores. CES-D scores were grouped as “Low Depressive Symptoms” if the participant had a CES-D score less than 16. The “Depressive Symptoms” group was identified as a CES-D score greater than or equal to 16.

Results

Descriptive data for participants is located in Table 6. One hundred fifty seven participants were eligible for this study who attended two clinic visits consecutively and thereby had completed two food recalls. Participant data was excluded from analysis for those participants whose energy consumption was not within 3 standard deviations (95th percentile) of the average energy intake average (a range between 499 and 3900 kilocalories) for the dataset. In total, 10 participants were eliminated and considered outliers, and a total of 147 participants remained. Of these participants, 99 were breast cancer survivors, 48 were colorectal cancer survivors, with 131 females and 16 males. 94
participants were categorized in the “Low Depressive Symptoms” group and 53 in the “Depressive Symptoms” group (Table 6).

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer Survivor</th>
<th>Colorectal Cancer Survivor</th>
<th>Female</th>
<th>Male</th>
<th>Low Depressive symptoms</th>
<th>Depressive Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer Survivor</td>
<td>99 participants</td>
<td>48 participants</td>
<td>131 participants</td>
<td>16 participants</td>
<td>94 participants</td>
<td>53 participants</td>
</tr>
<tr>
<td>Colorectal Cancer Survivor</td>
<td>131 participants</td>
<td>16 participants</td>
<td>94 participants</td>
<td>53 participants</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total Sample: N=147, both breast and colorectal cancer survivors. Low Depressive Symptoms: mean CES-D score less than 16 Depressive Symptoms: mean CES-D equal to or greater than 16

Table 6: Characteristics of Participants
Depressive symptoms were measured by Center for Epidemiologic Studies – Depression (CES–D) scale. Baseline CES-D Scores were measured prior to cancer treatment. Each bar on this graph represents an individual participant’s CES-D score. Scores are listed in ascending order. CES-D scores equal to or greater than 16 (solid line) indicate presence of depressive symptoms.

Figure 4. Baseline Depressive Symptom Scores

Figure 4 illustrates individual participant depressive symptoms scores assessed with the Center for Epidemiologic Studies – Depression (CES–D) scale at baseline after cancer diagnosis and prior to any cancer treatment. The mean baseline CES-D score for the population was $13.3 \pm 11.8$. At baseline, 60.5% of the population had a CES-D score less than 16, and 39.5% of the population had a CES-D score equal to or greater than 16.
CES-D scores were measured from baseline to six and 18-month visits post-treatment. Table 2 portrays the percent and frequency of participants’ CES-D scores during each clinic visit. At six months post-cancer treatment, 64.6% of the population had a CES-D score less than 16, and 34.4% of the population had a CES-D score greater than or equal to 16. At 18 months post-cancer treatment, 73.5% of the population had a CES-D score less than 16 and 26.5% of the population had a CES-D score greater than or equal to 16. The mean CES-D score at the six month visit was 13.0±11.6 and the mean CES-D score at 18-months was 11.7±11.65 (Figure 5).

<table>
<thead>
<tr>
<th>CES-D Scores</th>
<th>Participants at Baseline (n=147)</th>
<th>Participants at Six Month Visit (n=145)*</th>
<th>Participants at 18 Month Visit (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Percent of population</td>
<td>Frequency</td>
</tr>
<tr>
<td>Low Depressive Symptoms</td>
<td>89</td>
<td>60.5</td>
<td>95</td>
</tr>
<tr>
<td>Depressive Symptoms</td>
<td>58</td>
<td>39.5</td>
<td>50</td>
</tr>
</tbody>
</table>

Baseline depressive symptoms scores were measured by Center for Epidemiologic Studies – Depression (CES–D) scale prior to cancer treatment. CES-D Scores were also completed at six-months post-cancer treatment and at 18-months post-cancer treatment. Participants with Low Depressive Symptoms were characterized by a CES-D score less than 16 and participants with Depressive Symptoms were characterized by a CES-D score equal to or greater than 16. *Two participants did not complete CES-D at the 6-month visit.

Table 7. Depressive Symptom Scores for Total Population at Each Visit
Each bar on this graph represents an individual participants’ depressive symptoms scores as measured by Center for Epidemiologic Studies – Depression (CES–D) scale; participants are listed in ascending order by CES-D scores at baseline represented by blue bars. CES-D scores are overlayed for each subsequent visit for each individual participant.

- CESdepress.1= Participant’s CES-D Score at Baseline (blue)
- CESdepress.2= Participant’s CES-D Score at 6-months post-cancer treatment (red)
- CESdepress.3= Participant’s CES-D Score at 18-months post-cancer treatment (green)

Figure 5. Graphic Representation of Trends in Depressive Symptom Scores From All Participants for All Visits
## Nutrients and Index of Diet Quality

<table>
<thead>
<tr>
<th>Nutrients and Index of Diet Quality</th>
<th>Total Population (N=147)</th>
<th>Low Depressive Symptoms* (N=94)</th>
<th>Depressive Symptoms** (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Total Fat (g)</td>
<td>71.4</td>
<td>30.8</td>
<td>72.0</td>
</tr>
<tr>
<td>Omega-3 Fatty Acids (g)</td>
<td>1.7</td>
<td>1.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Omega 6 Fatty Acids (g)</td>
<td>14.0</td>
<td>7.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Omega 6:3 ratio</td>
<td>8.9</td>
<td>3.3</td>
<td>9.0</td>
</tr>
<tr>
<td>AHEI</td>
<td>34.5</td>
<td>11.0</td>
<td>37.0</td>
</tr>
<tr>
<td>AHEI without Alcohol included</td>
<td>33.5</td>
<td>10.3</td>
<td>35.7</td>
</tr>
</tbody>
</table>

Depressive Symptoms were measured by Center for Epidemiologic Studies–Depression (CES–D) scores. Average Nutrients were calculated as a mean from NDSR nutrient data output from two separate 24-hour food recalls for each participant. Diet quality was assessed with the Alternative Healthy Eating Index (AHEI); best possible score = 80.

*Low depressive symptoms group was classified as an average CES-D Score less than 16 from six and 18 month clinic visits.

**Depressive symptoms group was classified as an average CES-D score equal to or greater than 16 from six and 18 month clinic visits.

Table 8 provides the average daily intake for nutrients of interest for the total population and subgroups of individuals when grouped by their CES-D scores. The average daily intake of total fat for the total population was $71.4 \pm 30.8$ grams. When separated by depressive symptom scores, the low depressive symptoms group had an average total fat intake of $72.0 \pm 30.7$ grams. For the depressive symptoms group, the average total fat intake was $70.2 \pm 31.2$ grams.

The average daily intake of omega-3 fatty acids for the population was $1.7 \pm 1.0$ grams. When the population was separated by depressive symptoms score, the low depressive symptoms group had higher average intakes of omega-3 fatty acids ($1.8 \pm 1.0$ grams/day) compared to the depressive symptoms group ($1.3 \pm 0.9$ grams/day) but this difference was not statistically significant.
The average omega 6:3 ratio for the population was 8.9±3.0. When the population was separated by depressive symptoms, the low depressive symptoms group had a mean ratio was 9.0±3.6, and the depressive symptoms group had a mean omega 6:3 ratio of 8.8±2.7. As shown in Figure 3, there was a wide range in the variability of omega 6:3 ratios consumed among the population, with a maximum value of 19 and minimum value of 2.

The quality of the dietary intake is shown as an average AHEI score for the population which was 34.5±11.0. When alcohol consumption was not included as a factor in the diet quality score, the overall AHEI for the population was very similar at 33.5 ±10.3. When groups were separated by depressive symptoms, the low depressive symptoms group had a mean AHEI of 37.0±10.8 and the mean for the depressive symptom group was 30.1 ±10.1.
Table 9. Correlations Between Nutrient Intake and Depressive Symptom Scores

Table 9 provides data showing the relationships between nutrients of interest and depressive symptoms scores at baseline or as an averaged CES-D score. Although the relationships have negative trends, there were no significant relationships found between individual nutrient intake and depressive symptoms score.
Each data point shown represents an individual participant (n=147). The data point per individual is the average across two days of dietary intake calculated from NDSR nutrient analysis.

Figure 6. Variability of Omega 6:3 Ratio Among All Participants
<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation Statistics for AHEI Score</th>
<th>Correlation Statistics for AHEI Score Without Alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
</tr>
<tr>
<td>CES-D score</td>
<td>-0.378</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total Fat (g)</td>
<td>0.093</td>
<td>0.261</td>
</tr>
<tr>
<td>Total PUFA (g)</td>
<td>0.314</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Omega-3 Fatty Acids (g)</td>
<td>0.326</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Omega-6 Fatty Acids (g)</td>
<td>0.304</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Omega 6:3 ratio</td>
<td>-0.015</td>
<td>0.853</td>
</tr>
</tbody>
</table>

A Priori was set at 0.05. Significant relationships are displayed in bold. Diet quality was assessed with the Alternative Healthy Eating Index (AHEI); best possible score = 80. Depressive Symptoms were measured by Center for Epidemiologic Studies – Depression (CES–D) scores. CES-D score was calculated as an average of six and 18 month visits post cancer treatment for each individual participant. Dietary data were calculated from NDSR nutrient data as an average from two separate 24-hour food recalls at six and 18 month visits for each participant. Correlation Statistics for AHEI Scores were calculated for each participant based on an average of their AHEI scoring from six and 18-month visits.

Table 10. Relationships Between Specific Nutrients of Interest, Depressive Symptom Scores, and the Diet Quality Indicator

Table 10 provides the correlation statistics for the relationship between overall diet quality, as assessed with the AHEI, and both the individual nutrients and the depressive symptoms score, assessed by CES-D scores. As expected, since total PUFAs are a component of the AHEI, there are significant relationships (see bolded nutrients and p values). There was a statistically significant (P<0.001) inverse relationship (R=-0.378), between AHEI and CES-D score among individual participants. These relationships remain regardless of whether or not the AHEI included alcohol consumption.
Discussion

Our results suggest a potential inverse association between dietary intake of omega-3 fatty acids and depressive symptoms, though they did not reach statistical significance. Maes et al. (8) evaluated the relationships between serum phospholipid PUFA and depression in a sample of majorly depressed individuals versus a control group of healthy volunteers. Similarly, Edwards et al. evaluated the relationships between red blood cell membrane PUFA and depression in a sample of depressed patients versus a healthy control group. (9) The measurements of total PUFA in each cell membrane from both studies were completed in order to obtain a measure of dietary consumption and absorption of fatty acids for the individuals in the study. Both studies specifically found that lower omega-3 fatty acid values measured from corresponding cell membranes were directly associated with the severity of depression. While our study did not evaluate serum phospholipid PUFA or red blood cell PUFA, the results from our study aligned with this relationship by demonstrating an inverse relationship between dietary measures of omega 3 fatty acid intake and depressive symptom scores, though it did not reach statistical significance. Such findings from our study and other literature raise the possibility that depressive symptoms may be alleviated by foods rich in omega-3 fatty acids or omega-3 fatty acid supplementation, however more research is needed in this area (8,9).

McCullough et al. (35) began demonstration that lower AHEI was associated with chronic disease risk, primarily a strong association with cardiovascular disease and type 2 diabetes (35). Our data demonstrated that high AHEI is associated with lower depressive
symptoms, suggesting that the AHEI may not only useful for indication of a heart healthy diet, but also that increasing AHEI is associated with lower depressive symptoms. Kuczmarski et al. (16) evaluated the relationships between diet quality as measured by HEI-2005 and depressive symptoms measured by CES-D for participants in the aging population. Daily dietary intakes were collected by 24-hour food recalls. The HEI-2005 was created in 1995 by the Center for Nutrition Policy and Promotion and consisted of 12 dietary components. This study found that diet quality was significantly associated with reported symptoms of depression as measured by CES-D scores. Tasnime et al. (15) evaluated relationships with depressive symptoms as measured by CES-D and dietary quality in a middle-aged population. Dietary data was determined from FFQ measurements, and quality was determined by grouping participants to either “whole food” category (high in consumption of fruits, vegetables and fish) or “processed food” category (high in processed meat, chocolates, sweet desserts, fried food, refined cereals and high-fat dairy products) based on their FFQ data. This study found that diets high in consumption of fruits, vegetables and fish affords protection against the onset of depressive symptoms, whereas a diet rich in processed meat, chocolates, sweet desserts, fried food, refined cereals and high-fat dairy products increases vulnerability towards depressive symptoms as measured by CES-D scores (15). We did not find any significant relationships with individual specific nutrients (i.e. omega 3 fatty acids, omega 6:3 ratio, or total fat) and depressive symptoms. However, we elected to use AHEI to evaluate diet quality, an index that scored diet quality from 24-hour food recall data based on a combination of eight different dietary components and their associations with chronic disease risk. When the AHEI for each participant was compared with reported depressive
symptoms as measured by CES-D, significant inverse relationships were found among all participants, indicating that better diet quality is associated with lower depressive symptoms. Such findings align with results from previous literature, and suggest that existing healthy eating guidelines as measured by the AHEI may generate additional benefits to health and well-being, such as the prevention or treatment of depressive disorders (15,16).

As our sample was made up primarily of females with a history of breast cancer, our study also supported other findings in literature regarding depression upon breast cancer survivorship. One cohort study of 222 women with breast cancer found that nearly 50% of the women with early breast cancer had depression, anxiety, or both in the year after diagnosis, 25% in the second, third, and fourth years, and 15% in the fifth year (42). Interestingly, clinical factors were not associated with depression and anxiety, at any time (42). Our study was aligned with these findings by demonstrating a decrease in depressive symptoms for the total population studied upon cancer diagnosis as evidenced by CES-D scores over each visit from baseline, six months, and 18-months, regardless of dietary measures. CES-D scores began with 39.5% of the population having depressive symptoms as measured by the CES-D at baseline. At six months post cancer treatment, the percentage of the population decreased to 34.4% having depressive symptoms as measured by CES-D, and at 18-months post cancer treatment, the incidence further decreased to 26.5% of the population having depressive symptoms.

Limitations of this study included the use of 24-hour food recalls at only two separate time points and without combination use of a food frequency questionnaire. Carroll et al. (38) reviewed the precision, power, and sample size for various dietary
collection instruments. This study found that the gold standard for dietary collection
techniques is administration of four to six 24-hour food recalls to optimally capture most
nutrients and food groups, and that a combined use of a food frequency questionnaire
(FFQ) with a 24-hour recall was superior to use of either method alone, especially to
capture foods that are not regularly consumed (38). The number of repeat administrations
of 24-hour food recalls needed to capture intake of sporadically consumed foods or
nutrients (i.e., those that are not consumed every day by most people, such as omega-3
fatty acids which were of interest in this study) may be impractical due to the respondent
burden and cost. The FFQ, despite its imprecision and cognitive difficulty, has the
strength of querying about long-term intake, thereby aiming to obtain data on usual intake
with a single administration (38). Our study intended to accurately capture intakes of fats
and other sporadically consumed nutrients, specifically PUFAs. According to Carroll et
al. (38) and Freedman et al. (40), these specific nutrients could have been better obtained
with a combination use of a FFQ during each visit of dietary intake collection in addition
to at least two more 24-hour food recalls during the course of the THRIVE study to
achieve the gold standard for dietary collection (38,40).

Although the use of an omega-3 fatty acid supplement was controlled in this
analysis, the quantity and source of omega-3 fatty acids in the supplements was not
obtained by the THRIVE research team. The quantity of omega-3 fatty acids from
supplements could possibly have had an effect on participants’ depressive symptoms.
This warrants future research that evaluates both the source and quantity of omega-3 fatty
acid intake, as well as their resulting blood values of omega-3 fatty acids for more
quantifiable results.
The sample of participants enrolled in this study who had attended both consecutive clinic visits where dietary intakes were collected by 24-hour food recalls also provided some limitations. The exclusion of participants who had not gone to the two clinic visits of interests during the THRIVE study left a remaining sample for our study that was unevenly distributed between males and females, and also between breast and colorectal cancers, in which females with a history of breast cancer dominated the sample. Since controlling for gender or cancer type did not change results for the hypothesis being tested, the sample accounted for both genders.

Conclusions

We hypothesized that high intakes of omega-3 fatty acids (0.3-3.0 g/day) with healthy diet quality is associated with decreased depressive symptoms, and that low intakes of omega 3 fatty acids (<0.3 g/day), with poor diet quality including consumption of a high omega 6:3 ratio and total fat is associated with increased depressive symptoms. We found evidence that healthy diets as evidenced by AHEI are associated with low depressive symptoms. Our study is unique in expanding the focus from associations with single nutrients to overall diet quality measured from a combination of nutrients. In conclusion, while the cancer survivors in our study portrayed depressive symptoms in dichotomous groups (low depressive versus depressive symptoms), we did not find that specific nutrients were associated with depressive symptoms. However when we evaluated overall diet quality using the AHEI, which includes specific components of high total PUFA and low total fat, we found that consumption a diet with a high AHEI score was associated with low depressive symptoms. Future research to understand the impact of diet in health and recovery of depressive symptoms is warranted.
REFERENCES


(2) Kiecolt-Glaser, Janice K. PhD. Stress, Food, and Inflammation: *Psychoneuroimmunology and Nutrition at the Cutting Edge Volume* 72(4), May 2010, pp 365-369


(10) Durrington PN. Lipids and their metabolism. Hyperlipidemia, diagnosis and management. Cambridge, UK: Butterworth Heinemann, 1995;4-24


(37) Dr. Janet Kiecolt-Glaser, THRIVE Protocol


Sarah Rusnak, MS, RD, LD. Clinical Research Bionutritionist. (2013, April 5). Email Interview.

APPENDIX A – Center for Epidemiologic Studies on Depression Scale (CES-D)

Please mark the response that best describes how you felt or behaved DURING THE PAST WEEK.

1. I was bothered by things that usually don’t bother me.
2. I did not feel like eating; my appetite was poor.
3. I felt that I could not shake off the blues, even with help from my family or friends.
4. I felt that I was just as good as other people.
5. I had trouble keeping my mind on what I was doing.
6. I felt depressed.
7. I felt that everything I did was an effort.
8. I felt hopeful about the future.
9. I thought my life had been a failure.
10. I felt fearful.
11. My sleep was restless.
12. I was happy.
13. I talked less than usual.
15. People were unfriendly.
16. I enjoyed life.
17. I had crying spells.
18. I felt sad.
19. I felt that people disliked me.
20. I could not get going.

### Table 1: Center for Epidemiologic Studies on Depression Scale (CES-D)

<table>
<thead>
<tr>
<th>Question</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Occasionally</th>
<th>Most or all</th>
</tr>
</thead>
<tbody>
<tr>
<td>I was bothered by things that usually don’t bother me.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>I did not feel like eating; my appetite was poor.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>I felt that I could not shake off the blues, even with help from my family or friends.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I felt that I was just as good as other people.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I had trouble keeping my mind on what I was doing.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I felt depressed.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I felt that everything I did was an effort.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I felt hopeful about the future.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I thought my life had been a failure.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I felt fearful.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>My sleep was restless.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I was happy.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I talked less than usual.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I felt lonely.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>People were unfriendly.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I enjoyed life.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I had crying spells.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I felt sad.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I felt that people disliked me.</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>I could not get going.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
APPENDIX B – Multiple Pass Approach (MPA)

Multiple Pass Approach:

- **Step 1: Quick List**
  - reports an uninterrupted listing of all foods and beverages consumed

- **Step 2: Forgotten Foods List**
  - answers a series of 9 food category questions for additional foods

- **Step 3: Time and Occasion**
  - answers the time they consumed foods and what they called eating occasions

- **Step 4: Detail Cycle**
  - provides descriptions and amounts of each food reported, reviews each occasion and times between occasions

- **Step 5: Final Review Probe**
  - a final probe for anything else consumed

**Nine Categories:**

- “So did you have any...?”
- Cereals, Breads, Snacks
- Meat, Fish, Eggs
- Spaghetti, Mixed Dishes, Soups
- Dairy Products
- Vegetables and Grains
- Sauces and Condiments
- Fruits
- Sweets
- Beverages and Alcohol

**FOODS**

- **Bread**
  - White/Wheat/Type of wheat? Reg/low cal/high fiber?
  - Cake
  - Flavor? Homemade/store?
  - Frosting? Frosting flavor?
  - Cheese
  - Natural/process? Low fat/Na+?
  - Milk & Other Dairy
  - % Fat?
- **Fats**
  - Type? Regular/light? Salted?
  - Fish
  - Pre-breaded/fresh/froz./smoked/canned/dried? Type/bread?
  - Fruit
  - Fresh/froz./canned/cooked/dried
  - Skin eaten?
- **Grains**
  - Salted water? Fat or salt added?
  - Meat
  - Cut? % Fat? Visible fat eaten?
  - Skin eaten? Browned/braised?
  - How prepared? Fat/salt added?
  - Breadcr/marinated?
- **Nuts/Seeds**
- Raw/browned? Oil/dry roast?
  - Salted?
  - **Vegetables**
  - Raw/blanched/cooked from fresh or frozen/canned?
  - Fat or salt added?

**Amounts:**

- Use measurements like cups or ounces.
- Stay away from words such as “medium”
- Use objects like a “fist” or “baseball” to explain size
- Give dimensions for pan cut foods such as lasagna, cake, and brownies. (3”x3”)

**BEVERAGES**

- **Coffee**
  - Reg/donut? Ground/inst/vend?
  - Sugar? Creamer?
- **Juice**
  - One juice.blend? 100%/cocktail? Fortified? Ice?
- **Soda**
  - Reg/diet? Reg/caff-free? Ice?
- **Tea**
  - Brewed/herbal/green/inst? Ice? Caffeine?
- **Water**

**Some other things to think about:**

- Do you have any food or beverages at your desk, in your car, or in your book bag that you may have snacked on?
- What did you do when you got home from work/school?