

**THE INFLUENCE OF A CANCER DIAGNOSIS ON AN INDIVIDUAL'S
MENTAL HEALTH: A RETROSPECTIVE CANADIAN COHORT STUDY**
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Abstract

Rationale: There is currently little literature available that discusses the link between cancer and mental illness outside of the diagnosis of depression.

Objective: The primary objective of this thesis project is to assess the impact of a cancer diagnosis on indicators of an individual's mental health, that is, the diagnoses of mental health disorders, the use of psychotropic drugs, and/or a referral to a mental health specialist after index diagnosis for cancer.

Hypothesis: It is hypothesized that there will be an increase in both the diagnosis of mental illness and the use of psychotropic drugs following a diagnosis of cancer.

Method: The study was conducted using the Canadian Primary Care Sentinel Surveillance (CPCSSN) database. The electronic medical records of patients with incident cancer diagnoses, i.e. diagnosed within the past three years, were identified. Those cases were then followed for a year, examined for mental health condition diagnoses and prescription of psychoactive drugs, and compared to a cancer-free, matched cohort.

Results: It was found that oncology patients were twice as likely to have a subsequent mental illness indicator in the year after diagnosis (OR=2.05, 95% CI=1.68-2.50, p=0.001). The type of cancer did not appear to have an impact on whether or not the patient would experience a mental illness indicator ($\chi^2=0.074$, p=0.626). It did, however, impact the type of mental illness diagnosed ($\chi^2=40.522$, p<0.001) and the type of psychoactive drug prescribed ($\chi^2=30.679$, p<0.001).

Conclusion: Implications of this study encourage the promotion of screening for mental illness in oncology patients.

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List of Abbreviations & Symbols

α	Significance level
β	Type II error rate (1-power)
BHS	Beck Hopelessness Scale
CMD	Common Mental Disorders
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
DALY	Disability Adjusted Life Years
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMR	Electronic Medical Record
GAD	Generalized Anxiety Disorder
GP	General Practitioner
HREB	Health Research Ethics Board
ICD	International Classification of Diseases
MAC	Mental Adjustment to Cancer scale
MDD	Major Depressive Disorder
n	Population
OR	Odds Ratio
p_1	Proportion of individuals with a mental health disorder in unexposed group
p_2	Proportion of individuals with a mental health disorder in exposed group
PD	Panic Disorder
PECO	Population, Exposure, Control, Outcome
PTSD	Post-Traumatic Stress Disorder
PTS	Post-Traumatic Stress
QOL	Quality of Life
SD	Standard Deviation
SES	SocioEconomicStatus
SPSS	Statistical Package for the Social Sciences
SWL	Satisfaction With Life
WHO	World Health Organization
Z	Power

Chapter 1

1.1 Introduction

Two in five Canadians will be diagnosed with cancer in their lifetime and it is terminal in approximately 25% of those cases¹. Due to the severity of the disease, many patients interpret a diagnosis of cancer as a death sentence². The fear instilled by the diagnosis can lead to increased mental distress.

Twenty-five percent of the general population will experience a mental illness in their lifetime^{3,4}. The prevalence is higher for those suffering physical ill health, especially chronic conditions, such as cancer^{3,5}. Mental disorders, such as depression and anxiety, have been shown to increase patient's hospital stays and recovery time and reduce compliance and treatment efficiency⁶⁻⁸. Lengthened hospital stays increase the burden on Canada's health care cost; however, easing the psychological distress can improve a patient's quality of life (QOL) and offset medical costs⁹⁻¹¹.

There is currently little literature available that discusses the link between cancer and mental illness outside of the diagnosis of depression. This study aims to assess the effect of the first diagnosis of cancer on an individual's mental health using the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database.

1.2 Literature Review

1.2.1 Quality of Life (QOL) and Life Satisfaction in Cancer Patients

The World Health Organization (WHO)¹² defines QOL as “a state of complete physical, mental, and social well-being”, not necessarily absence of disease. WHO¹² further explains that an individual's perception of their position in the community, their relationships, and their personal beliefs have a large impact on QOL.

A number of factors influence the QOL of a patient diagnosed with cancer, such as acceptance of their diagnosis, body image, physical frailty and discomfort, ability for self-care, dependence on others, and perceived loss of dignity¹³⁻¹⁷. A decreased QOL will have a negative impact on an individual's mental health. While there is little research describing

the relationship, mental health disorders are common in cancer patients. This comorbidity harmfully affects QOL¹⁸. In those diagnosed with terminal cancer, and thus having a short life expectancy, QOL becomes a crucial aspect of patient care.

There are many features that encompass an individual's quality of life (QOL), such as life satisfaction and feelings of hope. Standardized tools exist to measure QOL whereas others exist to assess its components, such as hopelessness. Life satisfaction is affected by a myriad of factors and is subjective, making it difficult to compare among people. Tools have been created to measure life satisfaction, such as The Satisfaction with Life (SWL) Scale¹⁹. This scale correlates with mental health and is predictive of future behaviours, such as suicide attempts.

Hope is a key therapeutic factor that has been shown to affect cancer patients' immune function, adjustment and coping skills, QOL, and overall feelings of well being²⁰⁻²⁸. McMillian et al.²⁹ defines hopelessness as a general negative outlook of the future and it is possibly the most important predictor of suicide. The Beck Hopelessness Scale (BHS) is a 20-item true-false response scale that serves as the standardized measure of hopelessness in patients²⁹. Feelings of hopefulness are related to psychosocial elements of pain and therefore, pain can feel severe^{20, 30, 31}. Chronically ill individuals with feelings of hopelessness experience depression and a desire to hasten death²⁰.

1.2.2 Prevalence of Mental Disorders in Cancer Patients

Psychosocial problems are present in 25-50% of cancer patients and approximately 25-33% of these patients develop depression, adjustment disorders, anxiety, or sleep disturbances^{9, 18, 32-43}. Significant psychological distress is common across all stages of cancer¹⁶; however, uncertainty exists as to when the onset of mental disorders occurs in cancer patients. Some studies show that the prevalence of mental illness increases as death approaches¹⁵ while others confirm mental disorders present 6 months post diagnosis⁴⁴⁻⁴⁶. These studies differed in the type of cancer, cancer severity, and the type of mental health disorder analyzed as an outcome.

1.2.2.1 Adjustment Disorder and Major Depression

The DSM-5⁴⁷ defines adjustment disorder as “the presence of emotional or behavioural symptoms in response to an identifiable stressor occurring within 3 months of the stressor”. The symptoms associated with adjustment disorder must be out of proportion of expected reactions and cause significant impairment in the individual’s functioning. There are several subtypes of adjustment disorder that correlate with a patient’s symptoms. For example, adjustment disorder with depressed mood may be difficult to isolate from depression. Adjustment disorder is situational, dependant on a life change or stressor. Major depressive disorder occurs when a patient has a depressed mood or a loss of interest or pleasure for a period of 2 or more weeks⁴⁷. This mood is combined with several other symptoms, such as insomnia, diminished concentration, suicidal ideation, changes in appetite and weight, etc., that significantly impair a patient’s functioning.

It is well established that depression significantly reduces a patient’s subjective health, may lead to poor treatment compliance, and may result in a worse outcome^{16, 17, 48-50}. Patients with depression tend to have a worsened adjustment to cancer. That is, they experience greater feelings of helplessness, hopelessness, fatalism, and they have a lower fighting spirit⁶. Clinical depression is reported to be the most frequent psychopathological complication occurring in oncology patients^{6, 51-54}.

There are variations in the reported prevalence of adjustment disorder and depression among cancer patients; it has been documented to range between 9-35% and 8-26% respectively^{9, 16, 38, 39, 48, 55-77}. Some studies have reported that the prevalence of adjustment disorder and depression in a population can reach as high as 50-65%^{9, 38, 39, 66, 68, 78, 79}. Not all depressed patients request treatment. One study by Okuyama *et al.*⁶⁷ showed that only 28% of cancer patients that were considered depressed after nurse screening accepted psychiatric referral^{67, 80}.

Some drugs used in cancer treatment, such as interferons, produce depression as a side effect. Patients that are prescribed these types of drugs are at an elevated risk of developing depression^{2, 81}.

Depressive symptoms that do not fit the Diagnostic and Statistical Manual of mental disorders (DSM) criteria for depression are regularly occurring in oncology patients^{6, 82, 83}. Symptoms can range from typical reactions to their condition to extreme

anxiety or major depressive disorder (MDD)^{84, 85}. Levels of depression are often underestimated by health care professionals^{18, 86, 87}.

Depression disorders are on a spectrum. It is possible for a patient's depression to worsen over time and even persist after their cancer treatment⁸⁴. Depressed patients may request euthanasia and are prone to a high risk of suicide⁸⁴.

Cancer has the potential to be life-threatening and anti-cancer treatments can be physically and psychological traumatic. The increased mental distress seen in these patients leads to an increased risk of developing a mental disorder and suicide ideation^{36, 72, 88}. Oncology patients with depression are at an increased risk of suicide because of the strong correlations were seen between suicidal ideation and mental health, poor physical functioning, and significant pain^{72, 89-92}. A study by Harwood⁹³ reported that 62% of individuals who had committed suicide had a physical health condition, including cancer.

1.2.2.2 Anxiety and Post-Traumatic Stress Disorder (PTSD)

Anxiety disorders are highly prevalent in oncology patients and may exceed that of depression^{16, 94}. Like depression, anxiety disorders have the potential to adversely affect an individual's functional status^{16, 94}. Anxiety disorders, most commonly generalized anxiety disorder (GAD), panic disorder, adjustment disorder with anxious mood, and PTSD, are diagnosed in 10-30% of oncology patients^{16, 94, 95}.

Generalized anxiety disorder causes excessive anxiety and worry, more days than not, for at least 6 months. Individuals with GAD find it difficult to control the worry and have accompanying symptoms such as fatigue, sleep disturbances, restlessness, etc. These symptoms cause significant impairment in the individual's daily functioning⁴⁷. PTSD is an anxiety disorder that develops after an exposure to traumatic life events which are out of the range of normal human experience. An individual reacts with psychological and physiological distress having symptoms lasting more than one month and significantly affecting their functioning⁴⁷.

Because of the severity of the disease, a diagnosis of cancer meets the DSM criteria of a traumatic event. Therefore, cancer patients are capable of experiencing full-PTSD or PTS-symptoms and 3-35% are diagnosed with the disorder^{38, 96-103}. PTS symptoms tend to

be more frequent in cancers with an acute onset or a more fluctuating course when compared to a more stable or slowly progressing cancer¹⁰⁴.

1.2.2.3 Psychological Distress and Sleep Disturbances

Cancer diagnoses and interventional procedures contribute to psychological distress and mood disturbances seen in patients. This disruption in the patient's psyche can impede clear and rational thought^{36, 88, 105, 106}. Patients with a strong desire to overcome their disease tend to have lower levels of psychological distress¹⁰⁷. This phenomenon, known as the 'fighting spirit', can be measured using the mental adjustment to cancer (MAC) scale^{107, 108}.

Sleep disturbances are a common complaint in cancer patients. Twenty to seventy percent of women with breast cancer and 30-50% of men with prostate cancer reported difficulties sleeping at some point in their illness¹⁰⁹⁻¹¹². Oncology patients may be a population with an increased risk for sleep problems when compared to non-cancer controls¹¹³.

It is possible that problems with sleep and anxiety disorders are clinically linked because sleep disturbances are included in 2 of 6 categories for anxiety in the DSM^{82, 114, 115}. Inadequate sleep may also lead to the development of other mood disorders and depressive symptoms^{105, 116}. Some cases of severe insomnia were related to anxiety, depression, feelings of guilt, and significantly worse physical pain^{114, 117}.

1.2.3 Detection and Current Treatment Approaches

Cancer patients and individuals with comorbid conditions were most likely to contact their general physician about mental, emotional, or nervous problems when compared to the general population³³. Self-reported anxiety and depression scores can be used to predict the development of adjustment disorders and major depression in patients without clinical psychological distress at baseline. These symptoms should be controlled to prevent the development of psychological distress, even if it is at a subclinical level³⁸.

Kim *et al.*⁹ reported consultation rates from oncologists to consultation psychiatrists to be only 4%-10% among cancer patients and psychiatric assessment was

only given to 44.7% of patients with significant psychological distress^{9, 118-120}. These findings are higher than a previous study that reported 28.2% of patients in need received necessary psychiatric treatment^{9, 80}. Psychological distress is increasingly assessed in clinical trials but it is not yet a standard component of routine care³². Some oncology guidelines focus on distress management but other mental illnesses such as depression, anxiety, and sleep disorders may not be revealed in examinations^{32, 121}.

Mild to moderate symptoms of mental disorders such as anhedonia, guilt, and hopelessness are not easily recognized by oncologists⁶. Accurate diagnoses of depression depend on the training of the physician, the instruments used for evaluation, and the timing of evaluation relative to diagnosis and treatment^{32, 41, 68, 122-126}. There are many factors that interfere with treatment for mental illness, but low mental literacy is a big patient-related barrier⁶⁷. Some studies^{113, 127} show that only 30%-40% of the lay public can recognize depression accurately and many do not believe treatment is effective¹²⁸.

Psychological and pharmacological approaches have both been shown to be effective. However, combining both psychological and pharmacological interventions can maximize the desired outcome^{18, 38, 129, 130}. De Fazio *et al.*⁶ showed that antidepressant treatments reduced anxiety and depression in oncology patients that accepted treatment; however, anxiety and depression worsened in patients that refused pharmacotherapy.

Mental health disorders are under-diagnosed and undertreated in oncology patients but assessing mental health continues to attract attention as researchers try to improve their QOL¹⁶. Effective diagnosis and treatment of psychiatric disorders has a positive effect on physical functioning and reduces morbidity and mortality^{3, 131, 132}. Greater clarity of the nature of anxiety and depression in cancer patients would enhance our ability to recognize and treat it effectively¹⁶.

1.2.4 Cancer Treatment in Canada

Primary care providers are typically the initial point of contact for patients and therefore, have a key role in cancer detection. This is reinforced by the fact that primary care providers are responsible to conduct routine screening for their patient population. Primary care providers function as a gatekeeper to the hospital and the specialists as well as an individual to provide continuity of care¹³³. A cancer diagnosis, the initiation of

investigation into a possible cancer diagnosis, or the referral to a specialist is conducted by the primary care practitioner. The decision of cancer treatment is then managed by the specialists, typically medical and/or radiation oncologists. Finally, the primary care practitioner can continue caring for the patient with follow-up and managing other comorbidities.

1.2.5 Literature Review Summary

Based on the literature, there appears to be a strong relationship between cancer and mental health disorders. It remains uncertain as to the exact nature of the relationship. Previous research describes the relationship, but those studies varied on cancer type and severity, as well as the type of mental health disorder. Of the mental health disorders studied, it appears as though depression and anxiety are the most common psychiatric comorbidities in oncology patients. Primary care practitioners and oncologists should remain aware of this relationship and investigate for psychological distress in their patients.

This study uses Canada-wide, primary care data from the CPCSSN database. The purpose is to compare data of individuals with and without a cancer diagnosis and analyze for subsequent mental health disorder indicators. The results from this analysis will add to the literature in this area as it looks at a generalized relationship between cancer and mental health. This generalization is beneficial as previous literature tends to focus on a specific subtype of either disease, cancer or mental health. There are limitations, however, with using this type of data and are identified in the discussion section.

1.3 Study Objective:

The primary objective of this thesis project is to assess the impact of a cancer diagnosis on indicators of an individual's mental health.

1.3.1 Research Question

The study question is whether a diagnosis of cancer increases the likelihood of a subsequent diagnosis of a mental health condition. Specifically, in a cohort of patients, age 20-65 years of age, will a first diagnosis of cancer result in an increased probability of

developing a mental health condition, (defined as an ICD9 code for a mental health condition being stated in the patient medical record, the use of psychotropic drugs, and/or a referral to a mental health specialist in the year after the cancer diagnosis) compared to a similar cohort who do not receive a diagnosis of cancer?

1.3.2 Main Hypothesis

The underlying hypothesis for this study is that patients who are diagnosed with cancer will be more likely to experience a mental health condition (as defined above) compared to individuals without a cancer diagnosis.

1.3.2.1 Null Hypothesis

Patients with cancer will not be more likely to be diagnosed with a mental health condition (as defined above) when compared to a control.

1.3.2.2 Alternative Hypothesis

Patients with cancer will be more likely to be experience a mental health condition (as defined above) when compared to a control.

Chapter 2

2.1 Methods

2.1.1 Sampling Frame/Data Source

The Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database was used in the study. CPCSSN contains de-identified health information on patients of participating primary care providers from across Canada¹³⁴. It includes information of doctor-patient encounters, patient problem lists, prescriptions, laboratory data, investigations, etc. Each data item is coded and can be requested by researchers using such codes, e.g. ICD9 codes for diagnoses, DIN numbers for prescriptions, etc. The network data abstraction process has passed ethics review at nine universities as well as the Health Canada Ethics Review Board. Each regional network that contributes to the national CPCSSN database has gone through privacy impact assessments. Case-definitions for the eight key chronic diseases being monitored have been developed and have undergone validity studies¹³⁵⁻¹³⁷. Data is collected from the EMRs of over 750 sentinels (i.e. primary health care providers) and stored on secure servers at Queen's University¹³⁴. The purpose of the CPCSSN database is to provide data for researchers and policy/decision makers on the prevalence and management of chronic disease in Canada¹³⁴.

The diagnosis of cancer will be included in CPCSSN if the primary care provider enters it in the EMR. This would be done at the time of diagnosis or during a subsequent follow-up appointment. Cancer is a medical condition that requires follow-up, and thus, a patient is likely to see their primary care provider throughout their cancer treatment. It is possible that this does not occur, in which case, the primary care provider would not enter the diagnosis in their EMR. This could be a source of non-identification of the dependent variable, however, the likelihood of this occurring is probably low.

It was decided to use the CPCSSN database for this study due to its large size, including sentinels from across the country. It was selected for use, rather than hospital or cancer clinic data, as a control cohort was also needed for analysis. Ideally, oncology patients will be following-up with their primary care provider, and thus, included in the database.

2.1.2 Study Design

This study used a retrospective (historical) cohort design. This study design occurs in present time and involves selecting participants based on existing status of a variable of interest. The outcome data, also measured in the past, can then be used for analysis¹³⁷. The data for the exposed and unexposed groups and the data for the outcomes all existed in the database prior to the beginning of the study. The study examined the effect of a diagnosis of cancer on mental health. A study participant was determined to have developed a “mental health condition” during the year after a diagnosis of cancer if, in the CPCSSN database (patient medical records), there was, i) an ICD9 code for a mental health condition was present, ii) a DIN number for a prescription for psychotropic drugs, and/or iii) a referral to a mental health specialist). The exposure group (those with a diagnosis of cancer) was compared with a control group (those who did not receive a diagnosis of cancer) in terms of whether a mental condition occurred in the year after the cancer diagnosis. For the purpose of this study, the date of a diagnosis was considered to be the day in which the diagnosis was entered into the EMR. The data, coded in CPCSSN, could then be extracted from the database for a specified period of time, i.e. for a year from the diagnosis.

2.1.3 Study Cohort

The study population was obtained from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database.

Cohort Inclusion Criteria

To be included in the study cohort, a person must

1. be between the ages of 20 and 65 as of January 1, 2012
2. not have had a prior diagnosis of cancer
3. not have had a prior mental health condition (as defined in the Study Design section above) There were 92,305 individuals identified in the CPCSSN Database who met these inclusion criteria

To clarify, each individual will not have had a diagnosis of cancer or mental health disorder listed in the EMR. To aid in reliability, the data for each individual is reviewed prior to January 1, 2012. This is done as a safeguard to avoid missing an existing cancer or mental health diagnosis.

Exposure Group

This group contains people in the study cohort who receive a diagnosis of cancer (excluding brain and non-melanoma skin cancers) during the three-year period from January 1, 2012 to December 31, 2014. Non-melanoma skin cancers were excluded because once treated, they do not generally carry the same risk of death and the fear that most cancers carry. Brain tumours were excluded because the effect on mental health might be more directly caused by a physical impact on the brain, and thus, skew the results.

Control Group

This group contains people in the study cohort who did not receive a diagnosis of cancer during the three-year period from January 1, 2012 to December 31, 2014. The cohort was further defined from these unexposed individuals. For every exposed individual, 4 unexposed individuals who are the same sex and who were born in the same year were randomly selected.

2.1.4 Primary Outcome Variable

The primary outcome examined is the occurrence of a mental health condition during the first year after cancer diagnosis. A mental health condition was deemed to have occurred if:

- i) an ICD9 code was identified in the CPCSSN database indicating a mental health disorder diagnosis (ICD9 290-319).
- ii) there were one or more prescriptions for psychoactive drugs (antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants, and psychostimulants), identified by DIN number.
- iii) and/or there was a referral made to a mental health specialist.

2.1.5 Process of Establishing the Exposure Groups and Determining the Primary Outcome

The results of the process of establishing the exposed and control groups, and determining the primary outcome, are detailed in Figure 1 and Tables M1 and M2 at the end of this chapter.

2.1.6 Statistical Analyses

The main aim of the analyses was to assess the risk of developing a mental health condition after acquiring a cancer diagnosis. The independent variable defines the cohort, that is, whether or not an individual has a diagnosis of cancer. The dependent variable is the development of a mental health condition. Univariate analysis describes the demographics of both the exposed and control groups was described using proportions and Mean (SD) depending on variable type. Bivariate analysis was conducted to compare outcomes between the two cohorts, assessing for statistical significance (using chi-squared analysis for categorical variables and t-test analysis for continuous variables). The relative risk and confidence intervals of the outcome given the exposure group was also determined. Missing data was identified and stated with the baseline characteristics of the cohort. Analysis was not conducted on a variable if it was missing for more than 20% of the cohort. If less than 20% was missing, the analysis was conducted and interpreted while considering the possible effects of the missing data.

Multiple logistic regression analysis was conducted due to the dichotomous nature of the dependent variable. The regression serves to adjust for possible confounders based on the results of the univariate analysis. Variables were chosen as independent variables if they achieved a significance level of 0.2 or less under univariate analysis.

There were limited number of variables available for use in the analysis due to limitations of the CPCSSN database and the matching process. Age and sex were used even though the groups were matched using those variables. This limited looking at differences by group (Exposed vs Control) of those variables but differences in development of mental health conditions could still be assessed. There was not reliable data on variables which might be related to cancer, such as smoking status, occupation, and other SocioEconomicStatus (SES) variables. Furthermore, the breakdown of some variables had large differences, such as health care providers consisting of more than 95% Family Physicians. These variables were still used in the logistic regression as control variables. That is, to see if the relationship between mental health disorders and cancer persisted while controlling for other variables.

Hence, the independent variables under logistic regression were cohort (whether they were in the cancer group or no cancer group); whether they were below or above the

median age (50 years) for the full study population; male or female; whether they lived in Western Canada or Eastern Canada; and whether their provider was a family doctor or some other provider designation. All analysis will be performed using SPSS Statistical Software 22.0¹³⁹.

2.1.7 Sample Size Adequacy

The general population is expected to have a 25% prevalence of mental disorders^{3, 4}. The sample size was calculated to detect a 10% difference between the control group and the exposure group. The sample size to compare two proportions can be calculated using the formula:

$$n = (Z_{\alpha/2} + Z_{\beta})^2 * (p_1(1-p_1) + p_2(1-p_2)) / (p_1 - p_2)^2$$

The study has an 80% power (Z_{β}) to detect a 10% difference with an alpha (α) value of 0.05 if 2155 participants were enrolled. This population hold the control group at a 4:1 ratio with the exposure group. Detecting a 10% difference between the control group and exposure group, assuming they have a 45% (p_1 = control population proportion) and 55% (p_2 = exposed population proportion) prevalence, respectively. The sample will have a 95% power with a significance level (α) value of 0.05 if 4019 participants were analysed at a 4:1 ratio of control group to exposure group. This ratio of 4 control group participants to 1 exposure group participant was implemented in order to increase the statistical power¹⁴⁰. The final sample size is 6576 with an exposed group of 1316 and unexposed group of 5260.

2.1.8 Ethical Considerations

The provincial Health Research Ethics Board (HREB), established through the Health Research Ethics Authority, provided ethics approval (HREB File Number: 20170328). The level of intended data identification in the analysis was the location (province and urban/rural) of participant. This was based on the first three digits of the postal code associated with each physician practice. A postal code with the second digit “0” is considered rural and any other digit is considered urban.

The following safeguards were put in place to protect the identity of the patient’s information:

- All members of the research team were briefed on their responsibility for privacy protection
- As a general principle, no names, addresses, telephone numbers were recorded on paper or requested in data files
- Any data-sharing agreements between the researcher and other researchers and/or institutions were signed prior to providing or obtaining access to data
- All computer files pertaining to the study were password protected

**Figure 1:
Establishing Exposed and Control Groups and Counting Primary Outcomes**

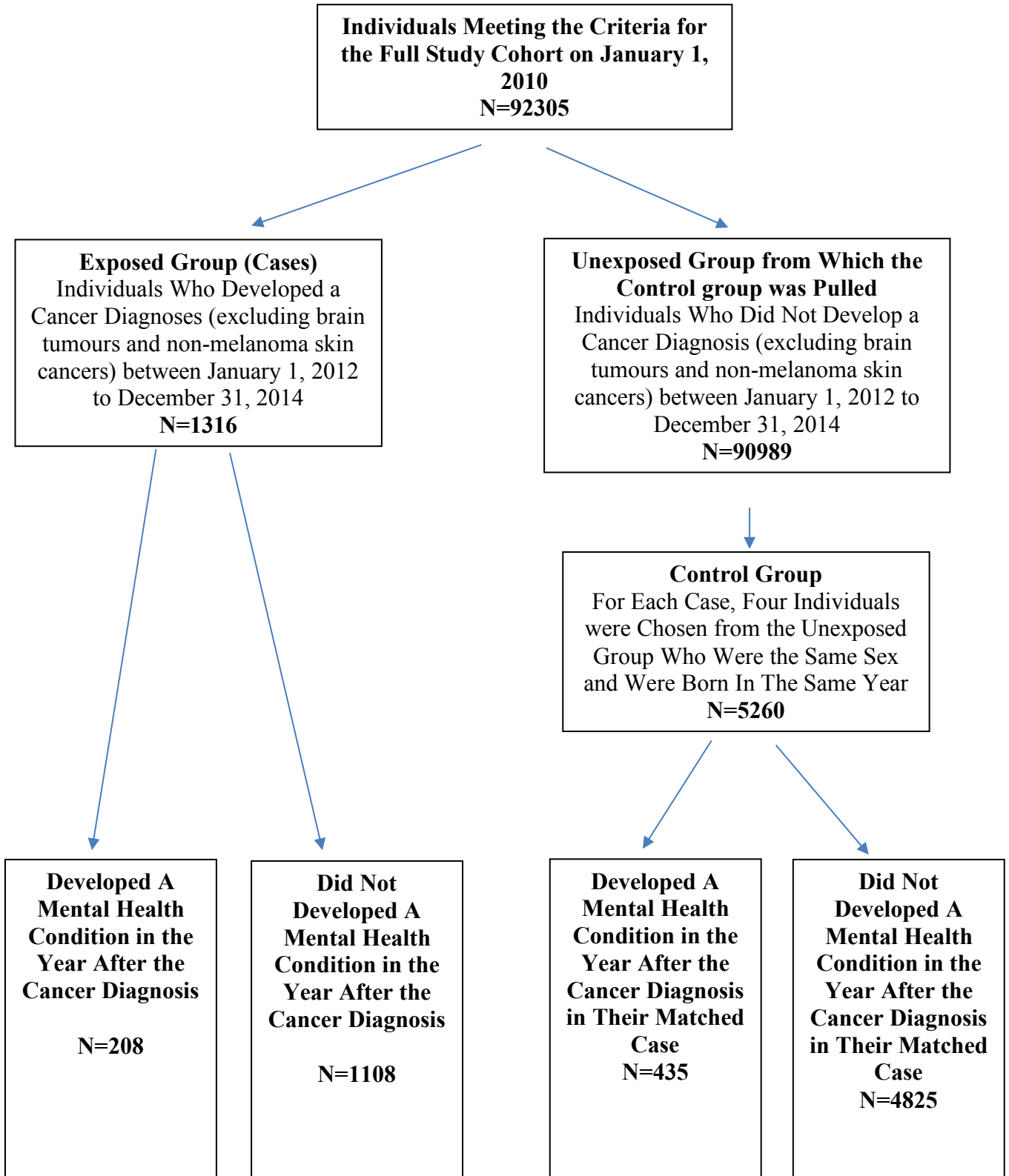


Table M1. Cancers in the Exposed Group

Cancer Type Only index diagnosis	Total <i>N=1303</i>
Respiratory & intrathoracic organs	66 (5.0%)
Bone, connective tissue, skin, breast (male)	114 (8.7%)
Genitourinary organs	152 (11.7%)
Lymphatic & hematopoietic tissue	96 (7.4%)
Carcinoma in situ	134 (10.3%)
Colon	63 (4.8%)
Breast (female)	232 (17.8%)
Prostate	120 (9.2%)
Neoplasms of uncertain behaviour	131 (10.1%)
Other*	195 (8.5%)

**Other* is defined as cancers of lip, oral cavity, pharynx, liver, and pancreas. Also included are Kaposi's sarcoma, neuroendocrine tumors, and neoplasms of unspecified behavior and other/unspecified sites.

Table M2. Mental Health Conditions Identified in Exposed and Control groups

Indicator of a Mental Health Condition		Cohort		Total <i>N= 6576</i>
		<i>Exposed</i> <i>N= 1316</i>	<i>Unexposed</i> <i>N= 5260</i>	
Mental Disorder Diagnosis	<i>Drug and Alcohol Use</i>	15 (1.14%)	41 (0.78%)	56 (0.85%)
	<i>Anxiety, Depression, Mood, & Stress-Related</i>	125 (9.50%)	246 (4.67%)	371 (5.65%)
	<i>Psychosis & Other</i>	13 (0.99%)	39 (0.74%)	52 (0.79%)
Psychoactive Drugs	<i>Antipsychotics</i>	5 (0.38%)	18 (0.34%)	63 (4.8%)
	<i>Anxiolytics</i>	44 (3.34%)	69 (1.31%)	232 (17.8%)
	<i>Hypnotics and Sedatives</i>	37 (2.81%)	46 (0.87%)	120 (9.2%)
	<i>Antidepressants</i>	64 (4.86%)	184 (3.50%)	131 (10.1%)
	<i>Psychostimulants</i>	2 (0.15%)	9 (0.17%)	195 (8.5%)
Mental Health Referral	<i>Yes</i>	6 (0.46%)	15 (0.29%)	21 (0.32%)
	<i>No</i>	1310(99.54%)	5245(99.71%)	6555 (99.68%)

Chapter 3

3.1 Results

Table 3.1 details the baseline characteristics of the two groups (Exposed and Control) described in Chapter 2: Methods. As expected, since the groups were matched on age and sex, there was no significant difference between the groups on these two variables. There was also no difference in the proportion of people in the two groups who lived in rural vs urban areas. Most lived in rural areas in both groups.

There was a significant difference in the groups based on the proportion of patients seen at academic clinics vs community clinics, although overwhelmingly, the patients in both groups were seen in community clinics – 87.9% of the Exposed Group and 90.7% of the Control Groups.

We had data on two western provinces (British Columbia and Alberta) and three eastern provinces (Ontario, Nova Scotia, and Newfoundland). Since there are more patients from the eastern provinces compared to the western provinces, it is not surprising that there were more Eastern Canadians in both groups (Exposed and Control). However, in the Exposed Group, 72.5% of patients were from the east and in the Control Group, 55.7% were from the east. This difference was statistically significant.

The data on the patient's main primary care provider is divided into Family Physician or Other. Almost 99% of the patients had a Family Physician as their primary care provider. The remaining care providers were either nurse practitioners or listed as general practitioner rather than family physician; they are categorized as Other. It is difficult to interpret the analysis of data that has such large skewing. However, since there was a statistically significant difference it was used for analysis. There were more care providers categorized as Other in the Exposed (Cancer) Group.

Table 3.2 is a contingency table comparing the primary outcome in the two groups (Exposed and Control). This table answers the main question in this study — “Are people with a new cancer diagnosis more likely to develop a mental health condition within a year after the cancer diagnosis compared to people who have not had a cancer diagnosis?” The answer is yes. Patients who developed cancer were 2.08 times more likely to develop a

mental health condition within a year of the cancer diagnosis [OR 2.08 (CI: 1.74 – 2.49); P 0.001].

Table 3.3 looks at our other available variables in terms of their association with the primary outcome – mental health condition. Our available variables were: Sex, Age, Location of Residence(rural/urban), Practice Type (Academic/Community), Region of Canada (West/East), and Primary Care Provider (Family Physician/Other). People who were less than age 50 years old, lived in eastern Canada, and had a primary care provider that was not a Family Physician were significantly more likely to develop a mental health condition. Only those three variables, plus sex, were added into the multiple logistic regression along with the grouping variable (Exposed vs Control). The dependent variable was the primary outcome – development of a mental health condition indicator. The purpose of the regression analysis was to adjust the OR determined in the primary univariate analysis which showed an OR of 2.08 for the effect of cancer diagnosis on development of a mental health condition indicator(Table 3.4). Because we determined that other variables were also associated with the primary outcome we wanted to account for any effect these may have had on our results. Unfortunately, and as previously stated in the Method section, we did not have data on variables that are known to be associated with the development of mental illness, such as smoking status, education, occupation, and income.

The adjusting of the OR based on the logistic regression decreased the OR slightly from 2.08 to 2.05 which does not affect the essence of our finding that the diagnosis of cancer doubles the likelihood of developing a mental health condition during the year after the cancer diagnosis.

Other variables included in the logistic regression were age, where you live in Canada, and whether your primary care provider is a family doctor. Based on this analysis they all significantly affect the likelihood of developing a mental health condition (Table 3.4). Individuals who were >50 years of age were 1.52 times more likely to develop a mental health condition. Eastern Canadians were 1.64 times more likely to develop a mental health condition than Western Canadians. Finally, patients who were treated by a family physician were 4.35 times less likely to develop a mental health condition than patients who were treated by another type of health care provider. The intention of this

analysis was to control for these variables when analyzing the primary outcome. As mentioned above, there are discrepancies in the distribution of these variables. For example, primary care provider broken into two groups, Family Physician (over 95%) and Other (less than 5%). Due to this limitation, the results of the logistic regression for these variables should be interpreted with caution.

Table 3.1: Baseline characteristics of exposed (developed cancer) and unexposed (did not develop cancer) groups described in Chapter 2.

		Developed Cancer (Exposed) N= 1316	Did not Develop Cancer (Unexposed) N=5260	P Value*
Sex	Male	621 (47.7%)	2377 (45.5%)	0.163
	Female	682 (52.3%)	2852 (54.5%)	
Age (Mean and SD)		1084 (49.01)	4610 (49.13)	0.712
Age	<50 years	536 (49.4)	2365 (51.3%)	0.272
	50+ years	548 (50.6%)	2245 (48.7%)	
Location of Residence	Urban	1053(20.6%)	1017 (20.0%)	0.272
	Rural	241(81.4%)	4059 (80.0%)	
Practice Type	Academic Centers	159 (12.1%)	490 (9.3%)	0.003
	Community Clinics	1157 (87.9%)	4770 (90.7%)	
Province	BC	43 (3.3%)	154 (2.9%)	0.001
	AB	319 (24.2%)	2175 (41.3%)	
	ON	623 (47.3%)	1948 (37.0%)	
	NS	166 (12.6%)	725 (13.8%)	
	NL	165 (12.5%)	258 (4.9%)	
Region in Canada (West East)	West (BC/AB)	362 (27.5%)	2329 (44.35)	0.001
	East (ON/NS/NL)	954 (72.5%)	2831 (55.7%)	
Provider	Family Physician	1252 (95.1%)	5239 (99.6%)	0.001
	Other	64 (4.9%)	21 (0.4%)	

Missing data: Sex – 44 cases; Age – 882 cases; Rural/Urban – 206 cases

* Pearson Chi-Square (Continuity Correction) for categorical variables. ANOVA for continuous variables.

Table 3.2: Primary Outcome: Relationship Between Having A Diagnosis of Cancer and The Development of a Mental Health Condition Within the Next Year.

	Developed A Mental Health Condition	Did Not Develop A Mental Health Condition	
Exposed Group (Cancer Diagnosis)	208 (15.8%)	1108 (84.2%)	1316
Control Group (No Cancer Diagnosis)	435 (8.3%)	4825 (91.7%)	5260
	643	5933	6576
OR 2.08 (CI: 1.74 – 2.49); P 0.001			
Interpretation: Patients who developed cancer were 2.08 times more likely to develop a mental health condition within a year of the cancer diagnosis.			

Table 3.3. Univariate Analysis of the Relationship Between Other Available Variables and the Development of a Mental Health Condition.

		Developed a Mental Health Condition		OR (95% CI) P Value*
		Yes	No	
Sex	Male	362 (10.2%)	3172 (89.8%)	1.12 (0.95 – 1.32) 0.187
	Female	277 (9.2%)	2721 (90.8%)	
Age (Mean and SD)		47.34 (10.17)	49.29 (9.50)	P=0.001
Age (Dichotomized)	<50 years	308 (10.6%)	2593 (89.4%)	1.38 (1.15 – 1.65) 0.001
	50 + years	222 (7.9%)	2571 (92.1%)	
Location of Residence	Urban	507 (9.9%)	4605 (90.1%)	1.03 (0.83 – 1.26) 0.833
	Rural	122 (9.7%)	1136 (90.3%)	
Practice Type	Academic Centers	65 (10.0%)	584 (90.0%)	1.03 (0.78 – 1.35) 0.786
	Community Clinics	578 (9.8%)	5349 (90.2%)	
Region in Canada (West East)	West (BC/AB)	203 (7.5%)	2488 (92.5%)	0.64 (0.54 – 0.76) 0.001
	East (ON/NS/NL)	440 (11.3%)	3445 (88.7%)	
Primary Care Provider	Family Physician	625 (9.6%)	5866 (90.4%)	0.39 (0.23 – 0.67) 0.001
	Other	18 (21.2%)	67 (78.8%)	

Table 3.4. Logistic Regression of Variables Associated With the Development of a Mental Health Condition During the Follow-Up Period.

Variables	B/SE	Odds Ratio Exp(B)	Lower limit of 95% CI	Upper limit of 95% CI	P Value
Group (Exposed vs Control)	.717 .102	2.05	1.68	2.50	0.001
Age	0.420 0.097	1.52	1.26	1.84	0.001
Sex	.082 .095	1.09	0.90	1.30	0.388
Region of Canada (East/West)	.493 .101	1.64	1.33	2.00	0.001
Provider (Family Physician or Other)	1.48 .588	4.35	1.39	14.3	0.012

Chapter 4

4.1 Discussion

In this thesis project, it was hypothesized that patients who are diagnosed with cancer will experience more mental health conditions than individuals without a cancer diagnosis. It was found that those exposed to a diagnosis of cancer are twice as likely to develop a mental health condition within the first year of diagnosis compared to those without a cancer diagnosis. A mental health condition was assumed to have occurred if the patient was given a diagnosis on the EMR, prescribed psychoactive drugs, or given a mental health referral.

A recently published article¹⁴¹ supports this finding as their study determined that depression affects up to 20%, and anxiety 10%, of patients with cancer. This compares to the general population rates of 5% and 7%, respectively. McDaniel's¹⁴² results suggested that the prevalence of depression was substantially higher with the severity of the medical illness. A study published by Pitman et al¹⁴¹, however, found that there was no difference in prevalence of depression between oncology patients receiving end-of-life care when compared to oncology patients actively living with the disease. A Swedish study¹⁴³ focused solely on men with prostate cancer. It found that the use psychotropic drugs for mood disorders was increased in terminal disease, indicating higher levels of psychological distress. Lycken¹⁴³ suggested early identification of mental illness and improved counselling may help reduce the amplified distress seen in terminal patients. Approximately 15% of individuals diagnosed with cancer have a concurrent diagnosis of major depression. If dysthymia and minor depression is considered, this statistic rises to 20%¹⁴³. Exact numbers are difficult to determine because of the magnitude of influencing factors, i.e. stage of cancer, type of anticancer treatment, and screening and diagnostic tools¹⁴³.

Breitbart¹⁴⁴ identified risk factors for developing a mental illness in oncology patients for early recognition and effective treatment of psychiatric comorbidities. He also found that depression, anxiety, and delirium were common mental illness experienced by many oncology patients¹⁴⁵. Like McDaniel's¹⁴² study, mental illness was correlated with advanced disease and aggressive anticancer treatment, ranging from 25%-

77%. Breitbart¹⁴⁴ concluded that additional risk factors for developing a mental disorder included uncontrolled symptoms, functional limitations, lack of social support, and a past psychiatric history.

Desplenter et al.¹⁴⁵ conducted a study titled Incidence and drug treatment of emotional distress after cancer diagnosis: A matched primary care case-control study. They found that cancer patients were more likely to experience more emotional distress when compared to controls (15.6% vs 1.4%). This patient population was also found to be on a higher volume and duration of psychoactive drugs¹⁴⁵. It is thought that cancer increases an individual's vulnerability to developing depression in many ways. That is, the reaction to a diagnosis of cancer and the deterioration of health are both considered risk factors¹⁴⁶. Anticancer treatments, including chemotherapy and corticosteroids and surgical treatment, pathological and medically-induced alterations to the patient's physiology, and chronic pain pose additional risk for developing a mental illness, such as depression^{141,146}. Furthermore, the study conducted by Pitman et al.¹⁴¹ concluded that some cancers (e.g. pancreatic and lung cancers) release chemicals that are thought to cause depression.

Identifying oncology patients who have psychiatric comorbidities is key in order to assess and treat the patient holistically. These mental illnesses are known to cause a decreased quality of life, lower compliance with anti-cancer treatment, prolonged hospitalization, higher suicide risk, and greater psychological burden on caregivers¹⁴⁶. In addition to these negative effects caused by psychiatric illness, depression is considered an independent risk factor for mortality in cancer patients¹⁴⁶. In patients with depressive symptoms or a diagnosis of major depressive disorder, there is a greater mortality rate among cancer patients of 26% and 39%, respectively¹⁴⁶.

According to our results, people whose primary care provider was a family physician were less likely to develop a mental health condition. Another study, "Improving the detection and management of depression in primary care"¹⁴⁷, determined that primary care and non-specialist practitioners may not be using current guidelines for diagnosis and treatment of depression. Use of simple questionnaires designed to measure depression and/or quality of life has not shown to impact recognition, management, or outcome of depression in non-specialist situations. Another perspective would be that patients of

family physicians may result in fewer mental health conditions because of the care received. Perhaps the patients are feeling more supported by their family physician and are not developing a mental illness indicator. It is important to remember that other healthcare providers are able to offer counselling for a patient's mental health. Therefore, patients could be benefiting from the support of counsellors, psychologists, social workers, etc. These patients may not be followed by their primary care practitioner for this issue, and thus, appear to not have a mental health disorder.

A Canadian study by Sunderland and Findlay¹⁴⁸ assessed rates of unmet mental health care needs in individuals with mental illness. This becomes particularly concerning because, in 2012, approximately 10% of Canadians have a mental health condition, and these rates are estimated to increase. This study further evaluated the mental health care need in a 1-year span. Of their study population, 21% had their need partially met and 12% had unmet needs. Sunderland and Findlay¹⁴⁸ identified distress as a predictor of mental health care need, which arguably could include presence of a physical illness. This is further supported by Statistics Canada¹⁵⁷ who found that a chronic condition can precipitate a mood, anxiety, and substance use disorders. In order to provide holistic medical care to oncology patients and address these needs, the primary practitioner should collaborate with mental health specialists¹⁵¹.

Although it was not reported, our analysis indicated that there was no significant difference found between cancer type and the presence of a mental health condition indicator. Contrary to this, Lichtenthal et al.¹⁵¹ concluded that 10.8% of deceased oncology patients had met the criteria for at least one of the following diagnoses: MDD, GAD, PD, or PTSD. The prevalence of these was highest in patients who were diagnosed with lung, colon, pancreatic, and breast cancer. Furthermore, a meta-analysis focusing on depression in oncology patients¹⁵², found differences in rates of depression differed in patients based on cancer type. That meta-analysis¹⁵² found cancers of the digestive tract, brain, and female genitalia, along with hematological malignancies, to have highest rates of depression. Definitive conclusions cannot be made due to small sample sizes, limited number of studies, and variation within cancer type.

Again, although not reported in the results section, we found significant differences noted between the presence of a cancer diagnosis and the type of mental disorder diagnosis

experienced. This was also the case for the presence of a cancer diagnosis and the type of psychoactive drug prescribed. Anxiety, depression, mood, and stress-related disorders were found to be the most common category of mental health disorders diagnosed. Furthermore, this study determined that antidepressants were most the frequently prescribed psychoactive drug in the exposed cohort while anxiolytics were most frequently prescribed overall. A study by Derogatis et al.¹⁵³ conducted in 1979 found that 51% of oncology patients were using psychoactive medications. Of these, 48% were hypnotics, 26% were anti-psychotics, 25% were anti-anxiety agents, and 1% were antidepressants. Years later, a Jaeger¹⁵⁴ conducted a study in 1985 that stated 61.3% of patients had psychotropic drug prescriptions. The breakdown of those being 55.8% hypnotics and 10% antidepressants. Both Derogatis et al.¹⁵³ and Jaeger¹⁵⁴ reported hypnotics as being the highest prescribed psychoactive drug and antidepressants as the lowest. This study found that antidepressants were prescribed to oncology patients more frequently than sedatives/hypnotics (4.86% vs 2.81%). It is thought that this change in prescription frequency is due to the advancements made in psychoactive drugs. The first antidepressants, monoamine oxidase inhibitors and tricyclic antidepressants, had unpleasant side effects and issues with safety and toxicity. Progress has been made with the development of selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors. These medications are successful in treating depression with fewer unwanted side effects¹⁵⁵.

4.2 Study Limitation

CPCSSN data has certain limitations. With the increased incorporation of technology in medical practice, paper charts are being replaced for EMRs. Not all physicians are embracing this change which results in a fraction of Canadian practitioners using EMRs and only a portion of those choosing to participate with CPCSSN. A study published in 2015 estimated EMR use in 62% of practitioners in 2013. They reported being limited as they conducted a survey to a small percentage of Canadian physicians¹⁵⁶. However, CPCSSN does have data on about 1.5 Million patients from 750 physician practices and some work has been done on the representativeness of the data¹⁵⁷. Due to the fact that CPCSSN extracts data from electronic medical records (EMR), there are

differences among patients that is healthcare provider dependent. The EMRs are used for clinical care and therefore, the data that researchers find useful are not always reported, such as SES variables. Depending on the patient and provider, the documentation may not be fully completed. The healthcare provider may choose to omit certain information for some or all patients, e.g. employment. Relevant descriptors of an illness may not be recorded, e.g. staging of cancer. Similar limitations are documented in other research projects. For example, one study, by Abidi et al.¹⁵⁶ described an underreporting of alcohol use disorders from GPs when using an EMR. It was theorized that it could be due to barriers related to alcohol screening but also avoidance due to the stigma around alcohol abuse. This stigma is seen in many aspects of mental health conditions and could be affecting the documentation on EMRs. Statistics Canada¹⁵⁷ reported that only 57% of Canadians consulted their family doctor or general practitioner for mental health care when seeking help. The other fraction was divided among social workers, nurses, psychiatrists, psychologists, and others. If the patient sought counseling on their mental health from a healthcare professional other than a practitioner participating with CPCSSN, it would not appear in the database. In terms of prescriptions, the reason for use is not described rendering it challenging to determine if the medication is for traditional or off-label use. For example, Zaini et al.¹⁶⁰ discussed the use of antidepressant medications for other somatic complaints, other than depressed mood, such as hot flashes, sexual dysfunction, pruritus, nausea, cachexia, fatigue, nicotine dependence, and others. Unfortunately, with the limitations presented by the CPCSSN database, these prescriptions are not screened for and their use are assumed to be due to mental illness. Due to limitations of the dataset, this study was unable to analyze time from diagnosis of cancer to mental illness. A meta-analysis by Krebber et al.¹⁵² was able to look at point prevalence of depression in patients throughout the first year after a diagnosis of cancer. Highest rates were seen acutely after diagnosis which then decreased. Burgess et al.¹⁶¹ conducted a similar study, including the point prevalence of anxiety. They too, found that 33% of oncology patients experienced depression and/or anxiety at time of diagnosis. This decreased to 24% at 3 months post diagnosis and 15% at 1 year after treatment.

This study focused on the presence of any mental health condition; however, the majority of literature focuses on the presence of depression. One study, *The increasing*

*burden of depression*¹⁶², looked at the prevalence of and burden caused by depression. It used disability adjusted life-years (DALY), a sum of life-years lost due to premature death and years of life with disability, taking severity into consideration. This study, conducted in 2011, considered depression among the leading causes of worldwide disease and burden and predicted it to become the major health burden worldwide by 2030. Thus, it becomes crucial to recognize risk factors and the presence of depression in patients. Due to the increased frequency of depression and the often large negative effect on QOL, most research on mental health in cancer patients has this focus. There are, however, many other mental health conditions that may form in the year following a diagnosis of cancer. Based on current literature, there needs to be a wider focus to include these in future research endeavors. As mentioned earlier, poor QOL can negatively impact mental health. Unfortunately, it was not possible to control for QOL in this study due to the nature of the CPCSSN data.

4.3 Summary of Findings

This study aims to evaluate the relationship between a first diagnosis of cancer and the development of subsequent mental health disorders. Results from this study show that a diagnosis of cancer doubles an individual's risk of developing a mental health disorder indicator, i.e. were diagnosed with a mental health disorder, prescribed psychoactive drugs, and/or given a referral for a mental health specialist. There was not found to be a significant difference between the type of cancer diagnosed and the presence of a mental health condition indicator. There was, however, a significant difference found between the presence of cancer and the type of mental disorder diagnosis as well as the type of psychoactive drug prescribed. Anxiety, depression, mood, and stress-related disorders were most commonly diagnoses. Anxiolytics were the most frequently prescribed psychoactive drug overall, however, antidepressants were most common in the exposed cohort.

4.4 Implication of Study

There is currently little literature available that discusses the link between cancer and mental illness outside of the diagnosis of depression. While this project broadened that focus to include other mental health disorder diagnoses, it was limited by the available

data. Researchers should continue to explore the relationship between cancer diagnoses and mental health disorders to promote change in practice.

Findings from this study should oblige clinical healthcare practitioners to promote screening for mental illness in their oncology patients as routine care. Findings from this study should encourage policy change to incorporate counsellors, psychologists, and/or social workers on the team for management of oncology patients. Collaboration of the oncology patients' primary healthcare providers and providers specializing in mental health care should be increased to address the higher rates of mental illness and unmet needs of this population.

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