MENTAL HEALTH DISORDERS, CANCER RISK, AND THE MEDIATING ROLE OF LIFESTYLE BEHAVIOURS IN THE CARTaGENE COHORT STUDY

by

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Abstract

Background: Mental health disorders are highly prevalent in the Canadian population and has been associated with cancer risk; however, previous findings in literature are inconsistent (1–4). This study aims to elucidate the relationship between mental health disorders and cancer risk, as well as explore the potential mediating effects of lifestyle behaviours.

Methods: A cohort study was conducted with 34,571 participants aged 40-69 years from the province of Quebec. Depression was conceptualized from the PHQ-9, antidepressant use, and either a positive screen from PHQ-9 scores, antidepressant use, or self-report of physician diagnosis. Anxiety was defined using the GAD-7, and co-morbid depression and anxiety was assessed using the PHQ-9 and the GAD-7. Cox proportional hazards regression models were used to investigate the association between mental health exposures and risk of prostate, lung, and all cancers combined. Mediating effects of health behaviours were assessed using Baron and Kenny mediation criteria., then a Quasi-Bayesian/Monte Carlo approximation was used to obtain confidence intervals.

Results: For risk of all cancers combined, there was a modest positive association with all mental health exposures, however none reached significance with full adjustment. No relationships reached significance for prostate cancer. There were positive associations between mental health disorders and lung cancer risk, but only anxiety and lung cancer in women was significant with full adjustment (HR = 1.67, 95% CI: 1.01-2.76). Women had consistently higher risk estimates than men for all cancer and lung cancer risk for the majority of exposures. Smoking status mediated the relationship between depression (PHQ-9) and lung cancer, anxiety and lung cancer, and co-morbidity and lung cancer by 27%, 18%, and 26%, respectively in

women. In men, smoking status mediated 17% of the relationship between depression (PHQ-9, antidepressant use, or self-report of physician diagnosis) on all cancers.

Conclusions: Positive associations were observed between mental health disorders and overall and lung cancer risk, however few relationships reached significance. Risk estimates were generally higher in women than in men, suggesting a differential risk. Smoking status mediated a significant proportion of the relationships between mental health disorders and cancer risk.

Lay Summary

Cancer is the leading cause of death globally, and many cancers can be prevented through modifiable lifestyle factors, such as physical activity, diet, and smoking. Mental health disorders also represent a serious public health burden and have been associated with many of the same lifestyle factors. Research has shown that there may be a relationship between mental health disorders and cancer risk, but the mechanisms involved are unclear. Therefore, is important to understand the relationship between mental health disorders and cancer incidence, as well as the role of healthy lifestyle behaviours in this relationship. These objectives were studied using a cohort of approximately 35,000 people in Quebec. This study showed that some mental health disorders were associated with an increased risk of cancer, and these risks were different between men and women. Smoking status was shown to be a significant mediator in the pathway from mental health disorders to cancer.

Preface

This thesis was reviewed and approved by the Clinical Research Ethics Board at the University of British Columbia (Certificate # H17-02706).

The data request and ethics application were completed by Dr. Rachel Murphy. All other work presented in this thesis was conducted by Kaitlyn Gilham under the supervision of Dr. Rachel Murphy, and guidance from the supervisory committee: Dr. Anne Gadermann and Dr. Trevor Dummer.

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List of Abbreviations

AICR – American Institute for Cancer Research

BMI – Body mass index

CCHS – Canadian Community Health Survey

CHMS – Canadian Health Measures Survey

COPD – Chronic obstructive pulmonary disease

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EWCFG – Eating Well with Canada's Food Guide

GAD-7 – Generalized Anxiety Disorder-7

HBM – Health Belief Model

HPA – Hypothalamic-pituitary-adrenal

IARC – International Agency for Research on Cancer

IPAQ – International Physical Activity Questionnaire

MAR – Missing at random

MCAR – Missing completely at random

MVPA – Moderate or vigorous physical activity

NPHS – National Population Health Survey

PHQ – Patient Health Questionnaire

RAMQ – Regie de l'assurance maladie du Quebec

TILDA – The Irish Longitudinal Study on Ageing

WCFRI – World Cancer Research Fund International

WHO – World Health Organization

WMH-CIDI – World Mental Health-Composite International Diagnostic Interview

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Chapter 1: Introduction

1.1 Cancer incidence, mortality, and survival in Canada

Approximately 1 in 2 Canadians will develop cancer in their lifetime, and 1 in 4 Canadians will die from cancer (5). Cancer is the leading cause of death in Canada, responsible for approximately 30% of all deaths (6). In 2020 there was an estimated 225,800 new cancer cases and 83,300 cancer deaths, and cancer incidence and mortality is projected to increase in Canada with the growing and aging population (6,7). In Canadian males, cancer incidence is expected to increase by 84%, from 80,800 in 2003-2007, to 148,400 in 2028-2032 (8). For Canadians females, there is a projected increase of 74%, from 74,200 to 128,800 in the same time frame (8).

In Canada, lung cancer is the most commonly diagnosed cancer, with an estimated 29,800 cases, followed by breast (27,400), colorectal (26,900), and prostate (23,300) cancer in 2020 (7). These four cancers are expected to make up 48% of incident cancer cases in Canada in 2020 (7). Lung cancer is the leading cause of cancer death, accounting for more cancer deaths (21,200) than the next three leading causes – colorectal, pancreatic and breast – combined (20,100) in 2020 (7). These five cancers, along with prostate cancer account for more than half (55%) of all expected cancer deaths in Canada in 2020 (7).

The financial and emotional cost of cancer in Canada is substantial – impacting patients, their caregivers, and the healthcare system. Between 2005 and 2012, the direct economic burden of cancer care in Canada rose from $2.9.billion to $7.5 billion annually (9). However, this figure does not account for the indirect burden, which includes the monetary losses associated with lost patient/caregiver time and lost opportunities. A systematic review on this issue found that societal productivity losses associated with cancer in Canada were estimated between $75

million to $317 million, annually (10). Preventive interventions are crucial to minimize the economic and social impact of Canada's rising cancer burden.

1.2 Lifestyle factors and cancer risk

It is estimated that approximately 4 in 10 cancer cases in Canada can be prevented through healthy lifestyles (11). Lung cancer, the highest in incidence and mortality in Canada, is estimated to be one of the most preventable cancers, second only to cervical cancer (7,11). It is estimated that 86% of lung cancer cases are preventable with 72% attributable to tobacco smoke (7,11). The other preventable factors include environmental exposures, and a variety of other lifestyle factors such as fruit and vegetable consumption and physical activity (11).

In order to reduce cancer risk, the Canadian Cancer Society recommends individuals to live smoke-free, be sun safe, maintain a healthy body weight, eat a diet rich in fruits and vegetables, limit red meat and processed meat consumption, avoid alcohol, and aim for at least 30 minutes of physical activity per day (12). A cross-sectional study in the Alberta Tomorrow Project examined adherence to global cancer prevention recommendations in adults, and assigned a score from 0 to 7 based on physical activity, diet, body size, and tobacco use, with higher scores reflecting greater adherence (13). The authors found that of the 24,988 participants, only 14% had adherence scores of 5 or greater, and 60% had scores lower than 3 (13). An analysis of the same cohort found that participants with a score of 4 to 6, reflecting greater adherence to cancer prevention recommendations were 13% less likely to develop cancer compared with those with a score between 0 and 2 (14). The projected increase of the cancer burden in Canada necessitates research on risk factors to reduce increasing incidence. Given that approximately 4 in 10 cancer cases in Canada are preventable, the ability to identify new risk factors, and sub-populations that have high risk behaviours will be key to reducing cancer

incidence in the coming decades (11). This study aims to evaluate mental health as a risk factor to support cancer prevention.

1.3 Mental health disorders and cancer incidence

Mental health disorders are a range of health conditions. They involve combinations of changes in mood, cognitive function, and behaviour, and are associated with significant distress and impaired functioning in social, work, or personal activities (15). Mental health disorders are predominant in Canada. It is estimated that 1 in 5 Canadians are affected annually by mental health disorders (16). By the time a person reaches 40 years of age, 1 in 2 have—or have had—a mental health disorder (16).

Depression is one of the most common mental health disorders, with an annual prevalence of approximately 4.7% in Canada (17). According to Pearson et al., 11.3% Canadian adults have met the criteria for a depression disorder at some point in their lifetime (18). A diagnosis requires five or more symptoms presented by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), with one being either depressed mood or anhedonia (loss of capacity to enjoy normally pleasurable activities), the named main criteria (19). Anxiety, or generalized anxiety disorder (GAD), is a mental health disorder characterized by excessive worry that impairs social or occupational functioning. Diagnostic criteria in the DSM-5 includes six items that assess the severity of impairment and symptoms, and whether the disturbances could be attributed to substance use or another medical disorder (19). In Canada, although the annual prevalence of depression and anxiety has been shown to be relatively stable over time, help-seeking behaviours and medication use has been increasing which may indicate an increase in mental health awareness or in severity (17,20). The proportion of the Canadians with past-year depression that are receiving treatment has increased about 10% over the past 10 years and is

now about 50% (17). These figures may also indicate a reduction of stigma for accessing mental health services (17,20).

Individuals with mental health disorders have an increased risk of several chronic illnesses, including cardiovascular disease and diabetes (21–23). However, empirical evidence on the association between cancer and mental health disorders are largely inconclusive. One meta-analysis of nine studies assessed the relationship between depression and risk of all cancers (24). They found no statistically significant association, but reported high heterogeneity across studies and inadequate consideration of covariates such as smoking (24). A systematic review and meta-analysis studying the association of depression and anxiety and cancer risk in n=1,469,179 participants found that depression and anxiety were associated with an increased risk of all cancer, as well as cancers of the lung, oral cavity, prostate and skin (25). Importantly, none of the abovementioned meta-analyses included studies on a Canadian population but were based primarily in the United States. Feeny et al. found that the population of Canada is significantly healthier from the American population with respect to life expectancy and health-related quality of life, which limits generalizability of studies done outside of Canada (26).

Several lines of evidence provide biological plausibility for a relationship between mental health disorders and cancer. Recent meta-analyses have found that severe mental health disorders such as schizophrenia, bipolar disorder, and major depressive disorder are associated with systemic inflammation, peripheral inflammatory markers, and oxidative stress—leading to a cellular environment optimal for malignant growth (27–29). The literature has also demonstrated a consistent relationship between depression and increased risk of cardiovascular disease. A review of longitudinal studies of depression and cardiovascular disease onset indicated that the elevated risk likely involved both pathophysiologies such as immune-inflammatory,

hypothalamic-pituitary-adrenal (HPA)-axis, and metabolic dysregulations and unhealthy lifestyle behaviours such as smoking, excess alcohol use, physical inactivity, and unhealthy diet (30). This dual pathway between mental health disorders and cardiovascular disease could have implications for cancer risk because of the shared risk factors between cardiovascular disease and cancer, such as physical activity, diet, and smoking (31). It is of interest to study whether the inconsistencies in mental health and cancer incidence research could be due to lack of consideration of the impact of unhealthy lifestyle behaviours.

1.4 Mental health disorders and lifestyle factors

Individuals with mental health disorders have excess mortality, largely due to associated co-morbidities and behavioural factors that negatively affect physical health (32–34). One of the primary lifestyle behaviours associated with negative health outcomes among individuals with mental health disorders is cigarette smoking. Data from the Canadian Community Health Survey (CCHS) indicates that the relative risk of being a current smoker was 2.08 for individuals who have experienced a mental health or substance use disorder in their lifetime, compared to those who had not (35). Alcohol use disorders are also prevalent among individuals with depression and anxiety disorders (36–39).

Unhealthy behaviours associated with mental health disorders extend beyond use of substances such as tobacco and alcohol. Individuals with depression and anxiety typically engage in low levels of physical activity, and have poor adherence to exercise interventions (40–42). Diet quality are lower in individuals with mental health disorders (43–45). Furthermore, disturbed sleep in people with depression and anxiety have been described extensively in both clinical and epidemiological studies. For example, difficulty sleeping is part of the diagnostic

criteria for generalized anxiety disorder and sleep disorders are widely acknowledged as core symptoms of depression (19,46).

Many of the risk factors and behaviours associated with mental illness are also risk factors for cancer. Together with evidence of shared biological pathways (e.g., inflammation) suggests a link between these two outcomes. However, the data on mental health disorders and cancer risk is inconsistent, and studies investigating the exact role of mental health disorders and cancer is low. Given that both of these illnesses are significant public health burdens, further research is warranted. Understanding the association between mental health disorders, cancer incidence, and healthy lifestyle behaviours in Canada may help encourage cancer prevention lifestyles, and in turn reduce cancer outcomes.

1.5 Research questions

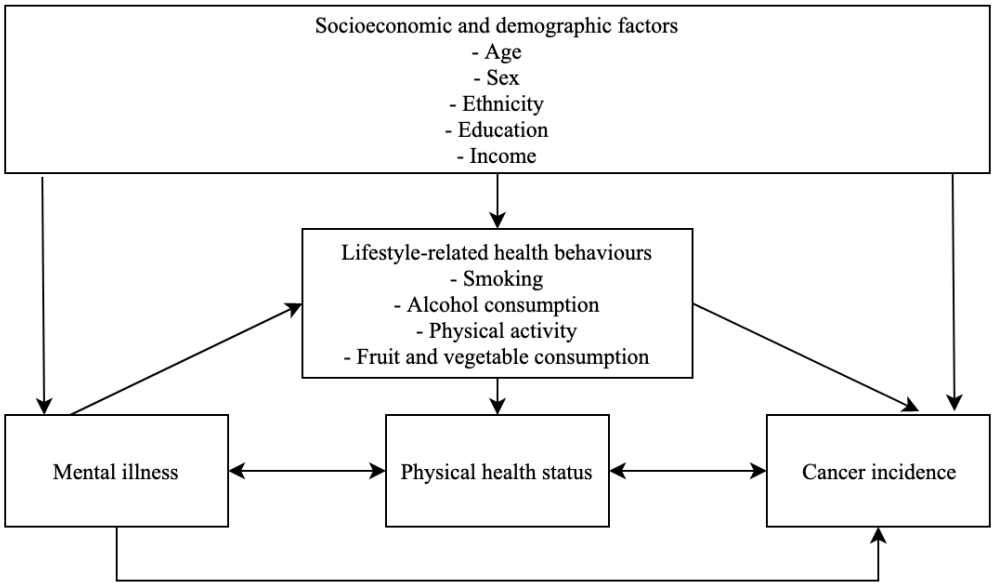
The primary goal of this study is to determine the relationship between different domains of mental health and risk of incident cancer, in a large cohort of Canadian adults. Considering the complex and multi-faceted nature of both mental health disorders and cancer, this research makes use of the detailed demographic, socioeconomic, lifestyle, and disease outcome data available through CARTaGENE: a longitudinal cohort study of 43,000 Quebec residents between 40 to 69 (47).

Given the inconsistent evidence on the relationship between mental health disorders and cancer incidence and the potential mediating mechanisms underlying this relationship, the present study investigated how depression and anxiety is associated with incidence of 1) all cancers, 2) lung cancer, and 3) prostate cancer. Lung and prostate cancer were examined separately based on their high incidence rates in Canada, and thus larger sample size, and

availability for this study (7). This study uniquely uses three distinct definitions of depression (positive result from PHQ-9 scores, antidepressant use at baseline, and one of either a positive result from PHQ-9 scores, antidepressant use, or self-reported physician diagnosis of depression), drawing on data from provincial health databases to better capture participants who were affected by a depressive disorder at baseline. Due to the potential influence of lifestyle-related behaviours on both mental health disorders and cancer, this study further assessed the potential mediating effect of factors such as smoking status, alcohol consumption, physical activity, and sleep.

Figure 1.1 Illustrates the concepts and relationships that are explored in this study. Given the complex pathological nature of both mental health disorders and cancer, this research draws on many sociodemographic characteristics, lifestyle behaviours, and physical health status that have been shown to be associated with both illnesses. The first research question aims to assess the relationship between mental health disorders and cancer incidence, while adjusting for relevant sociodemographic, lifestyle, and health factors. The second research question aims to assess the potential mediating role of lifestyle behaviours in the relationship between mental health disorders and cancer incidence.

Figure 1.1 A conceptual framework to summarize the research questions.



The specific research questions are as follows:

1. Assess the relationship between mental health disorders and cancer risk in a cohort of Canadian adults.
    a) Association between mental health disorders and cancer incidence.
        i. Depression and cancer incidence.
            1. PHQ-9 scores.
            2. Antidepressant use.
            3. PHQ-9 scores, antidepressant use, or self-report of physician diagnosis.
        ii. Anxiety (GAD-7) and cancer incidence.
        iii. Co-morbid anxiety and depression (PHQ-9 and GAD-7) and cancer incidence.

    b) Association between mental health disorders and prostate cancer incidence.
        i. Depression and prostate cancer incidence.
            1. PHQ-9 scores.
            2. Antidepressant use.
            3. PHQ-9 scores, antidepressant use, or self-report of physician diagnosis.
        ii. Anxiety (GAD-7) and prostate cancer incidence.
        iii. Co-morbid anxiety and depression (PHQ-9 and GAD-7) and prostate cancer incidence.

    c) Association between mental health disorders and lung cancer incidence.
        i. Depression and lung cancer incidence.
            1. PHQ-9 scores.
            2. Antidepressant use.

3. PHQ-9 scores, antidepressant use, or self-report of physician diagnosis.

ii. Anxiety (GAD-7) and lung cancer incidence.

iii. Co-morbid anxiety and depression (PHQ-9 and GAD-7) and lung cancer incidence.

2. Clarify the role of lifestyle-related behaviours (e.g., smoking, alcohol consumption, body mass index (BMI), physical activity, sleep, and fruit and vegetable intake) in the relationship between mental health disorders and cancer risk.

This study adds to the existing body of literature on mental health disorders and cancer incidence, specifically within the context of a Canadian population. The results aim to clarify the inconsistent relationships observed between mental health disorders and cancer incidence, understand whether individuals with mental health disorders may be at risk, and if so, inform preventive strategies that may be required.

1.6 Thesis overview

Five chapters are included in this thesis. Chapter 1 introduced the concepts and relationships to be discussed and evaluated in further chapters. Chapter 2 reviews literature that illustrates the association of mental health disorders on cancer incidence, and the role that lifestyle behaviours plays in both of these pathologies. Chapter 3 details the statistical methods used to carry out this research study. Chapter 4 presents descriptive characteristics of the CARTaGENE cohort, as well as results from the Cox regression analyses and mediation analyses. Chapter 5 provides a discussion of the findings presented in Chapter 4, along with strengths and limitations of the study, as well as policy implications and future recommendations based on results from this study.

Chapter 2: Literature Review

The databases Medline, PubMed, and PsychINFO were used for this literature review. Search terms were mapped on to relevant medical subject headings and combined using Boolean operators where applicable. Search terms for the following sections included but were not limited to: cancer; lung; prostate; risk; risk factors; chronic disease; cardiovascular disease; diabetes; lifestyle behavio*rs; health behavio*rs; sociodemographic; socioeconomic; smoking; alcohol; diet; nutrition; obesity; physical activity; exercise; depression; anxiety; mental health.

2.1 Cancer

2.1.1 All cancer incidence and mortality

Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020 (48). The global cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020 (48). In Canada, it is projected that 225,800 Canadians will be diagnosed with cancer and 83,300 will die of cancer in 2020 (7). The number of cancer deaths is expected to be 12% higher among males (44,100) than females (39,300) in 2020 (7). The age-standardized incidence rates and age-standardized mortality rate for 2020 was estimated to be higher in eastern and central Canada and lower in Western Canada (7). Of the cancers diagnosed in Canada, lung and prostate cancer are among the most common. As they are the focus of this theses' objectives they are discussed in more detail below.

2.1.2 Prostate cancer incidence, mortality, and risk factors

Prostate cancer accounts for 14.1% of incident cancers, and 6.8% of cancer deaths in men globally (48). Globally, it is the second most commonly diagnosed cancer in men, second to lung cancer, and the fifth leading cause of cancer death (48). The 5-year net survival for prostate

cancer in Canada is relatively high, at 93% (49). However, many men will receive treatment for prostate cancer which significantly impacts their quality of life and may increase their subsequent risk of other chronic diseases like diabetes and cardiovascular disease. In Canada, prostate cancer was expected to be the most commonly diagnosed cancer in men for 2020, accounting for about 1 in 5 new cases in males (7).

The proportion of prostate cancer that can be explained by known risk factors is one of the lowest of all common cancers (11,50). The heritability of prostate cancer is among the highest across cancer sites, and many prostate cancer susceptibility genes have been identified (51,52). However, it is estimated that family history accounts only for 5-10% of all prostate cancer cases (53–55). In a recent review of prostate cancer progress, Kensler and Rebbeck determined that the only clear and consistent risk factors identified for prostate cancer are age, race, and family history (51). Obesity is one modifiable risk factor that has frequently been associated with prostate cancer. However, Allot et al. and Kensler and Rebbeck have concluded that obesity is not associated with overall risk of prostate cancer, but may be associated with a higher risk of advanced or aggressive prostate cancer (51,56). Since there are few known risk factors for prostate cancer, and it is one of the most prevalent cancers, it is important to clarify inconsistent risk relationships and identify new risk factors.

2.1.3 Lung cancer incidence, mortality, and risk factors

Lung cancer is the leading cause of cancer death among men, and the second leading cause of cancer death among women worldwide (48). It is the second most commonly diagnosed cancer, behind only female breast cancer, accounting for 11.4% of global cancer cases (48). Lung cancer incidence and mortality rates are 3 to 4 times higher in developed countries than in

developing countries, although this pattern may change given that 80% of smokers aged 15 years or older resided in low-income and middle-income countries in 2016 (48,57).

While the majority of lung cancer cases in Canada can be attributed to tobacco smoking, lung cancer incidence is not limited to individuals with a history of smoking. An estimated 10-25% of lung cancers worldwide occur in never smokers (individuals having smoked less than 100 cigarettes in their lifetime) (58,59). Given the high burden of lung cancer in Canada and worldwide, it is important to clarify risk factors other than smoking.

2.1.4 Risk factors associated with cancer

2.1.4.1 Physical health factors

Chronic diseases such as cardiovascular disease, diabetes, and cancer have common risk factors, such as smoking, diet, and physical activity (60). Several mechanisms are also shared including increased inflammation and oxidative stress (31). Evidence relating cancer risk to cardiovascular disease and diabetes is suggestive but not conclusive. A prospective cohort study assessed the extent to which co-occurrence of cardiovascular disease and cancer is due to shared risk factors. Cardiovascular disease risk, as captured by traditional cardiovascular risk factors (age, sex, smoking status), 10-year atherosclerotic risk score, and natriuretic peptide concentrations were found to be associated with increased risk of subsequent cancer (61). Conversely, a heart healthy lifestyle—defined by not smoking, low blood pressure, low cholesterol, low blood sugar, high physical activity, high diet quality, normal BMI—was associated with a lower risk of cancer (61,62). However, results from this study indicate that prevalent cardiovascular disease was not found to be associated with a higher risk of incident

cancer, indicating that the shared risk factors may increase risk for cancer, not the cardiovascular disease itself (61).

Diabetes is another chronic illness with similar risk factors as cancer. For example, low physical activity, obesity, poor diet, alcohol consumption, and smoking have all been associated with a higher risk of diabetes and cancer (63–65) However, diabetes has also been associated with cancer risk as an independent risk factor. A meta-analysis found that diabetes independently increased the risk of breast cancer in women, but not among men (66). Diabetes has also been identified as a risk factor for pancreatic cancer (67), colorectal cancer (68), bladder cancer (69), and liver cancer (70). However, a modest decreased risk has been observed for prostate cancer among men with diabetes (71). It is possible that decreased insulin could have a growth-inhibitory effect on these cells. Insulin has been shown to stimulate growth of a rat prostate cancer cell line *in vitro* (72).

A 2019 umbrella review of meta-analyses and systematic review concluded that diabetes may be positively associated with cancer, but additional research is needed (73). However, a recent Mendelian randomization analysis within a Japanese population-based study found little evidence to support the genetic role of type 2 diabetes in cancer development (74). It is possible that epigenetic changes associated with diabetes could influence subsequent cancer risk, however further research is required.

2.1.4.2 Sociodemographic factors

Age is a primary risk factor for cancer, with risk generally increasing with older age. However, socioeconomic factors, such as income and education, have been consistently associated with cancer incidence. A systematic review and meta-analysis of 64 studies found an

overall increased risk of lung cancer incidence among people with low education and low income (75). To assess trends over time Singh and Jemal assessed socioeconomic and racial/ethnic disparities in United States incidence rates from major cancers from 1950 to 2014 (76). Individuals in more deprived areas or lower education and income groups had higher incidence rates than their more affluent counterparts, with excess risk being particularly marked for lung, colorectal, cervical, stomach, and liver cancer (76).

Furthermore, sociodemographic status can influence an individual's probability of engaging in healthy lifestyle behaviours and developing physical health factors that are related to cancer risk. Cancer mortality and incidence disparities observed in lower socioeconomic groups may reflect these inequalities in smoking, obesity, physical activity, diet, and alcohol use. A study of lifestyle behaviours in Canada found that being female, single, highly educated, or having higher income decreased the likelihood of exposure to multiple cancer lifestyle risk factors (77).

2.2 Cancer and lifestyle factors

In addition to the subtype-specific risk factors mentioned in the above sections, many lifestyle behaviours are modifiable risk factors for cancer. An estimated 33% of cancer cases diagnosed in 2015 in Canada were attributable to modifiable risk factors, led by tobacco smoking, physical inactivity, and excess weight (78).

2.2.1 Smoking and cancer

Smoking is one of the most well-known carcinogens, with its association to cancer incidence and mortality being well-documented for many decades (79–81). It is most commonly

attributed to lung cancer, but research by the International Agency for Research on Cancer (IARC) has shown that it also increases risk for oral, pharynx, larynx, esophagus, pancreas, bladder, pelvis, nasal cavities and paranasal sinuses, nasopharynx, stomach, liver, kidney (renal cell carcinoma) and uterine cervix, and for adenocarcinoma of the oesophagus and myeloid leukaemia (82,83).

There has been a remarkable reduction in smoking prevalence in Canada, a credit to effective public health messaging and legislation such as the Tobacco Sales to Young Persons Act (1988) and the Tobacco Act (1997) (84,85). Between 1950 and 2011, the prevalence of current smoking (including daily and non-daily use) among adults aged 20 years and older has decreased from 68.9% to 18.6% in men, and from 38.2% to 15.4% in women (84).

Although smoking rates have fallen over the past decades, there are disparities in smoking behaviours. Smoking prevalence peaked later in lower socioeconomic groups, compared to higher socioeconomic groups in earlier decades. Furthermore, rates of decline in lower socioeconomic groups and certain provinces, such as the Atlantic provinces and Quebec, have been less steep than other parts of Canada (84). There are also concerns about increased smoking activity among younger cohorts with the rise in popularity of vaping. A robust association has been found between smoking and vaping. Young people who vape have an increased risk of subsequent smoking, and vice versa (86–88). Between 2017 and 2018, among 16 to 19 year olds, the prevalence of vaping and smoking increased in Canada (87).

However, even with successful public health efforts and a decline in smoking behaviours nationwide, smoking is still a major contributor to cancer incidence in Canada (35,77,84). Analysis of CCHS data and cancer incidence data from the Canadian Cancer Registry estimated that 17.5% of all cancers and over 70% of lung cancer cases diagnosed in Canada in 2015 were

attributable to tobacco smoking (89). Although passive smoke exposure in leisure and work spaces has been largely eliminated, it is still a potential exposure in home environments. Furthermore, due to the long latency of cancer, it takes decades to see the impacts of lower levels of smoke exposure to be seen in cancer incidence. The same 2015 study found that 0.8% of cancers diagnosed in Canada were attributable to passive tobacco smoke exposure (89).

2.2.2 Alcohol consumption and cancer

Alcohol is another exposure that has been closely linked to cancer. Canada's Low-Risk Drinking Guidelines recommends reducing long-term health risks by drinking no more than 10 drinks a week for women, with no more than 2 drinks a day (90). For men, 15 drinks a week for men, with no more than 3 drinks a day is recommended. However, North American low-risk drinking guidelines have been criticized as being high compared to international standards (91). A Canadian study from the University of Victoria found that adherence to Canadian guidelines did not eliminate alcohol-caused harm (91). The authors also noted that guidelines of around one drink per day may be more appropriate for such as Canada (91).

Similar to national smoking behaviour, alcohol consumption has declined in recent decades. From 1950 to 1975 in Canada there was an increase in alcohol consumption, then a decline until the 1990s (92–94). From 1996 to 2013, data from the National Population Health Survey (NPHS) and the CCHS suggests that the proportion of people exceeding low-risk drinking guidelines or people abstaining has not changed significantly (95).

Weekly and daily average alcohol consumption of Canadians is not the only measure of concern. The proportion of binge drinkers, defined as the consumption of 5 or more drinks at least once a month in the past year, has increased steadily from 13.7% in 1996 to 19.7% in 2013

(77,95). The corresponding proportions for men were 20.8% in 1996 to 25.7% in 2013, for women these proportions were 6.9% to 13.8% in the same time frame (95). This is supported by an analysis of Canadian consumer trends showing that alcoholic drink sales grew steadily between 2015 and 2020 and were projected to continue to grow (96,97). This evidence suggests that drinking, binge drinking in particular, remains a public health concern.

Alcohol has been classified as a human carcinogen by the IARC since 1988 (98). Although national guidelines vary worldwide, the World Cancer Research Fund International (WCFRI), the American Institute for Cancer Research (AICR) and the Canadian Cancer Society recommend individuals avoid alcohol as any amount of alcohol consumption may increase cancer risk (99). Analysis of CCHS data and cancer incidence data from the Canadian Cancer Registry estimated that 5.2% of alcohol-associated cancers and 1.8% of all cancers combined in 2015 were attributable to alcohol consumption (100). This translated to an estimated attributable cases of 2,089 for men and 1,193 for women (100). It is projected that up to 70,000 cancer cases could be prevented by 2042 if Canadians drank 50% less alcohol by 2032 (100).

2.2.3 Diet and cancer

Eating Well with Canada's Food Guide (EWCFG) was released in 2007, and emphasized consumption of the four food groups: grains, meats and alternatives, vegetables and fruit, and milk products (101). In 2017, Jessri et al. reported that the mean diet score for the Canadian population was 50.8 out of 100, indicating a poor adherence to the EWCFG, and a decrease from the previous 2004 assessment (102,103). In January of 2019, the Government of Canada released Canada's Food Guide, an update of EWCFG (101,104). In contrast to the previous emphasis on food groups, the new Canada's Food Guide focuses on dietary patterns, making water a drink of

choice, limiting processed foods, and cooking more frequently (104). It also highlights eating plenty of fruits and vegetables, whole grain foods, and protein foods, and choosing protein foods that come from plants more often (104). These new guidelines are in line with general recommendations for chronic disease prevention.

A healthy diet has long been an important aspect of disease prevention. The WCFRI recommends eating a diet rich in wholegrains, vegetables, fruit, and beans, aiming for five or more servings of fruits and vegetables a day (105). A diet that is primarily plant-based (i.e., high intake of fruit, vegetables, and whole grains, and a lower consumption of processed foods, and red and processed meat) may decrease cancer risk. A Canadian population-based study found that high meat and sugary diet patterns increased risk of colorectal cancer, while a plant-based diet pattern decreased it (106). Poirier et al. estimated that low fruit and vegetable consumption was attributed to 6.1% and 2.2% of colorectal cancers diagnosed in 2015 in Canada, respectively (107). A similar analysis found that red meat (beef, lamb, and pork) and processed meat (bacon, sausage) were attributed to 0.9% and 0.7% of all cancers in Canada in 2015, respectively (108).

2.2.4 Sedentary behaviour, physical activity, and cancer

Physical activity and inactivity are other key modifiable behaviours for cancer risk. According to Owen et al, sedentary jobs have increased significantly in the past decades, with twice as many workers in jobs involving light activity (109). This contributes to population inactivity levels and as a result, sedentary time is becoming increasingly supported in the literature as an independent cancer risk factor. It is defined as any prolonged, non-sleep activity, absent of bodily movement with a low energy expenditure of 1.0 to 1.5 metabolic equivalents

(110). The proportion of all incident cancer cases diagnosed in Canada in 2015 that were attributable to three hours of more of daily leisure-time sedentary behaviour was 1.7% (111).

Sedentary behavior and physical activity are two different constructs, with each having distinct physiological health effects and outcomes including cancer (109,112). The Canadian Physical Guidelines for Adults recommends 150 minutes of moderate to vigorous intensity physical activity (MVPA) per week, in bouts of at least 10 minutes, in addition to engaging in muscle and bone strengthening activities at least twice a week (113,114). In order to reduce risk of multiple cancers, the Canadian Cancer Society recommends that adults aim for 30 minutes of daily physical activity including MVPA and strengthening exercises (12).

From 2007 to 2009, accelerometer-measured physical activity data was collected for the first time as part of the Canadian Health Measures Survey (CHMS). CHMS launched in 2007 and works to collect health information from Canadians through surveys and direct physical measurements, with the intention of creating a nationally representative sample (115). Results showed that only 15% of adults were meeting MVPA guidelines (116). These results were significantly lower than the previous self-reported data from CHMS, which indicated that nearly two-thirds of Canadian adults were meeting physical activity guidelines (117). This suggests that Canadians generally overestimate their physical activity levels in self-reported data.

More recent data assessing accelerometer-measured activity levels of Canadian adults found that there were no significant temporal changes in average daily minutes of MVPA from 2007 to 2017 (118). In 2016 and 2017, 16% of Canadian adults met the Canadian Physical Activity Guidelines of 150 minutes of MVPA per week, as measured by accelerometer (118). This represents quite a low proportion of Canadians that are meeting the minimum guidelines and illustrates a need for targeted engagement in physical activity programming. Particularly

considering the burden of cancers that could be prevented by sufficient physical activity. A study by Friedenreich et al. found that the proportion of cancers attributed to a lack of physical activity in Canada in 2015 was 4.9% (119).

2.2.5 Obesity and cancer

Excess body weight is another indicator of activity levels and is generally assessed independently of sedentary behaviour and physical activity. The World Health Organization (WHO) considers the overweight (BMI: 25.0-29.9) and obese (BMI ≥ 30) BMI categories to be indicative of excess weight (120). The WCFRI recommends a BMI in the normal range (BMI: 18.5-24.9) from age 21 onwards, and to avoid weight gain and increases in waist circumference, to reduce the risk of developing cancer (99).

Dianne et al. found that 5.7% of all cancer cases in Canada in the year of 2010 were attributable to excess weight (121). Brenner et al. found a similar estimate for the year of 2015, with 3.1% of all incident cancers and 7.2% of associated cancers being attributable to excess weight (122). A new report by Statistics Canada in 2018, showed that 26.8% of Canadians adults reported a height and weight that classified them as obese, and another 36.3% were classified as overweight (123). Overall, 63.1% of Canadians have an increased risk of cancer due to excess weight, highlighting this risk factor as a focus for cancer prevention (123).

2.3 Mental health disorders

Mental health disorders have a high social and economic burden both worldwide and in Canada. Mental disorders, including substance use disorders, affect up to one in five Canadians each year (16). In total, the total annual economic burden of mental health disorders in Canada

has been estimated to be approximately $51 billion dollars (124). Projections by Smetanin et al. estimate that the total cumulative costs of mental health disorders in Canada over the next 30 years could exceed $2.5 trillion dollars (16).

2.3.1 Anxiety

Anxiety disorders are a group of disorders that include social anxiety, phobias, panic disorder, with the most common being generalized anxiety disorder (GAD). Anxiety disorders are characterized by persistent feelings of excessive fear and anxiety and related behavioural disturbances. Anxiety is the second most common mental health disorder in Canada, behind depression. The past-year prevalence of anxiety disorders in Canadians is approximately 3%, according to a 2019 study (125).

One of the most common screening tools for anxiety is the seven-item Generalized Anxiety Disorder (GAD-7) questionnaire, a subscale of the longer Patient Health Questionnaire (PHQ). The PHQ is a multiple-choice self-report inventory that is used as a screening and diagnostic tool for a variety of mental health disorders (126). When using a cut-off score of 10, the GAD-7 has demonstrated a sensitivity of 89% and specificity of 82% for detecting GAD in an adult clinical research sample (127).

2.3.2 Depression

Depression is the most common mental disorder in Canada, characterized by the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function (19,125). Data from CCHS estimates

that approximately 5% of Canadian adults have depression and the prevalence has been relatively stable between 2000 and 2016 (1,125).

There is a wide range of screening tools available to identify depressive disorders, that vary in their psychometric properties, target populations, and length. One of the primary and most extensively tested screening tool for depression in adults is the nine-item PHQ (PHQ-9), which like the GAD-7 is a derivative of the PHQ (128,129). The PHQ-9 has high sensitivity and specificity values for diagnosing depression. A review of 14 papers across 11 countries found that the sensitivity of the PHQ-9 ranged from 28% to 95% and specificity ranged from 61% to 98% on the general adult primary care population (129). Given its high sensitivity and specificity and breadth of data on its reliability and validity, there is a high level of evidence supporting its use as a primary depression screening tool across primary healthcare settings (129).

2.3.3 Co-morbid anxiety and depression

Anxiety and depressive disorders commonly co-occur. A Canadian study found 50% of individuals with anxiety also displayed depressive symptoms (130). Another study with CCHS data from 2020 estimated that comorbid depression and anxiety prevalence was 1.2% among Canadian adults (1). Clinically, comorbidity is associated with greater severity of symptoms, increased risk of suicide, poorer quality of life, and a lower level of cognitive functioning (131,132).

2.3.4 Antidepressant use

From 2015-2018, 13.2% of American adults aged 18 and over used antidepressant medications in the past 30 days (133). Use was higher among women (17.7%) than men (8.4%)

(133). Data on nationwide antidepressant use in Canadian adults is lacking, however there is some evidence to estimate recent trends. Statistics Canada analyzed results from the combined 2007 to 2009 and 2009 to 2011 CHMS and found that antidepressant use in the 45 to 64 age group was 17% among women and 8% among men, a prevalence similar to that observed in the United States (133,134). Three Canadian studies identified that the prevalence, but not incidence of antidepressant use has been increasing over time (135–137). According to the Organization for Economic Co-operation and Development 2019 Health at a Glance report, Canada was the second highest user of antidepressants (110 defined daily dose, per 1000 people per day), second only to Iceland (141 defined daily dose, per 1000 people per day) (138).

2.3.5 Risk factors associated with mental health disorders

2.3.5.1 Sociodemographic factors

Mental health disorders vary widely by age, with 70% of people experiencing onset of mental health problems during childhood or adolescence (139). Young people aged 15 to 24 are more likely to experience mental health disorders and/or substance use disorders than any other age group (18). There is also a key difference in mental health disorder prevalence between women and men. Epidemiological studies throughout the world consistently reported higher rates of depression and anxiety disorders in women, whereas men consistently show higher rates of substance disorders (18,140,141). The most recent CCHS data indicates that females had a higher rate of depression within the previous 12 months (5.8%), than males (3.6%) (18). Similar results were seen in anxiety, with females having a higher rate of GAD (3.2%) compared to males (2.0%) (18). Males had higher rates of substance use disorders (6.4%), than females

(2.5%) (18). These sex differences have not been able to be explained by sociodemographic factors such as marital status, number of children, parenthood, and social class (142).

A systematic review of social inequalities and common mental health disorders found that mental health disorders are more frequent in those who were unemployed, had lower levels of education, and low income (143). These findings were replicated in a study of CCHS data in Ontario, which also observed a higher prevalence of depression among individuals who were divorced, compared to those living with married partners (144).

2.3.5.2 Physical health factors

The link between mental health disorders and physical health has become increasingly clear over the years. Mental health disorders often co-exist with chronic illnesses, and many bidirectional relationships have been observed (145,146). Medical conditions that are accompanied by a high symptom burden, such as chronic pain or cardiovascular disease, can lead to the development of high stress and subsequent mental health disorders (147). Conversely, some mental health disorders that are characterized by inflammation, such as depression, can be a risk factor for chronic conditions like cardiovascular disease (148)

In 2016, the Mood and Anxiety Disorders in Canada report was published, using data from the Canadian Chronic Disease Surveillance System for the national surveillance of mood and anxiety disorders among Canadians aged one year and older (149). A higher prevalence of asthma and chronic obstructive pulmonary disease (COPD), and to a lesser degree ischemic heart disease, diabetes and hypertension, was observed among people who used health services for mood and anxiety disorders compared to those who did not (145,149).

Scott et al. used the cross-national World Mental Health-Composite International Diagnostic Interview (WMH-CIDI) survey (n=52,095) to examine associations between DSM-5

mental disorders and subsequent heart disease onset (150). A significant positive association was found between both depression and panic disorder, and heart disease onset (150).

COPD is another illness that has frequently been studied for a bidirectional relationship with mental health disorders. A study using the WMH-CIDI study found that both depression and GAD were associated with increased risk of COPD (151). There was a substantive cumulative risk of COPD among those who had multiple mental disorders over their lifetime (151).

Diabetes and mental health disorders have been linked for centuries. In the 17th century Thomas Willis speculated that diabetes was caused by "*long sorrow and other depressions*". A meta-analysis of 42 studies, with a combined sample size of 21,351 subjects, assessed the prevalence of depression in adults with type 1 or type 2 diabetes (152). The odds of depression in the diabetic group were twice that of the nondiabetic comparison group (OR = 2.0, 95% CI 1.8-2.2), and did not differ by sex or type of diabetes (152). Another meta-analysis found significant associations in both directions, with diabetes increasing risk for depression, and depression increasing risk for subsequent diagnosis of diabetes (153).

2.4 Mental health disorders and lifestyle factors

2.4.1 Smoking and mental health disorders

The American Cancer Society found that although smoking rates have decreased in the United States, the prevalence of cigarette smoking is still higher among certain subpopulations, including individuals with mental health disorders (154). A study in New Jersey assessed differences in smoking rates and temporal trends of smoking prevalence of individuals with poor mental health, compared to those with better mental health. They found that smokers with poor

mental health are more likely to be current smokers and less likely to be never smokers compared to those with better mental health (155). The authors also noted that this disparity has increased over time (155). A 2014 study in England had similar findings. While there were steady declines in smoking prevalence from 1993 to 2011 among the general population, there were no significant long-term changes in smoking prevalence and cigarette consumption among those who reported a mental health disorder (156). In a Canadian study of CCHS data, participants who had experienced a substance use or mental health disorder in their lifetime had over a two-fold higher risk of being a current smoker than those who had not (35).

While evidence regarding smoking behaviours among individuals with mental health disorders are well-established, identifying the causal pathway is difficult. A systematic review of 148 studies on the association of cigarette smoking with depression and anxiety concluded that the results were too heterogenous to support a causal relationship either way (157). Plurphanswat et al. used the method of instrumental variables (using a third variable which affects the outcome only through its effect on the exposure) to address plausible reverse causality (158). They used state cigarette excise tax as an instrument for smoking (158). Their findings showed that smoking increases the number of days with poor mental health, especially among individuals with more severe mental health disorders, indicating that smoking may cause poor mental health (158).

Mendelian randomization is another technique to identify causal effects of a modifiable exposure on disease, by using genetic variants as an instrument for the exposure. The underlying principle is that genetic variants that mirror the effect of a modifiable environmental exposure (e.g., smoking) that itself alters disease risk (e.g., lung cancer), should also be related to disease risk (159). The genetic variant can then be used as an instrument for the environmental exposure

to predict a causal relationship, as genetic variants are not generally associated with the behavioural, social, or physiological factors that could confound the relationship between smoking and lung cancer (159). A Mendelian randomization study assessed the association of smoking initiation with seven psychiatric disorders and found significant positive associations between genetically predicted smoking initiation and suicide attempts (OR = 1.96, 95% CI: 1.70, 2.27), post-traumatic stress disorder (OR = 1.69, 95% CI: 1.32, 2.16), schizophrenia (OR = 1.54, 95% CI: 1.35, 1.75), bipolar disorder (OR = 1.41, 95% CI: 1.25, 1.59), insomnia (OR = 1.20, 95% CI: 1.14, 1.25), and major depressive disorder (OR = 1.38, 95% CI: 1.31, 1.45) (160). This data suggests that there is a potential causal link between smoking and mental health disorders, which may warrant supportive services in clinical and primary care settings.

2.4.2 Alcohol consumption and mental health disorders

To clarify the temporal sequence between alcohol consumption and mental health a prospective cohort study compared four dynamic latent change scores models, a statistical technique used to estimate longitudinal relationships, and concluded that the model where mental health influenced changes in alcohol consumption was the best fit (161). In this model, those with better mental health tended to have greater reductions (or smaller increases) in their drinking (161). A small Mendelian randomization study (n = 476) in China indicated that alcohol use was causally associated with a lower risk of depression (162). The effect size was larger after adjustments for confounders and the exclusion of heavy or former drinkers (162). These findings are in line with previous research that reported regular alcohol consumption was associated with better mental health and lower prevalence of depression (163–165). These conclusions may seem counterintuitive given that alcohol is considered a nervous system depressant (166). However, it

is hypothesized that there are potential psychological benefits of low to moderate alcohol consumption such as stress reduction and mood enhancement (162,163). It should be noted however that while lower levels of alcohol consumption may have some benefits, excessive drinking can be harmful to mental health. A Canadian study found that among persons who have experienced a depressive episode in the year prior to their interview, the prevalence of alcohol dependence was estimated at 32.3% while it was 9.5% for persons without depression (167). Prospective studies have shown that alcohol use disorders can predict development of major depressive disorder, and vice versa (37,168,169). The same bidirectional relationship has been observed between anxiety disorders and alcohol use disorders, with evidence also suggesting that anxiety disorders can contribute to risk of relapse (168,170,171).

2.4.3 Diet, physical activity, and mental health disorders

Research from the Netherlands Study of Depression and Anxiety found that diet quality was significantly worse among subjects with a current depressive or anxiety disorder than among healthy controls (43). Severity of depression or anxiety symptoms showed a dose-response association with poorer diet quality (43). Those with comorbid depressive and anxiety disorders had the lowest diet quality (43). Interestingly, a cohort study in Australia found that while individuals with current depression had lower diet quality, those who had been previously depressed and sought treatment had higher diet quality at a later assessment (172). This may indicate that management of depression has a positive impact on diet. In regard to depression incidence, a meta-analysis of prospective studies found that participants who had low-inflammatory diets had a lower depression risk (OR = 0.81, 95% CI: 0.71-0.92), however lower

quality diets and junk/fast foods were not associated with a higher depression risk (OR's range 1.03-1.11) (173).

A meta-analysis of 49 unique prospective studies (n = 266,939) found that compared with participants with low levels of physical activity, those with high levels had lower odds of developing depression (OR = 0.83, 95% CI=0.79, 0.88) (174). A subsequent meta-meta-analysis based on 92 studies found that physical activity reduced depression (standardised mean difference (SMD) = –0.50; 95% CI: –0.93 to –0.06) and anxiety (SMD = –0.38; 95% CI: –0.66 to –0.11) (175). These analyses suggest that there is a bidirectional relationship between mental health disorders and physical activity.

2.4.4 Obesity and mental health disorders

Both obesity and mental health disorders are major public health concerns and may be more closely related than immediately evident. A meta-analysis of longitudinal studies found a significant reciprocal link between depression and obesity (176). Obesity was found to increase the risk of depression, and depression was associated with increased risk of obesity (176). Another meta-analysis of cross-sectional studies by de Wit et al. found a significant positive association between depression and obesity, which appeared to be more robust among females (177). It is likely that this association is due to several shared psychological and physical pathways. Both obesity and depression are characterized in part by changes in HPA axis and cortisol regulation, as well as chronic low-grade inflammation (178,179). Furthermore, many psychosocial factors have been implicated in obesity risk that may influence the association with depression. A systematic review found that education, body image, binge eating, physical health, and psychological characteristics were consistently associated with the relationship between

obesity and depression (180). This could contribute to the finding of de Wit et al. which showed a more robust relationship among females, as body image issues have been found to be more prevalent and severe among women (181,182). However, similar to the health behaviours described in above sections, the evidence suggests that obesity and mental share a bidirectional relationship that warrants clinical and epidemiological attention.

2.5 The relationship between mental health disorders and cancer

2.5.1 Depression, anxiety, and cancer incidence

Given the public health burden of mental health disorders and cancer and their common risk factors, the relationship between them has been a significant research interest. A cohort study of n=24,066 participants in Taiwan assessed the relationship between anxiety disorders and risk of developing cancer. The relationship between anxiety and risk of all cancers was not significant, but participants with anxiety disorders had a higher risk of prostate cancer, and a lower risk of cervical cancer (183). However, a subsequent Taiwanese study found that all cancer risk, as well as lung and prostate cancer risk in men, was significantly higher in participants with GAD (184). In 2016, a third Taiwanese study found a significant association between anxiety disorders and urological cancer (185). Given that all of the above-mentioned studies used data from the National Health Database and used International Classification of Diseases ninth revision (ICD-9) codes to classify exposures, these results seem inconsistent. All three studies used data from between 2000 and 2010; however, sample sizes varied slightly with n=24,066, n=19,793, and n=58,603 for the first, second, and third papers, respectively. Furthermore, the authors noted that a major limitation of the National Health Database was that it did not have

information regarding health behaviours such as smoking or alcohol consumption, which could affect the relationship between mental health disorders and cancer.

In a multi-national study, O'Neill et al. used data from the WHO retrospective population surveys, which assessed lifetime prevalence of 16 DSM-5 mental disorders in nineteen countries (n=52,095) (3). Panic disorder, specific phobia and alcohol abuse were associated with reporting cancer in this study, and the risk of reporting cancer increased if a person had more mental disorders (3). The study also revealed a significant association between depression and self-reported cancer for women (3). While this study also did not adjust for health behaviours and was limited by recall bias, its geographic scope and sample size provide stronger insights into this relationship.

A systematic review and meta-analysis of 25 studies with a pooled sample of 1,469,179 participants and 89,716 incident cases of cancer assessed the association between depression and incident cancer risk (2). They found that depression was significantly associated with all cancer risk (RR = 1.15, 95% CI: 1.09-1.22), liver cancer (RR = 1.20, 95% CI: 1.01-1.43) and lung cancer (RR = 1.33, 95% CI: 1.04-1.72) (2). Subgroup analysis of studies in North America showed a summary relative risk for all cancers (RR = 1.30, 95% CI: 1.15-1.48) (2). No significant associations were found for breast, prostate, or colorectal/colon cancer (2). Furthermore, the authors noted that very few studies explored lifestyle cancer risk factors in patients with depression. For example, smoking status was not assessed in investigations of tobacco-related cancers, such as oral and lung cancer, and alcohol use was not assessed with respect to liver cancer (2). This is important given the established relationship between lifestyle behaviours and both mental health disorders and cancer. It is likely that lifestyle factors play an important mechanistic role in this relationship.

Furthermore, few studies have explored the potential confounding effects of sociodemographic factors (e.g., education, income, and ethnicity) and chronic conditions (e.g., diabetes, cardiovascular disease, and COPD). The three Taiwanese studies adjusted for chronic conditions and urbanization, but not health behaviours (183–185). O'Neill et al. adjusted for age and country alone, but noted that education was not a significant covariate and was thus excluded (3). Gross et al. adjusted for age, sex, and smoking status, and did not account for any chronic conditions or sociodemographic factors (4). As with lifestyle behaviours, sociodemographic factors and chronic conditions are associated with both mental health disorders and cancer. Therefore, it is important to take them into account when analyzing this relationship.

There is also some evidence to suggest that how the mental health disorder variable captures the severity and/or longevity of depression and anxiety may impact results. For example, a systematic review and meta-analysis of 51 cohort studies involving 2,611,907 participants found that clinically diagnosed depression and anxiety were related to higher cancer incidence, poorer cancer survival, and higher cancer-specific mortality (186). However, psychological distress (symptoms of depression and anxiety) was related only to higher cancer-specific mortality and poorer cancer survival and not increased cancer incidence (186).

Although there is a large literature base on mental health disorders and cancer incidence, findings are not conclusive. Studies that consider health behaviours and relevant confounders are lacking, and may contribute to inconsistent results in the relationship between mental health disorders and cancer risk (2,183–185). Furthermore, depression and anxiety can be defined using various methods that capture overlapping but different aspects of mental health disorders. Examining multiple definitions of mental health disorders in relation to cancer within a well-defined population may help clarify inconsistencies in the literature.

2.5.2 Mental health disorders, healthy lifestyle behaviours, and cancer

Given the shared risk factors and confounders between mental health disorders and cancer, a mediation analysis is a useful statistical tool to clarify this relationship. In the absence of a study design that can attribute cause-effect relationships, mediation analyses can contribute to a better understanding of the relationship between an exposure and outcome. It involves quantifying the causal sequence by which an exposure causes a mediating variable that causes an outcome. Studies have used mediation models to identify sociodemographic and psychosocial factors that contribute to the development of mental health disorders in cancer survivors or individuals with a current cancer diagnosis (187–191). Recent studies have also utilized mediation models to identify the mediation effect of healthy lifestyle behaviours on the relationship between sociodemographic factors and cancer outcomes (192,193). For example, Nejatinamini et al. assessed smoking, excess alcohol consumption, low fruit-and-vegetable intake, physical inactivity, and obesity as mediators in the relationship between socioeconomic position and cancer morbidity and mortality (193). They found that healthy lifestyle behaviours explained 45.6% of associations between low socioeconomic status and all cancer morbidity and mortality. Smoking was the largest mediator in the total population and for males, and obesity was the largest mediator for females (193).

Very few studies have examined how lifestyle behaviours may mediate the relationship between mental health disorders and cancer incidence. A cross-sectional analysis of n=8,175 adults aged 50 and over from The Irish Longitudinal Study on Ageing (TILDA) assessed the relationship between mental health difficulties and smoking related-diseases (respiratory disease, cardiovascular disease, and smoking-related cancers) (194). The authors found that while mental health difficulties were significantly associated with both smoking status and smoking-related

disease, smoking status was not a mediator in this relationship (194). However, it should be noted that smoking-related cancers were not assessed as an individual outcome but grouped with other smoking-related diseases.

A cohort study using data from the Nurses' Health Study found that among n=1,009 cases of lung cancer, women with the highest level of depressive symptoms had an increased lung cancer risk compared to the lowest level (195). In a test of mediation, lifetime pack-years of smoking accounted for 38% of the overall association between depressive symptoms and cancer risk (195). The authors also noted that results were similar or stronger when considering time-updated depression status (using depressive symptoms, physician diagnosis, and regular antidepressant use) and chronicity of depressive symptoms (195). Given the strong association between multiple health behaviours such as smoking, alcohol consumption, physical activity, diet, and obesity with mental health disorders and cancer incidence, analysis of these factors as mediators between mental health disorders and cancer could help elucidate the nature of this relationship.

Chapter 3: Methods

3.1 Study design

The current study used a cohort study design to investigate the relationship between anxiety and depression, and risk of cancer. Ethics approval for this project was obtained from the University of British Columbia Clinical Research Board (H17-02706). The CARTaGENE study obtained ethics approval from the CHU Sainte-Justine, reference: MP-21-2011-345, 3297.

3.2 CARTaGENE cohort

CARTaGENE is part of the national Canadian Partnership for Tomorrow's Health (CanPath), a prospective, longitudinal cohort study, and one of the largest research platforms in the world. CanPath was launched to investigate how environment, genetics and lifestyle factors interact to affect the development and progression of cancer and other chronic diseases (196). CanPath consists of seven regional cohorts across Canada; BC Generations Project, Alberta's Tomorrow Project, Saskatchewan PATH, Manitoba Tomorrow Project, Ontario Health Study, CARTaGENE and the Atlantic Path. CanPATH participants completed harmonized core questionnaires as well as questionnaires specific to a given cohort.

Participants for the present study were drawn from CARTaGENE due to the cohort-specific questionnaires on mental health. Details of the survey methods and cohort profile have previously been published (47). In brief, CARTaGENE was initiated in 2009 and by 2015 43,000 men and women aged 40-69 were enrolled in the study (47). The study was conducted in two phases. Phase A was conducted from July 2009 to October 2010, and Phase B ran from December 2012 to February 2015 (47). Participants were recruited in five municipal centres in the province of Quebec, Canada, from the Regie de l'assurance maladie du Quebec (RAMQ). (47). At study baseline participants completed self-report questionnaires that asked about

sociodemographics, medications, and health and lifestyle behaviours (47). A proportion (56%) of the cohort underwent physical measurements at assessment centres (47). Questionnaire data are available from baseline (2009-2015) with follow-up for incident cancer until 2018. Participants were also asked to consent to linkage of personal health identifiers to RAMQ administrative data.

3.3 Data source

Individual-level data were self-reported in the CARTaGENE questionnaires, or collected through the provincial administrative health database, RAMQ. This data includes hospitalizations, causes of death, types of cancer, and prescribed medications covered by the public health insurance system.

3.4 Study variables

3.4.1 Dependent variables

As part of the informed consent process of the CARTaGENE project, participants agreed to the linkage of their personal health number with administrative health databases including cancer registry, hospitalization, and medication data. Incident cancers were determined from the cancer registry until 2010. After 2010, incident cancers were defined from hospitalization data using Tonelli criteria (197). Tonelli criteria are a set of validated algorithms that can be used to identify chronic conditions from administrative data (197). First cancer diagnostic date was used for cases meeting Tonelli criteria, to derive a time variable for use in analysis. If a prostate or lung cancer case had a missing diagnosis date, it would be substituted with the corresponding any cancer diagnostic time, where possible.

3.4.2 Independent variables

3.4.2.1 Depression

Depressive symptoms at baseline were assessed using the PHQ-9, a nine-item questionnaire that assesses symptoms of depression over the past two weeks (198). A meta-analysis of 18 validation studies (n = 7180) in various clinical settings found that the optimal cut-off score for detecting major depressive disorders with the PHQ-9 has been determined to be 10 (199). This score has a has a sensitivity of 88% and a specificity of 88% in an adult primary care sample (199).

Self-reported depression data was also available from CARTaGENE. In the baseline questionnaire, participants were asked "has a physician ever told you that you have depression?" Positive responses to this question were recorded as a lifetime prevalence of depression. Payette et al. evaluated the agreement between self-reported medical diagnosis of depression and administrative health data and found a kappa statistic of 0.45 (95% CI: 0.43-0.47), indicating a moderate agreement (200). The authors noted that the results of their study suggested that CARTaGENE participants were generally able to correctly identify the kind of diseases they had (200).

CARTaGENE participants also brought their current medication or reported their current medication at their interview. Medication was classified as an antidepressant based on the ATC code that represented a specific medication name (201). A Quebec study by Wong et al. found that the majority of antidepressant medications (55.2%) were indicated for depression (201). The second most common indication was anxiety disorders (18.5%). (201).

Depression was modelled using three definitions: a binary variable defined by the validated PHQ-9 cut-off score, a binary variable of antidepressant use (yes/no), and a third

variable that defined depression as any of PHQ-9 score over the cut-off, use of antidepressants, or positive response for self-report of physician diagnosis.

The advantage of using different definitions of depression is that the PHQ-9 only assesses the most recent two weeks of symptoms. Utilizing the three measures described above provides multiple ways of assessing depressive symptoms within multiple time frames – at baseline, and prior to baseline.

3.4.2.2 Anxiety

Anxiety symptoms were assessed at baseline using the GAD-7, a seven-item self-report scale that assesses symptoms over the past two weeks (127). A cut-off of 10 was used to define cases with clinically relevant anxiety symptoms, this point has a sensitivity of 89% and specificity of 82% for detecting generalized anxiety disorders (127). Self-reported anxiety in the CARTaGENE cohort was determined by asking participants "Has a physician ever told you that you have an anxiety disorder?". However, this variable was only collected in Phase B of the CARTaGENE cohort study, resulting in a high proportion of missing data. Thus, anxiety was only assessed using the GAD-7 definition.

3.4.2.3 Co-morbid depression and anxiety

Co-morbid depression and anxiety was defined as participants who scored 10 or higher on both the PHQ-9 and the GAD-7 questionnaires.

3.4.3 Covariates

Covariates assessed for potential confounding and mediating effects included sociodemographic factors (age, sex, ethnicity, education, marital status, and income), lifestyle behaviours (smoking status, alcohol consumption, sleep, physical activity, body mass index (BMI), fruit and vegetable consumption (servings/day), and health status (previous diagnosis of diabetes or myocardial infarction).

Age was analyzed as a continuous variable. Ethnicity was dichotomized as white and non-white, as participants were predominately white (83.3%) (47). Education was categorized as high school or lower, college, and university or higher. Marital status was dichotomized as living with partners (married or common-law), and without partners (single, divorced, or widowed). Household income was categorized as less than $50,000, $50,000-74,999, $75,000-150,000, and greater than $150,000.

Smoking status was categorized as former smokers, consisting of those who have smoked at least 100 cigarettes during their lifetime but did not smoke within the past 30 days of the survey, current smokers as those who have smoked at least 100 cigarettes in their lifetime and smoked in the past 30 days. All other participants were categorized as non-smokers. Alcohol consumption is based on participant response at baseline when asked about drinking in the last 12 months. Participants were classified as abstainers (never drinking alcohol), former (drank alcohol before but not over the past 12 months), occasional ($\leq$2−3 times/month), regular ($\geq$ once/week but $\leq$2−3 times/week), and habitual drinkers ($\geq$ 4–5 times/week). Average hours of sleep were categorized as < 7 hours, 7-9 hours, and 9+ hours per night. Physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ). The baseline questionnaire included both the long- and short-form IPAQ. Long-form scores were used where

possible and substituted with short-form score values. IPAQ scores were categorized into low, moderate, and high as defined by the IPAQ scoring protocol (**Appendix A.1**) (202). BMI was categorized based on standard classification: less than 24.9 kg/m^2 as underweight/normal, 25.0 to 29.9 kg/m^2 as overweight, and over 30 kg/m^2 as obese. BMI measurements for participants were obtained by bio-impedance, based on height/weight measured by technician for those who attended in-person assessments, or from self-reported height/weight. The categories 'underweight' and 'normal' were combined due to low prevalence of underweight participants. The servings of fruits and vegetables per day were summed and dichotomized into: less than five, and greater than or equal to five servings of fruit and vegetables per day.

In addition to the above-mentioned covariates, cancer specific risk factors were evaluated. Covariates that were considered for models evaluating lung cancer risk were COPD and family history of lung cancer. Studies have shown that a previous COPD diagnosis can increase the risk of incident depression or anxiety (203–205). Family history of lung cancer was defined as a participant's mother, father, or sibling having been diagnosed with lung cancer. Family history of prostate cancer was considered for models evaluating prostate cancer risk and was defined as whether or not their father had ever been diagnosed with prostate cancer, or whether any number of their siblings had ever been diagnosed with prostate cancer.

3.5 Study sample

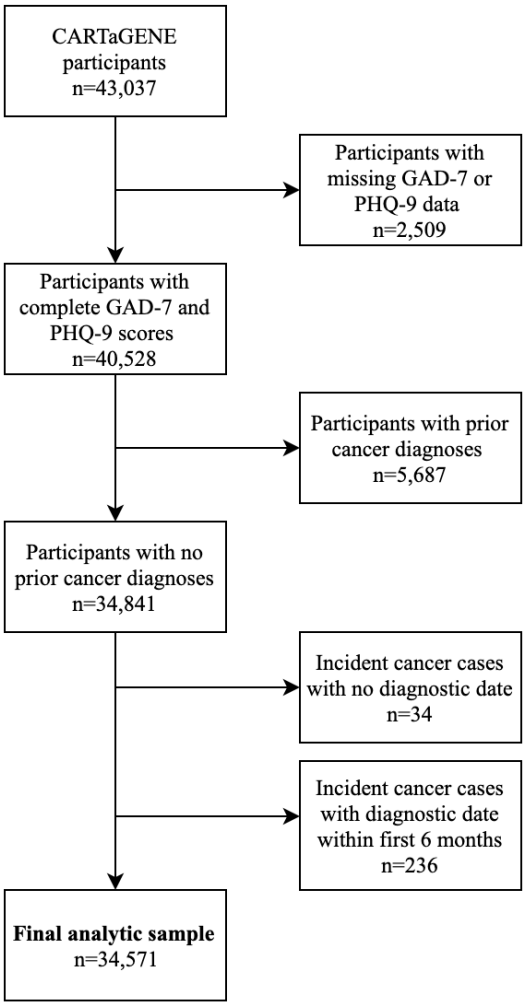
Participants were excluded if there was incomplete data from the PHQ-9 and GAD-7 questionnaires (n=2,509) (**Figure 3.1**). Additionally, participants were excluded if they reported a prior cancer diagnosis at baseline (n=6,847) (**Figure 3.1**). Individuals with a prevalent cancer have an increased risk for a second diagnosis (206,207). Donin et al. identified that nearly 1 in 12

patients diagnosed with a common cancer developed a second malignancy (206). A prevalent cancer case was defined by self-report and administrative health data: if a participant had a positive response to the question “has a doctor ever told you that you have a cancer or malignancy of any kind”, or had been identified as a cancer case through RAMQ data using criteria defined by Tonelli *et al* (one hospitalization or two claims in two years or less) they were defined as a prevalent cancer case (197). Individuals who did not have record of a prevalent cancer from either self-reported cancer or administrative health data were considered as not having a history of cancer (n=1096) (208).

Incidence of any cancer, lung cancer, and prostate cancer that were missing a diagnosis date (n=34) were excluded from the sample (**Figure 3.1**). Incidence cancers (all, lung and prostate) with diagnosis dates that occurred within six months of the baseline questionnaire were excluded from the study (n=236) (**Figure 3.1**) as it may suggest that a pathology may have been already present, but not yet detected and diagnosed.

The final analytical sample size was 34,571 participants including 329 prostate cancer cases, 305 lung cancer cases, 2,888 any cancer cases, and 31,049 participants without cancer (**Figure 3.1**).

Figure 3.1 A flow chart for the selection of the final analytic sample.



3.6 Missing data

Most independent variables and covariates had missing values (**Appendix A.2**). It is implausible that the data was missing completely at random (MCAR), meaning that the utilization of a complete-case analysis method would introduce bias (209). This method would also lead to an exclusion of a substantial proportion of the original sample, causing a loss of precision and power in the study (209). Therefore, multiple imputation was selected as a suitable approach to dealing with missing data. Instead of assuming data are MCAR, it is based on the assumption that data are missing at random (MAR) (209). This method uses patterns of observed values to predict

multiple plausible values for the missing data, creating a number of "completed" datasets (209–211). Uncertainty is accounted for in this process because random components are incorporated into different imputed datasets (209–211).

As mentioned previously, participants were excluded if they did not have data for the GAD-7 or PHQ-9 exposure variables. Participant responses for individual items on the GAD-7 and PHQ-9 questionnaires were not available from CARTaGENE and performing multiple imputation on a derived variable (the sum of the individual questionnaire items) would produce inconsistent imputations.

Multiple imputation was performed using the *'Multivariate Imputations by Chained Equation (MICE)'* package in R (212). The missing values of age, alcohol consumption, education, physical activity, ethnicity, smoking status, COPD, fruit and vegetable consumption, sleep, BMI, income, and depression occurrence were imputed. Sex and self-perceived health were included as auxiliary variables in the multiple imputation to increase the likelihood that the MAR assumption holds, as they were correlated with the variables with missing values.

Alcohol consumption and fruit and vegetable consumption were passively imputed by calculating the ratios of the imputed variables. MICE was utilized for this process, which is a method based on fully conditional specification where each incomplete variable is imputed by a separate model (212). The *'mice'* package allows for different data types to have assigned imputation methods (212). Predictive mean matching method was used for continuous variables, logistic regression for binary variables and multinomial logistic regression for categorical variables with more than 2 categories (212). Given that the highest fraction of missing information was approximately 0.1 in this dataset, 20 imputed datasets with 10 iterations were created to achieve sufficient statistical power, according to Graham and colleagues (213).

3.7 Descriptive analysis

Distributions of continuous and categorical variables were assessed with histograms and bar plots, respectively. Contingency tables were used to display the counts and frequencies that were calculated for categorical variables and means that were computed for continuous variables. If the number of cancer cases within levels of categorical variables were insufficient, the levels were collapsed to facilitate the analysis (e.g., BMI categories). Spearman correlation analysis was conducted among covariates to examine potential multi-collinearity.

3.8 Cox proportional-hazards regression models

Cox proportional hazards regression analysis was used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) between the exposure and outcome. Time-on-study was used as the time-scale (continuous in days) included as a covariate in the model (214). Days of follow-up for cases was determined from the difference between first hospitalization or first claim record in the case of Tonelli criteria or date of diagnosis from the cancer registry and date of consent for the baseline questionnaire. Follow-up for non-cases was determined as the difference between date of last linkage to the RAMQ database, or date of death, and date of consent for the baseline questionnaire.

Directed acyclic graphs were constructed to conceptualize potential confounders. Then as per Evans et al., a change in coefficient method was selected to simplify the full models (215). Model selection was performed by selecting significant confounders using a stepwise procedure, with a significance level of 10%. This method for covariate selection is widely used and the criterion has been standardized for use in Cox regression models (216–218). Significance criteria are generally applied to include confounders when the focus is selecting a model from a set of

plausible models. Since there was a small number of pre-specified comparisons, based on information from the directed acyclic graphs, the significance method was appropriate in this case.

Potential covariates for all cancer risk, as well as lung and prostate cancer risk, were assessed for their association to the model through the use of direct acyclic graphs, informed by scientific evidence collected during a literature review. Covariates that were determined to be associated with the outcome and exposure variables were fit in the models one at a time. If compared to the null model, the covariates changed the value of the coefficient by more than 10%, they were included in the next step. In the second step, the variables that were individually significant were fit together. Then the change in value of the coefficient was computed when each variable was omitted on its own from the set. Covariates that were not significant individually were then added back into the model, to determine if they became significant in the presence of other variables. A final check was made to ensure that no term in the model could be omitted without significantly changing the exposure coefficient, and that no excluded covariate could change the coefficient by more than 10%.

The proportional hazards assumption was verified using the *'survival'* package in R (221). For each covariate in the Cox regression model, time was correlated with a corresponding set of scaled Schoenfeld residuals, to test for independence between residuals in time. A significance level of $\alpha = 0.05$ was used, with a null result indicating a non-significant relationship between residuals and time. In order to detect any relationships with time that may not have been captured by the aforementioned statistical test, a graphical diagnostic was also conducted for each covariate. Graphs of the scaled Schoenfeld residuals against the transformed

time were generated to identify possible quadratic or logarithmic patterns, as well as check for undue influential outliers.

Variables that did not meet the proportional hazards assumption were stratified or an interaction term with time was added. Stratification was considered for variables for which the effect size was not of interest. Case distribution between variable levels was also considered before stratification, as dilution of cases across many levels of stratification would risk decreasing the power of the study.

Effect modification was evaluated by adding an interaction term between two variables to the model. Additionally, individual socioeconomic and health factors were examined as potential effect modifiers. Sex was identified as a covariate modifying the effect between mental health exposures and cancer outcomes. Therefore, models were stratified to reflect male and females risk estimates separately.

3.9 Research question 1: Assessing the relationship between mental health disorders and cancer risk

Sequential models were used to illustrate how the hazard ratios for all cancers and lung cancer were affected by adjustment with different covariates. Model 1 adjusted for age. Model 2 additionally adjusted for all sociodemographic and health-related covariates that were significant with the change in coefficient method, and Model 3 additionally adjusted for smoking status. Smoking status was not a significant covariate for prostate cancer, and therefore prostate cancer is confined to Model 1 and 2.

3.9.1 Research question 1a: Effect of mental health disorders on cancer risk

All three definitions of depression were analyzed using the same covariates. The same covariates were also used in models for males and females; therefore, the models shown below are representative of the models used for males and females.

Depression

Depression Model 1a (i): $All\ cancers\ =\ B_o\ +\ B_1(depression\ status)\ +\ B_2(age)$

Depression Model 1a (ii): $All\ cancers\ =\ Model\ 1a\ (i)\ +\ B_3\ (education)\ +\ B_4(ethnicity)\ +\ B_5\ (heart\ attack)\ +\ B_6(diabetes)\ +\ B_7(alcohol)\ +\ B_8(physical\ activity)\ +\ B_9\ (sleep)\ +\ B_{10}\ (family\ cancer)$

Depression Model 1a (iii): $All\ cancers\ =\ Model\ 1a\ (ii)\ +\ B_{11}(smoking)$

Anxiety

Anxiety Model 1a (i): $All\ cancers\ =\ B_o\ +\ B_1(anxiety\ status)\ +\ B_2(age)$

Anxiety Model 1a (ii): $All\ cancers\ =\ Model\ 1a\ (i)\ +\ B_3\ (education)\ +\ B_4(ethnicity)\ +\ B_5\ (heart\ attack)\ +\ B_6(diabetes)\ +\ B_7(alcohol)\ +\ B_8(physical\ activity)\ +\ B_9\ (sleep)\ +\ B_{10}\ (family\ cancer)\ +\ B_{11}(fruit\ and\ vegetable\ consumption)\ +\ B_{12}(income)$

Anxiety Model 1a (iii): $All\ cancers\ =\ Model\ 1a\ (ii)\ +\ B_{13}\ (smoking)$

Co-morbid depression and anxiety

Co-morbidity Model 1a (i): $All\ cancers = B_o\ +\ B_1(comorbidity\ status) + B_2(age)$

Comorbidity Model 1a (ii): $All\ cancers\ =\ Model\ 1a\ (i)\ +\ B_3\ (education)\ +\ B_4(ethnicity)\ +\ B_5\ (heart\ attack)\ +\ B_6(diabetes)\ +\ B_7(alcohol)\ +\ B_8(physical\ activity)\ +\ B_9\ (sleep)\ +\ B_{10}\ (family\ cancer)$

Comorbidity Model 1a (iii): $All\ cancers\ =\ Model\ 1a\ (ii)\ +\ B_{11}(smoking)$

3.9.2 Research question 1b: Effect of mental health disorders on prostate cancer risk

Depression

Depression Model 1b (i): $Prostate\ cancer\ =\ B_o\ +\ B_1(depression\ status)\ +\ B_2(age)$

Depression Model 1b (ii): $Prostate\ cancer\ =\ Model\ 1b\ (i)\ +\ B_3\ (education)\ +$
$B_4(ethnicity)\ +\ B_8(physical\ activity)\ +\ B_9\ (sleep)\ +$
$B_{10}\ (fruit\ and\ vegetable\ consumption)$

Anxiety

Anxiety Model 1b (i): $Prostate\ cancer\ =\ B_o\ +\ B_1(anxiety\ status)\ +\ B_2(age)$

Anxiety Model 1b (ii): $Prostate\ cancer\ =\ Model\ 1b\ (i)\ +\ B_3\ (education)\ +$
$B_4(ethnicity)\ +\ B_8(physical\ activity)\ +\ B_9\ (sleep)\ +$
$B_{10}\ (fruit\ and\ vegetable\ consumption)$

Co-morbid depression and anxiety

Co-morbidity Model 1b (i): $Prostate\ cancer\ =\ B_o\ +\ B_1(comorbidity\ status)\ +\ B_2(age)$

Comorbidity Model 1b (ii): $Prostate\ cancer\ =\ Model\ 1b\ (i)\ +\ B_3\ (education)\ +$
$B_4(ethnicity)\ +\ B_8(physical\ activity)\ +\ B_9\ (sleep)\ +$
$B_{10}\ (fruit\ and\ vegetable\ consumption)$

3.9.3 Research question 1c: Effect of mental health disorders on lung cancer risk

Depression

Depression Model 1c (i): $Lung\ cancer\ =\ B_o\ +\ B_1(depression\ status)\ +\ B_2(age)$

Depression Model 1c (ii): $Lung\ cancer\ =\ Model\ 1c\ (i)\ +\ B_3\ (education)\ +$
$B_4(ethnicity)\ +\ B_5(alcohol\ consumption)\ +\ B_6(COPD)\ +$
$B_7(fruit\ and\ vegetable\ consumption)\ +\ B_8(physical\ activity)$

Depression Model 1c (iii): $Lung\ cancer\ =\ Model\ 1c\ (ii)\ +\ B_9\ (smoking\ status)$

Anxiety

Anxiety Model 1c (i): $Lung\ cancer\ =\ B_o\ +\ B_1(comorbidity\ status)\ +\ B_2(age)$

Anxiety Model 1c (ii): $Lung\ cancer\ =\ Model\ 1c\ (i)\ +\ B_3\ (education) + B_4(ethnicity)\ + B_5(alcohol\ consumption) + B_6(COPD)\ + B_7(fruit\ and\ vegetable\ consumption)\ + B_8(physical\ activity)$

Anxiety Model 1c (iii): $Lung\ cancer\ =\ Model\ 1c\ (ii)\ +\ B_9\ (smoking\ status)$

Co-morbid depression and anxiety

Comorbidity Model 1c (i): $Lung\ cancer\ =\ B_o\ +\ B_1(comorbidity\ status)\ +\ B_2(age)$

Comorbidity Model 1c (ii): $Lung\ cancer\ =\ Model\ 1c\ (i)\ +\ B_3\ (education) + B_4(ethnicity)\ +\ B_5(alcohol\ consumption) + B_6(COPD)\ + B_7(fruit\ and\ vegetable\ consumption)\ +\ B_8(physical\ activity)$

Comorbidity Model 1c (iii): $Lung\ cancer\ =\ Model\ 1c\ (ii)\ +\ B_9\ (smoking\ status)$

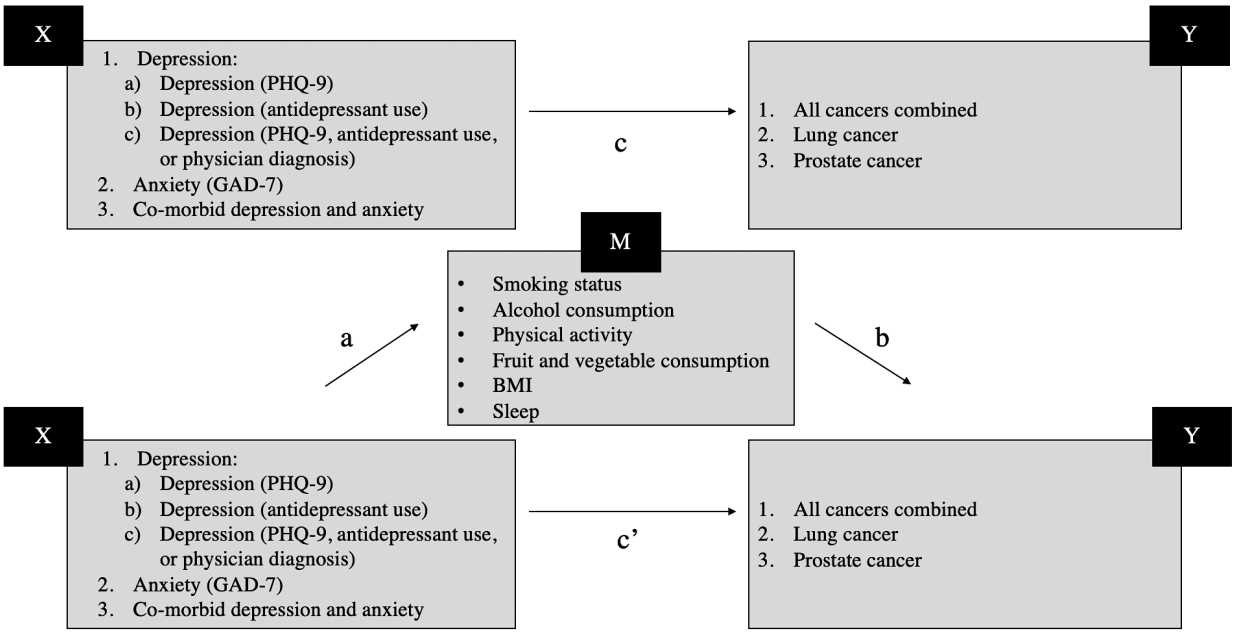
3.10 Research question 2: Assessing the role of lifestyle-related behaviours in the relationship between mental health disorders and cancer risk

The primary aim of this research question was to clarify the role of lifestyle behaviours on the causal pathway between mental health disorders and cancer risk. There are many methods to determine causality between an exposure and an outcome, one of the most prominent being the Bradford Hill criteria. Hill postulated that there is a set of nine criteria that can provide epidemiologic evidence of a causal relationship (222). These include effect size, consistency of findings, specificity of association, temporality of effect, dose-response relationship, plausibility, coherence between epidemiological and laboratory findings, experimental evidence, and analogy (222). While the Bradford Hill criteria are widely accepted guidelines for investigating causality, definitive conclusions cannot be drawn from this alone. As such, mediation analysis was conducted.

Mediation analysis is a useful tool for investigating causality, that involves disentangling the total, direct, and indirect (mediating) effects between an exposure and outcome (**Figure 3.2**)

(223,224). An advantage of the mediation analysis method (Baron and Kenny) utilized in this study is that the significance and magnitude of the indirect effect are quantified.

Figure 3.2 Direct, indirect, and total effects between an exposure and outcome



c = the total effect of X on Y, **ab** = indirect effect of X on Y, **c'** = the direct effect of X on Y after controlling for M

The analysis was performed to calculate the direct, indirect, and total effect using the *mediation* package in R software (225). First, potential mediating effects were assessed to establish relevant exposures, mediators, and outcomes using the Baron and Kenny mediation criteria, which is the most widely used method to assess mediation (223,224). The four criteria: show that the exposure variable is correlated with the outcome, the exposure is correlated with the mediator, that the mediator affects the outcome variable, and that the effect of the exposure on the outcome is non-significant (partial mediation) or zero (full mediation) when controlling for the mediator (223,224).

Firstly, as determined primarily through the first research question by use of the Cox regression models, mental health disorders were tested to see if they predicted the outcome

variable. Secondly, mental health disorders were tested to assess if they predicted the potential mediator. Thirdly, it was assessed whether the mediator predicted cancer even while adjusting for mental health disorders. Finally, the mediator was added to models predicting cancer and changes in the association between mental health disorders and cancer were observed for mediation effects.

The lifestyle factors (smoking status, alcohol consumption, BMI, average hours of sleep per night, fruit and vegetable consumption, and physical activity), mental health disorders (depression, anxiety, antidepressant use), and cancer risk (all cancers, lung cancer, prostate cancer) were analyzed (224). For relationships that met all Baron and Kenny criteria, confidence intervals were estimated using the quasi-Bayesian Monte Carlo method with 1000 simulations (226). A p-value below 0.05 (two-sided) was indicated as statistically significant.

Chapter 4: Results

4.1 Descriptive statistics for the analytic sample

A total of 34,571 participants aged 40 to 69 years old were eligible for the final analysis, including 2,888 cancer cases, and 31,683 non-cases. Participants' demographic, socioeconomic, lifestyle, and health-related characteristics are presented in **Table 4.1** and **Table 4.2**.

Participants were 53.1 years old on average. The sample had a higher percentage of females (54.0%) compared to males, whites (89.3%) compared to non-whites, and married people (68.8%) compared to those single, divorced, or widowed. Most participants also had a high socioeconomic status. There were 32.7% of participants who had completed a college degree, and 45.5% had a Bachelor's degree or higher. A large proportion of participants had high annual household incomes, with 43.6% of participants earning greater than $75,000, and 32.6% earning greater than $100,000. The prevalence of type II diabetes, heart attack, and COPD in the sample was 6.3%, 2.0%, and 2.8%, respectively. More than half of participants had a family history of cancer (55.5%), defined as a mother, father, or sibling having been diagnosed with cancer.

Table 4.1 Descriptive characteristics of the CARTaGENE sample (with exclusion criteria applied) with comparison of PHQ-9 scores.

	Depression status		**Overall Analytic Sample**	**p-value**
	No (PHQ-9 score <10)	**Yes** (PHQ-9 score ≥10)		
	n=32,652 (94.4%)	n=1,919 (5.6%)	n=34,571	
Age, Mean (SD)	53.2 (7.91)	52.0 (7.23)	53.1 (7.88)	<0.001
Sex				<0.001
Female	17474 (53.5%)	1178 (61.4%)	18652 (54.0%)	
Male	15178 (46.5%)	741 (38.6%)	15919 (46.0%)	

	Depression status		Overall Analytic Sample	p-value
	No (PHQ-9 score <10)	**Yes** (PHQ-9 score ≥10)		
	n=32,652 (94.4%)	n=1,919 (5.6%)	n=34,571	
Ethnicity				<0.001
White	29218 (89.5%)	1642 (85.6%)	30860 (89.3%)	
Non-white	3434 (10.5%)	277 (14.4%)	3711 (10.7%)	
Income				<0.001
<$50,000	9438 (28.9%)	982 (51.2%)	10420 (30.1%)	
$50,000-74,999	7091 (21.7%)	358 (18.7%)	7449 (21.5%)	
$75,000-100,000	5188 (15.9%)	230 (12.0%)	5418 (15.7%)	
>$100,000	10935 (33.5%)	349 (18.2%)	11284 (32.6%)	
Education				<0.001
High school or lower	6934 (21.2%)	627 (32.7%)	7561 (21.9%)	
College	10662 (32.7%)	632 (32.9%)	11294 (32.7%)	
University	15056 (46.1%)	660 (34.4%)	15716 (45.5%)	
Marital status				<0.001
Married	22797 (69.8%)	991 (51.6%)	23788 (68.8%)	
Single, divorced, or widowed	9855 (30.2%)	928 (48.4%)	10783 (31.2%)	
Diabetes				<0.001
Yes	1967 (6.0%)	223 (11.6%)	2190 (6.3%)	
No	30685 (94.0%)	1696 (88.4%)	32381 (93.7%)	
Myocardial infarction				0.299
Yes	661 (2.0%)	46 (2.4%)	707 (2.0%)	
No	31991 (98.0%)	1873 (97.6%)	33864 (98.0%)	
COPD				<0.001
Yes	820 (2.5%)	165 (8.6%)	985 (2.8%)	
No	31832 (97.5%)	1754 (91.4%)	33586 (97.2%)	

	Depression status		Overall Analytic Sample	p-value
	No (PHQ-9 score <10)	**Yes** (PHQ-9 score ≥10)		
	n=32,652 (94.4%)	n=1,919 (5.6%)	n=34,571	
Family cancer history				0.457
Yes	18135 (55.5%)	1083 (56.4%)	19218 (55.6%)	
No	14517 (44.5%)	836 (43.6%)	15353 (44.4%)	

Greater prevalence of high PHQ-9 scores were observed in female participants, participants with an annual household income of less than $50,000, participants with a high school education or lower, participants who were single, divorced, or widowed, participants with type II diabetes, and participants with COPD (**Table 4.1**).

Table 4.2 Characteristics of the CARTaGENE sample with exclusion criteria applied with comparison of GAD-7 scores.

	Anxiety status		Overall Analytic Sample	p-value
	No (GAD-7 score <10)	**Yes** (GAD-7 score ≥10)		
	n=32,982 (95.4%)	n=1,589 (4.6%)	n=34,571	
Age, Mean (SD)	53.1 (7.90)	52.3 (7.37)	53.1 (7.88)	<0.001
Sex				<0.001
Female	17641 (53.5%)	1011 (63.6%)	18652 (54.0%)	
Male	15341 (46.5%)	578 (36.4%)	15919 (46.0%)	
Ethnicity				<0.001
White	29491 (89.4%)	1369 (86.2%)	30860 (89.3%)	
Non-white	3491 (10.6%)	220 (13.8%)	3711 (10.7%)	

	Anxiety status			
	No (GAD-7 score <10)	**Yes** (GAD-7 score ≥10)	**Overall Analytic Sample**	**p-value**
	n=32,982 (95.4%)	n=1,589 (4.6%)	n=34,571	
Income				<0.001
<$50,000	9615 (29.2%)	805 (50.7%)	10420 (30.1%)	
$50,000-74,999	7160 (21.7%)	289 (18.2%)	7449 (21.5%)	
$75,000-100,000	5211 (15.8%)	207 (13.0%)	5418 (15.7%)	
>$100,000	10996 (33.3%)	288 (18.1%)	11284 (32.6%)	
Education				<0.001
High school or lower	6991 (21.2%)	570 (35.9%)	7561 (21.9%)	
College	10798 (32.7%)	496 (31.2%)	11294 (32.7%)	
University	15193 (46.1%)	523 (32.9%)	15716 (45.5%)	
Marital status				<0.001
Married	22897 (69.4%)	891 (56.1%)	23788 (68.8%)	
Single, divorced, or widowed	10085 (30.6%)	698 (43.9%)	10783 (31.2%)	
Diabetes				<0.001
Yes	2033 (6.2%)	157 (9.9%)	2190 (6.3%)	
No	30949 (93.8%)	1432 (90.1%)	32381 (93.7%)	
Myocardial infarction				0.467
Yes	670 (2.0%)	37 (2.3%)	707 (2.0%)	
No	32312 (98.0%)	1552 (97.7%)	33864 (98.0%)	
COPD				<0.001
Yes	859 (2.6%)	126 (7.9%)	985 (2.8%)	
No	32123 (97.4%)	1463 (92.1%)	33586 (97.2%)	
Family history of cancer				0.132
No	14677 (44.5%)	676 (42.5%)	15353 (44.4%)	
Yes	18305 (55.5%)	913 (57.5%)	19218 (55.6%)	

[†]Non-smoker: has never smoked, former smoker: has smoked at least 100 cigarettes before but not within the past 30 days, current smoker: has smoked more than 100 cigarettes in lifetime and has smoked within the last 30 days [‡]Abstainer: has never drunk alcohol, former: has drunk alcohol before but not over the past 12 months,

occasional: drank ≤2–3 times/month over the past 12 months, regular: drank ≥ once/week but ≤2–3 times/week, habitual drinkers: drank ≥ 4–5 times/week.

Similar to the observations of **Table 4.1**, greater proportions of high GAD-7 scores were observed in female participants, participants with an annual household income of less than $50,000, participants with a high school education or lower, participants who were single, divorced, or widowed, participants with type II diabetes, and participants with COPD (**Table 4.2**).

Table 4.3 Comparison of characteristics between participants who met the inclusion criteria for the analytic sample and those who did not.

	Excluded (N=8466)	**Included (N=34571)**	**p-value**
Age, Mean (SD)	55.8 (8.30)	53.1 (7.88)	<0.001
Sex			
Female	5148 (60.8%)	18652 (54.0%)	<0.001
Male	3318 (39.2%)	15919 (46.0%)	
Ethnicity			
White	7801 (92.1%)	30864 (89.3%)	<0.001
Non-white	665 (7.9%)	3707 (10.7%)	
Income			
<$50,000	2794 (33.0%)	10443 (30.2%)	<0.001
$50,000-74,999	1911 (22.6%)	7424 (21.5%)	
$75,000-100,000	1121 (13.2%)	5409 (15.6%)	
>$100,000	2640 (31.2%)	11295 (32.7%)	
Education			
High school or lower	1721 (20.3%)	7555 (21.9%)	<0.001
College	3136 (37.0%)	11291 (32.7%)	
University	3609 (42.6%)	15725 (45.5%)	
Marital status			
Married	6464 (76.4%)	23787 (68.8%)	<0.001
Single, divorced, or widowed	2002 (23.6%)	10784 (31.2%)	

	Excluded (N=8466)	Included (N=34571)	p-value
Smoking status			
Current smoker	1092 (12.9%)	6011 (17.4%)	<0.001
Past smoker	3592 (42.4%)	13607 (39.4%)	
Never smoked	3782 (44.7%)	14953 (43.3%)	
Alcohol consumption			
Abstainer	306 (3.6%)	1857 (5.4%)	<0.001
Former drinker	803 (9.5%)	3233 (9.4%)	
Occasional drinker	1872 (22.1%)	8661 (25.1%)	
Regular drinker	3601 (42.5%)	12878 (37.3%)	
Habitual drinker	1884 (22.3%)	7942 (23.0%)	
Physical activity			
Low	1499 (17.7%)	7178 (20.8%)	<0.001
Moderate	3016 (35.6%)	12451 (36.0%)	
High	3951 (46.7%)	14942 (43.2%)	
BMI			
Underweight	84.0 (1.0%)	260 (0.8%)	<0.001
Normal	1975 (23.3%)	10672 (30.9%)	
Overweight	4543 (53.7%)	14764 (42.7%)	
Obese	1864 (22.0%)	8875 (25.7%)	
Diabetes			
Yes	618 (7.3%)	2191 (6.3%)	0.00143
No	7848 (92.7%)	32380 (93.7%)	
Myocardial infarction			
Yes	228 (2.7%)	707 (2.0%)	<0.001
No	8238 (97.3%)	33864 (98.0%)	
COPD			
Yes	299 (3.5%)	985 (2.8%)	0.00106
No	8167 (96.5%)	33586 (97.2%)	

	Excluded (N=8466)	Included (N=34571)	p-value
Family cancer history			
No	3164 (37.4%)	15358 (44.4%)	<0.001
Yes	5302 (62.6%)	19213 (55.6%)	

Many participants (n = 8,466) were excluded due to either incomplete data regarding PHQ-9 or GAD-7, prevalent cancer, missing diagnostic dates, or an incident cancer in the first six months. Therefore, the participants who met the inclusion criteria were compared to those who did not. There was a significant difference between the two groups with respect to age, sex, ethnicity, income, education, marital status, smoking status, alcohol consumption, physical activity, BMI, diabetes, myocardial infarction, COPD, and family cancer history (**Table 4.3**). However, the magnitude of the differences was relatively low, around two percent points. The greatest differences were seen in sex, education, marital status, smoking status, alcohol consumption, BMI, and family cancer history (**Table 4.3**). Compared to participants who were excluded, the participants who were included in the final analytic sample were more likely to be female, have a college level education, be married, be a past smoker, be a regular drinker, be overweight, and have a family history of cancer (**Table 4.3**).

Characteristics of incident cancer cases are presented in **Table 4.4**. Among the final analytic sample, there was 2,888 all cancer, 305 lung cancer, and 329 prostate cancer cases. There was a slightly higher proportion of women among all cancer cases (52.9%) and lung cancer cases (50.8%). The mean age of diagnosis was similar among all three cancer outcomes and sex strata, with the highest being 63.4 years of age for lung cancer in men, and the lowest being 58.9 years of age for all cancers in women. Incident cancer cases with a follow-up time less than six months (180 days) were excluded from the sample; therefore, the minimum follow-

up time was 181 days. The median follow-up time among all cancer outcomes and sex strata ranged from 3.2 years for lung cancer in women, to 4.3 years for lung cancer in men.

Table 4.4 Profile of incident cancer characteristics

Cancer type	Sex	# of cases (%)	Mean age at diagnosis	Follow-up time (Median, [Min, Max])
All cancers (n = 2,888)	Men	1,361 (47.1%)	61.8 years	3.5 years [182 days, 8.5 years]
	Women	1,527 (52.9%)	58.9 years	3.4 years [181 days, 8.4 years]
Lung cancer (n = 305)	Men	150 (49.2%)	63.4 years	4.3 years [182 days, 7.9 years]
	Women	155 (50.8%)	61.1 years	3.2 years [200 days, 7.9 years]
Prostate cancer (n = 329)	Men	329 (100%)	63.1 years	3.6 years [208 days, 8.5 years]

Mental health characteristics of the analytic sample are presented in **Table 4.5.** The mean overall GAD-7 and PHQ-9 scores were 2.5 and 2.9, respectively. Antidepressant use was observed in 9.2% of the analytic sample, and depression defined by PHQ-9 scores was observed in 5.6% of the sample. Self-reported depression diagnosis by a physician was observed at a higher proportion of the sample than the other two definitions of depression at 21.5%. Anxiety defined by GAD-7 scores occurred in 4.6% of the sample, and comorbid anxiety and depression was observed in 2.7%.

Women had a higher mean GAD-7 score (2.8) and PHQ-9 score (3.2) compared to men (2.2 and 2.6, respectively) (**Table 4.5**). The proportion of women with a GAD-7 score over the threshold of 10 points indicating anxiety (5.4%) was also higher than men (3.6%) (**Table 4.5**). This disparity was also reflected in the proportion of women with anxiety (6.3%, compared to 3.6% for men), the proportion of women diagnosed with depression by a physician (26.0%, compared to 16.1% for men), proportion of women using antidepressants (12.2%, compared to

5.8% for men), and proportion of women with comorbid depression and anxiety (3.2%, compared to 2.1% for men) (**Table 4.5**).

Table 4.5 Profile of mental health characteristics

	Women n=18,652	**Men** n=15,919	**Overall** n=34,571	**p-value**
GAD-7 score				<0.001
Mean (SD)	2.8 (3.6)	2.2 (3.2)	2.5 (3.4)	
10th percentile	0	0	0	
90th percentile	7	6	6	
PHQ-9 score				<0.001
Mean (SD)	3.2 (3.7)	2.6 (3.5)	2.9 (3.6)	
10th percentile	0	0	0	
90th percentile	8	7	7	
Anxiety (GAD score ≥10)				<0.001
Yes	1011 (5.4%)	578 (3.6%)	1589 (4.6%)	
No	17641 (94.6%)	15341 (96.4%)	32982 (95.4%)	
Depression (PHQ score ≥10)				<0.001
Yes	1178 (6.3%)	741 (4.7%)	1919 (5.6%)	
No	17474 (93.7%)	15178 (95.3%)	32652 (94.4%)	
Depression diagnosis by physician				<0.001
Yes	4858 (26.0%)	2561 (16.1%)	7419 (21.5%)	
No	13794 (74.0%)	13358 (83.9%)	27152 (78.5%)	
Antidepressant use				
Yes	2271 (12.2%)	920 (5.8%)	3191 (9.2%)	<0.001
No	16381 (87.8%)	14999 (94.2%)	31380 (90.8%)	
Depression (PHQ-9, antidepressant use, or physician diagnosis)				<0.001
Yes	5975 (32.0%)	3168 (19.9%)	9143 (26.4%)	
No	12677 (68.0%)	12751 (80.1%)	25428 (73.6%)	
Comorbid depression and anxiety (GAD and PHQ-9 scores ≥10)				<0.001
Yes	599 (3.2%)	339 (2.1%)	938 (2.7%)	
No	18053 (96.8%)	15580 (97.9%)	33633 (97.3%)	

Lifestyle behaviours in men and women, with and without depression, are presented in **Table 4.6.** Among women with depression at baseline, there were greater proportions of current smokers, former drinkers, low fruit and vegetable intake, low physical activity, obesity, and low

sleep. Similar results were seen for men, however the discrepancy in fruit and vegetable intake between participants with and without depression was more pronounced. Of note, proportions of regular and habitual drinkers were lower in men and women with depression.

Table 4.6 Lifestyle behaviours in men and women, with and without depression, as defined by PHQ-9 scores

	Female			**Male**		
	Depression status			Depression status		
	No (PHQ-9 score <10) (N=17474)	**Yes** (PHQ-9 score ≥10) (N=1178)	p-value	**No** (PHQ-9 score <10) (N=15178)	**Yes** (PHQ-9 score ≥10) (N=741)	p-value
Smoking status†						
Current smoker	2757 (15.8%)	364 (30.9%)	<0.001	2652 (17.5%)	238 (32.1%)	<0.001
Past smoker	6761 (38.7%)	382 (32.4%)		6182 (40.7%)	277 (37.4%)	
Never smoked	7956 (45.5%)	432 (36.7%)		6344 (41.8%)	226 (30.5%)	
Alcohol consumption‡						
Abstainer	1080 (6.2%)	91.0 (7.7%)	<0.001	647 (4.3%)	40.0 (5.4%)	<0.001
Former drinker	1707 (9.8%)	226 (19.2%)		1172 (7.7%)	109 (14.7%)	
Occasional drinker	4713 (27.0%)	386 (32.8%)		3313 (21.8%)	234 (31.6%)	
Regular drinker	6666 (38.1%)	299 (25.4%)		5776 (38.1%)	189 (25.5%)	
Habitual drinker	3308 (18.9%)	176 (14.9%)		4270 (28.1%)	169 (22.8%)	
Fruit and vegetable consumption						
< 5 servings	6626 (37.9%)	627 (53.2%)	<0.001	9423 (62.1%)	519 (70.0%)	<0.001
5 + servings	10848 (62.1%)	551 (46.8%)		5755 (37.9%)	222 (30.0%)	
Physical activity						
Low	3732 (21.4%)	374 (31.7%)	<0.001	2831 (18.7%)	221 (29.8%)	<0.001
Moderate	6950 (39.8%)	450 (38.2%)		4807 (31.7%)	233 (31.4%)	
High	6792 (38.9%)	354 (30.1%)		7540 (49.7%)	287 (38.7%)	

	Female			Male		
	Depression status			Depression status		
	No (PHQ-9 score <10) (N=17474)	**Yes** (PHQ-9 score ≥10) (N=1178)	p-value	**No** (PHQ-9 score <10) (N=15178)	**Yes** (PHQ-9 score ≥10) (N=741)	p-value
BMI						
Underweight	204 (1.2%)	14.0 (1.2%)	<0.001	38.0 (0.3%)	4.00 (0.5%)	<0.001
Normal	6764 (38.7%)	289 (24.5%)		3449 (22.7%)	149 (20.1%)	
Overweight	6487 (37.1%)	429 (36.4%)		7527 (49.6%)	292 (39.4%)	
Obese	4019 (23.0%)	446 (37.9%)		4164 (27.4%)	296 (39.9%)	
Sleep						
< 7 hrs	3139 (18.0%)	408 (34.6%)	<0.001	3352 (22.1%)	279 (37.7%)	<0.001
7-9 hrs	12430 (71.1%)	546 (46.3%)		10677 (70.3%)	333 (44.9%)	
9 + hrs	1905 (10.9%)	224 (19.0%)		1149 (7.6%)	129 (17.4%)	

†Non-smoker: has never smoked, former smoker: has smoked at least 100 cigarettes before but not within the past 30 days, current smoker: has smoked more than 100 cigarettes in lifetime, and has smoked within the last 30 days ‡Abstainer: has never drunk alcohol, former: has drunk alcohol before but not over the past 12 months, occasional: drank ≤2–3 times/month over the past 12 months, regular: drank ≥ once/week but ≤2–3 times/week, habitual drinkers: drank ≥ 4–5 times/week.

Lifestyle behaviours in men and women, with and without anxiety, are presented in **Table 4.7.** Frequency distributions of lifestyle behaviours were similar to those observed in **Table 4.6**. Among women with anxiety at baseline, there were greater proportions of current smokers, former drinkers, low fruit and vegetable intake, low physical activity, obesity, and low sleep. Similar results were seen for men, however the discrepancy in fruit and vegetable intake between participants with and without anxiety was more pronounced.

Table 4.7 Lifestyle behaviours in men and women, with and without anxiety, as defined by GAD-7 scores

	Female			**Male**		
	Anxiety status			Anxiety status		
	No (GAD-7 score <10) (N=17641)	**Yes** (GAD-7 score ≥10) (N=1011)	p-value	**No** (GAD-7 score <10) (N=15341)	**Yes** (GAD-7 score ≥10) (N=578)	p-value
Smoking status[†]						
Current smoker	2835 (16.1%)	286 (28.3%)	<0.001	2703 (17.6%)	187 (32.4%)	<0.001
Past smoker	6803 (38.6%)	340 (33.6%)		6228 (40.6%)	231 (40.0%)	
Never smoked	8003 (45.4%)	385 (38.1%)		6410 (41.8%)	160 (27.7%)	
Alcohol consumption[‡]						
Abstainer	1089 (6.2%)	82.0 (8.1%)	<0.001	656 (4.3%)	31.0 (5.4%)	<0.001
Former drinker	1780 (10.1%)	153 (15.1%)		1198 (7.8%)	83.0 (14.4%)	
Occasional drinker	4759 (27.0%)	340 (33.6%)		3375 (22.0%)	172 (29.8%)	
Regular drinker	6687 (37.9%)	278 (27.5%)		5805 (37.8%)	160 (27.7%)	
Habitual drinker	3326 (18.9%)	158 (15.6%)		4307 (28.1%)	132 (22.8%)	
Fruit and vegetable consumption						
< 5 servings	6732 (38.2%)	521 (51.5%)	<0.001	9540 (62.2%)	402 (69.6%)	<0.001
5 + servings	10909 (61.8%)	490 (48.5%)		5801 (37.8%)	176 (30.4%)	
Physical activity						
Low	3825 (21.7%)	281 (27.8%)	<0.001	2902 (18.9%)	150 (26.0%)	<0.001
Moderate	7019 (39.8%)	381 (37.7%)		4872 (31.8%)	168 (29.1%)	
High	6797 (38.5%)	349 (34.5%)		7567 (49.3%)	260 (45.0%)	
BMI						
Underweight	204 (1.2%)	14.0 (1.4%)	<0.001	39.0 (0.3%)	3.00 (0.5%)	0.013
Normal	6764 (38.3%)	289 (28.6%)		3460 (22.6%)	138 (23.9%)	
Overweight	6545 (37.1%)	371 (36.7%)		7570 (49.3%)	249 (43.1%)	
Obese	4128 (23.4%)	337 (33.3%)		4272 (27.8%)	188 (32.5%)	

	Female			Male		
	Anxiety status			Anxiety status		
	No (GAD-7 score <10)	**Yes** (GAD-7 score ≥10)	p-value	**No** (GAD-7 score <10)	**Yes** (GAD-7 score ≥10)	p-value
	(N=17641)	(N=1011)		(N=15341)	(N=578)	
Sleep						
< 7 hrs	3218 (18.2%)	329 (32.5%)	<0.001	3426 (22.3%)	205 (35.5%)	<0.001
7-9 hrs	12458 (70.6%)	518 (51.2%)		10722 (69.9%)	288 (49.8%)	
9 + hrs	1965 (11.1%)	164 (16.2%)		1193 (7.8%)	85.0 (14.7%)	

†Never smoked: has never smoked, former smoker: has smoked at least 100 cigarettes before but not within the past 30 days, current smoker: has smoked more than 100 cigarettes in lifetime, and has smoked within the last 30 days ‡Abstainer: has never drunk alcohol, former: has drunk alcohol before but not over the past 12 months, occasional: drank ≤2–3 times/month over the past 12 months, regular: drank ≥ once/week but ≤2–3 times/week, habitual drinkers: drank ≥ 4–5 times/week.

4.2 Research question 1: Assessing the relationship between mental health disorders and cancer risk

4.2.1 Research question 1a: Effect of mental health disorders on cancer risk

Among all three depression definitions, male and female participants with depression had a non-significant increased risk of cancer across all models, with the exception of males with depression (PHQ-9) in Model 3 (HR: 0.99 [0.76-1.29]). All risk estimates were attenuated with the addition of covariates in each sequential model. HRs tended to be higher in males compared to females for two depression definitions: antidepressant use, and PHQ-9, antidepressant use, or self-report of physician diagnosis, across all models. Conversely, HRs tended to be higher across all models in females compared to males for depression defined by PHQ-9 scores.

There was a non-significant positive association with cancer among females with anxiety (HR: 1.08 [0.88-1.34]), but not among males (HR: 1.00 [0.75-1.34]). The relationship between comorbid anxiety and depression and all cancers in women was statistically significant in Model

1 (HR: 1.29 [1.00-1.66]), but statistical significance was attenuated with adjustment of additional covariates. Similarly, the relationship between depression (PHQ-9, antidepressant use, or self-report of physician diagnosis) and all cancer risk was significant in men in Model 1 (HR: 1.16 [1.02-1.32]). Risk estimates for women tended to be higher than those of men for anxiety (GAD-7), and comorbid anxiety and depression.

Table 4.8 Results of Cox regression for all cancers

	No. of Events/No. of Participants	**Person-years**	**Model 1†** HR (95% CI)	**Model 2‡** HR (95% CI)	**Model 3§** HR (95% CI)
Depression (PHQ-9)					
Women					
No	1419/17474	101460	–	–	–
Yes	108/1178	7045	1.15 (0.94-1.40)	1.11 (0.91-1.36)	1.08 (0.88-1.32)
Men					
No	1301/15178	91312	–	–	–
Yes	60/741	4570	1.04 (0.80-1.35)	1.02 (0.78-1.32)	0.99 (0.76-1.29)
Depression (Antidepressant use)					
Women					
No	1346/16381	95983	–	–	–
Yes	181/2271	12522	1.05 (0.90-1.22)	1.01 (0.87-1.19)	1.00 (0.85-1.17)
Men					
No	1280/14999	90627	–	–	–
Yes	81/920	5255	1.12 (0.90-1.40)	1.09 (0.87-1.36)	1.07 (0.85-1.34)
Depression (PHQ-9, antidepressant use, or self-report of					
Women					
No	1011/12677	73382	–	–	–
Yes	513/5975	35122	1.07 (0.96-1.19)	1.04 (0.93-1.16)	1.01 (0.91-1.13)
Men					
No	1057/12751	76477	–	–	–
Yes	303/3168	19404	**1.16 (1.02-1.32)**	1.13 (0.99-1.29)	1.11 (0.97-1.26)
Anxiety (GAD-7)					
Women					
No	1431/17641	95983	–	–	–
Yes	96/1011	12522	1.12 (0.91-1.38)	1.10 (0.89-1.36)	1.08 (0.88-1.34)

	No. of Events/No. of Participants	Person-years	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)	Model 3§ HR (95% CI)
Men					
No	1313/15341	90627	–	–	–
Yes	48/578	5255	1.03 (0.78-1.38)	1.02 (0.76-1.37)	1.00 (0.75-1.34)
Comorbid anxiety and depression					
Women					
No	1463/18053	104804	–	–	–
Yes	64/599	3701	**1.29 (1.00-1.66)**	1.25 (0.97-1.62)	1.21 (0.94-1.56)
Men					
No	1331/15580	93739	–	–	–
Yes	30/339	2143	1.16 (0.81-1.67)	1.13 (0.78-1.63)	1.09 (0.76-1.58)

†Model 1: Adjusted for age (continuous)
‡Model 2: Adjusted for age (continuous), education, ethnicity, income, myocardial infarction, diabetes, physical activity, fruit and vegetable intake, sleep, alcohol, family history of cancer §Model 3: Adjusted for all above covariates and smoking status

4.2.2 Research question 1b: Effect of mental health disorders on prostate cancer risk

There was a non-significant inverse association between prostate cancer and depression (PHQ-9) (HR: 0.72 [0.38-1.36]), anxiety (GAD-7) (HR: 0.82 [0.42-1.60]), and comorbid anxiety and depression (HR: 0.82 [0.34-1.99]). Participants with depression defined by antidepressant use and PHQ-9, antidepressant use, or self-report of physician diagnosis had a slightly higher non-significant risk compared to those without depression: HR: 1.03 (0.64-1.65), and HR: 1.02 (0.78-1.34), respectively.

Table 4.9 Results of Cox regression for prostate cancer

	No. of Events/No. of Participants	Person-years	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
Depression (PHQ-9)				
No	319/15178	94541	–	–
Yes	10/741	4725	0.73 (0.39-1.38)	0.72 (0.38-1.36)

	No. of Events/No. of Participants	Person-years	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
Depression (Antidepressant use)				
No	311/14999	93808	–	–
Yes	18/920	5458	1.03 (0.64-1.65)	1.03 (0.64-1.66)
Depression (PHQ-9, antidepressant use, or self-report of				
No	263/12751	79085	–	–
Yes	66/3168	20181	1.02 (0.78-1.34)	1.03 (0.78-1.35)
Anxiety (GAD-7)				
No	320/15341	93808	–	–
Yes	9/578	5458	0.83 (0.43-1.60)	0.82 (0.42-1.60)
Comorbid anxiety and depression				
No	324/15580	97037	–	–
Yes	5/339	2230	0.83 (0.34-2.02)	0.82 (0.34-1.99)

†Adjusted for age (continuous) ‡Adjusted for age (continuous), education, ethnicity, physical activity, fruit and vegetable consumption, and sleep

4.2.3 Research question 1c: Effect of mental health disorders on lung cancer risk

There was a significantly higher risk of lung cancer among women in the minimally adjusted models (Model 1) for depression (PHQ-9) (HR: 2.10 [1.28-3.43]), depression (PHQ-9, antidepressant use, or self-report of physician diagnosis) (HR: 1.40 [1.01-1.93]), and comorbid anxiety and depression (HR: 2.61 [1.45-4.71]). Additional adjustment of additional covariates in Model 2 and Model 3 attenuated associations. In contrast, the relationship between anxiety (GAD-7) and lung cancer in women was statistically significant in all three models – the hazard ratios were attenuated with each sequential model but remained statistically significant with full adjustment (HR: 2.30 [1.40-3.76]; HR: 1.81 [1.09-2.99]; HR: 1.67 [1.01-2.76]).

Table 4.10 Results of Cox regression for lung cancer

	No. of Events/No. of Participants	Person-years	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)	Model 3§ HR (95% CI)
Depression (PHQ-9)					
Women					
No	137/17474	105482	–	–	–
Yes	18/1178	7348	**2.10 (1.28-3.43)**	1.61 (0.97-2.68)	1.44 (0.87-2.40)
Men					
No	142/15178	95143	–	–	–
Yes	8/741	4750	1.29 (0.63-2.64)	0.99 (0.48-2.04)	0.88 (0.43-1.82)
Depression (Antidepressant use)					
Women					
No	133/16381	99870	–	–	–
Yes	22/2271	12960	1.29 (0.82-2.03)	1.13 (0.72-1.78)	1.05 (0.67-1.67)
Men					
No	141/14999	94399	–	–	–
Yes	9/920	5494	1.16 (0.59-2.27)	0.98 (0.50-1.94)	0.89 (0.45-1.75)
Depression (PHQ-9, antidepressant use, or self-report of					
Women					
No	94/12677	76277	–	–	–
Yes	61/5975	36554	**1.40 (1.01-1.93)**	1.23 (0.89-1.71)	1.12 (0.81-1.56)
Men					
No	116/12751	79584	–	–	–
Yes	34/3168	20309	1.18 (0.80-1.72)	0.99 (0.67-1.46)	0.89 (0.60-1.31)
Anxiety (GAD-7)					
Women					
No	137/17641	99870	–	–	–
Yes	18/1011	12960	**2.30 (1.40-3.76)**	**1.81 (1.09-2.99)**	**1.67 (1.01-2.76)**
Men					
No	142/15341	94399	–	–	–
Yes	8/578	5494	1.62 (0.80-3.32)	1.33 (0.65-2.73)	1.17 (0.57-2.42)
Comorbid anxiety and depression					
Women					
No	143/18053	108955	–	–	–
Yes	12/599	3875	**2.61 (1.45-4.71)**	**1.95 (1.07-3.57)**	1.72 (0.94-3.16)
Men					
No	145/15580	97659	–	–	–
Yes	5/339	2234	1.82 (0.75-4.46)	1.46 (0.59-3.59)	1.26 (0.51-3.10)

†Model 1: Adjusted for age (continuous)

‡Model 2: Adjusted for age (continuous), education, ethnicity, physical activity, alcohol, fruit and vegetable consumption, and COPD
§Model 3: Adjusted for all above covariates and smoking status

4.3 Research question 2: Assessing the role of lifestyle-related behaviours in the relationship between mental health disorders and cancer risk

4.3.1 Mediation effect of lifestyle-related behaviours

The results of the mediation analyses suggest the relationship between mental health disorders and incident cancer was partly mediated by smoking status (**Table 4.11**). The mental health-cancer associations with a statistically significant direct effect were included in **Table 4.11**. The mental health-cancer associations with a statistically significant indirect effect have been illustrated in **Figure 4.1.**

Smoking status was shown to partially mediate the relationship between depression (PHQ-9), anxiety (GAD-7), and co-morbidity on lung cancer in women by a proportion of 27%, 18%, and 26%, respectively. While the direct and total effect was significant for other mediators of interest (e.g., alcohol consumption, BMI, fruit and vegetable consumption, and sleep), no other indirect (mediation) effects reached significance in women. Of note, the direct effect between mental health disorders and cancer was not significant when the other two definitions of depression were assessed with respect to all cancer and lung cancer.

Mediation effects for male participants were examined for depression and cancer as that was the only relationship that was statistically significant. Smoking status was shown to partially mediate the relationship between depression (PHQ-9, antidepressant use, or self-report of physician diagnosis) on all cancer in men by a proportion of 17%, which was similar to the effect size observed between depression and lung cancer in women.

Table 4.11 Mediation effects investigating whether lifestyle behaviours mediated the relationships between mental health and lung cancer [a, b]

Mediation effects		Quasi-Bayesian estimates and 95% confidence intervals			Estimated proportion mediated
Mediators	Associations	Indirect effect of X on Y	Direct effect of X on Y	Total effect (95% CI)	
Women					
Smoking status	Depression (PHQ-9) on lung cancer	0.00 (0.0009-0.0030) ***	0.01 (0.0004-0.0142) *	0.01 (0.0008-0.0153) *	0.27
	Anxiety on lung cancer	0.00 (0.0006-0.0026) ***	0.01 (0.0005-0.0167) *	0.01 (0.0013-0.0175) *	0.18
	Comorbidity on lung cancer	0.00 (0.0012-0.0046) ***	0.01 (0.0002-0.0211) *	0.01 (0.0017-0.0225) **	0.26
Alcohol consumption	Depression (PHQ-9) on lung cancer	0.00 (-0.0003-0.0008)	0.01 (0.0004-0.0150) *	0.01 (0.0006-0.0150) *	0.03
	Anxiety on lung cancer	0.00 (-0.0002-0.0006)	0.01 (0.0015-0.0169) *	0.01 (0.0017-0.0170) **	0.02
	Comorbidity on lung cancer	0.00 (-0.0003-0.0009)	0.01 (0.0016-0.0232) *	0.01 (0.0017-0.0232) **	0.03
BMI	Depression (PHQ-9) on lung cancer	-0.00 (-0.0015-0.0003)	0.01 (0.0009-0.0145) *	0.01 (0.0006-0.0144) *	-0.09
	Anxiety on lung cancer	-0.00 (-0.0010-0.0001)	0.01 (0.0022-0.0170) **	0.01 (0.0021-0.0169) **	-0.04
	Comorbidity on lung cancer	-0.00 (-0.0015-0.0003)	0.01 (0.0021-0.0232) *	0.01 (0.0018-0.0228) *	-0.05
Fruit and vegetable consumption	Depression (PHQ-9) on lung cancer	0.00 (-0.0003-0.0009)	0.01 (0.0004-0.0149) *	0.01 (0.0005-0.0149) *	0.03
	Anxiety on lung cancer	0.00 (-0.0003-0.0009)	0.01 (0.0017-0.0174) **	0.01 (0.0019-0.0175) **	0.02
	Comorbidity on lung cancer	0.00 (-0.0004-0.0011)	0.01 (0.0017-0.0220) *	0.01 (0.0019-0.0222) *	0.03

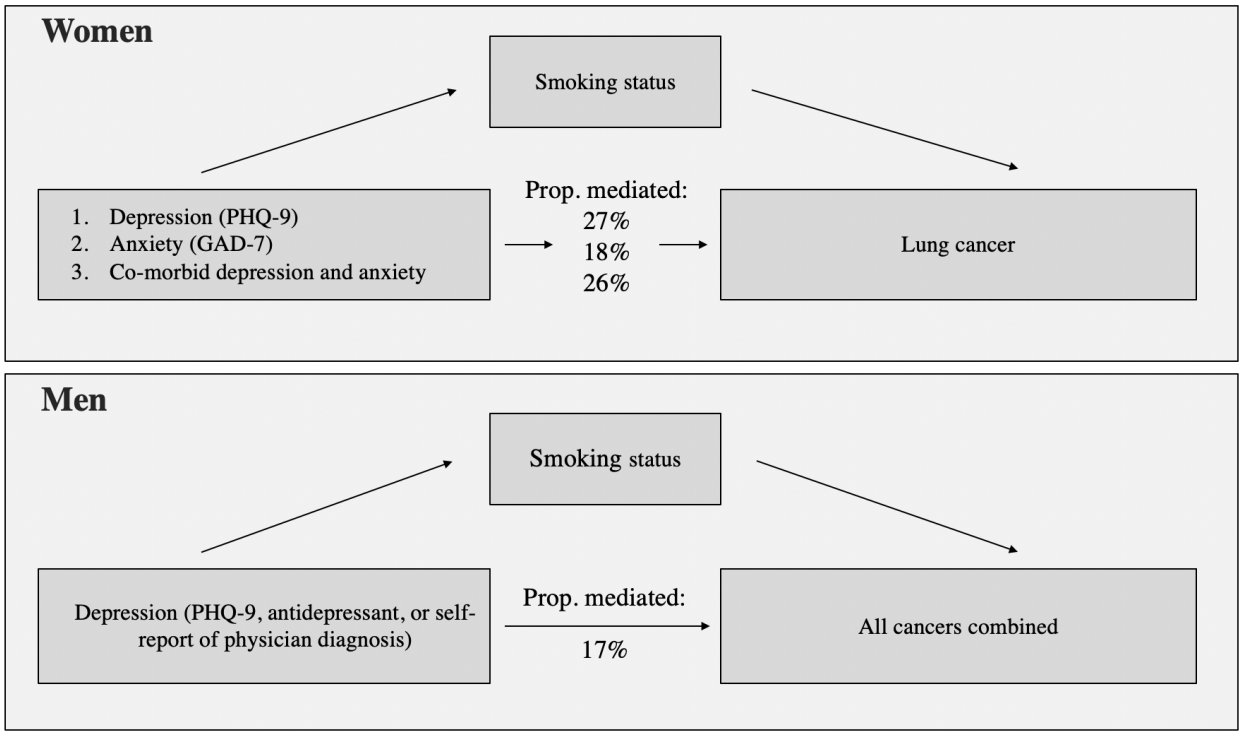
Mediation effects		Quasi-Bayesian estimates and 95% confidence intervals			Estimated proportion mediated
Mediators	Associations	Indirect effect of X on Y	Direct effect of X on Y	Total effect (95% CI)	
Sleep	Depression (PHQ-9) on lung cancer	-0.00 (-0.0008-0.0002)	0.01 (0.0014-0.0170) **	0.01 (0.0014-0.0168) **	-0.03
	Anxiety on lung cancer	-0.00 (-0.0007-0.0002)	0.01 (0.0019-0.0167) **	0.01 (0.0018-0.0166) **	-0.03
	Comorbidity on lung cancer	-0.00 (-0.0011-0.0003)	0.03 (0.0015-0.0229) *	0.01 (0.0014-0.0227) *	-0.03
Men					
Smoking status	Depression (PHQ-9, antidepressant, or self-report of physician diagnosis) on any cancer	0.00 (0.0011-0.0039) ***	0.01 (0.0003-0.0229) *	0.01 (0.0021-0.0247) *	0.17
Alcohol consumption	Depression (PHQ-9, antidepressant, or self-report of physician diagnosis)	0.00 (-0.0002-0.0003)	0.01 (0.0027-0.0252) *	0.01 (0.0027-0.0252) *	0.00
BMI	Depression (PHQ-9, antidepressant, or self-report of physician diagnosis)	0.00 (-0.0004-0.0005)	0.01 (0.0017-0.0247) *	0.01 (0.0018-0.0250) *	0.00
Fruit and vegetable intake	Depression (PHQ-9, antidepressant, or self-report of physician diagnosis) on any cancer	0.0000 (-0.0002-0.0002)	0.0134 (0.0026-0.0252) *	0.0134 (0.0026-0.0253) *	-0.00
Sleep	Depression (PHQ-9, antidepressant, or self-report of physician diagnosis) on any cancer	-0.0002 (-0.0007-0.0003)	0.0125 (0.0019-0.0234) *	0.0124 (0.0019-0.0232) *	-0.01

*p ≤ 0.05; **p≤ 0.01; ***p ≤ 0.001

[a] All models were adjusted for age, sex, education, ethnicity, income, and family history of cancer [b] quasi-Bayesian approximation based on 1000 simulations

†Anxiety defined as GAD-7 scores over or equal to 10 ‡Co-morbidity defined as both GAD-7 and PHQ-9 scores over or equal to 10

Figure 4.1 Significant indirect effects between mental health disorders and cancer outcomes



4.3.1.1 Relationship between smoking status and other lifestyle-related behaviours

Smoking status had a significant mediating effect on various mental health-cancer relationships among both men and women (**Table 4.11**). To investigate how other lifestyle behaviours may be associated with smoking status, the distributions of BMI, alcohol, fruit and vegetable consumption, physical activity, and sleep were evaluated within smoking status categories (**Table 4.12**).

Among women who were current smokers at baseline, there were greater proportions of normal BMI (41.1%), low fruit and vegetable intake (55.6%), low physical activity (26.0%), and short sleep (23.1%) observed compared to past smokers (35.3%; 35.5%; 21.6%; 17.8%) and never smokers (38.7%; 35.5%; 20.9%; 18.5%). Also of note, a higher proportion of women who were past smokers were regular (40.3%) or habitual (25.1%) alcohol drinkers and had an obese

BMI (26.2%) compared to current (33.3%; 20.3%; 20.4%) and never smokers (36.3%; 12.6%; 23.3%).

Among men who were current smokers at baseline, there were greater proportions of normal BMI (29.1%), low fruit and vegetable intake (73.4%), and short sleep (27.1%) observed compared to past smokers (18.3%; 60.1%; 21.3%) and never smokers (24.0%; 59.1%; 22.4%). A higher proportion of men who were former smokers had an obese BMI (32.1%), compared to current (24.7%), and never smokers (25.4%). Unlike women, levels of physical activity were distributed relatively evenly among smoking status in men.

Table 4.12 Distribution of lifestyle behaviours by level of smoking status, stratified by sex.

	Women				**Men**			
	Current smoker	**Past smoker**	**Never smoked**	**p-value**	**Current smoker**	**Past smoker**	**Never smoked**	**p-value**
	N=3121	**N=7143**	**N=8388**		**N=2890**	**N=6459**	**N=6570**	
Age				<0.001				<0.001
Mean (SD)	51.8 (6.93)	54.1 (7.58)	52.3 (8.16)		52.3 (7.36)	55.7 (7.92)	51.5 (7.69)	
Median [Min, Max]	51.3 [39.1, 70.0]	53.6 [38.4, 71.1]	50.8 [38.3, 71.6]		51.5 [39.1, 73.1]	55.9 [39.0, 71.5]	50.1 [38.6, 70.3]	
BMI				<0.001				<0.001
Underweight	60 (1.9%)	60 (0.8%)	98 (1.2%)		17 (0.6%)	13 (0.2%)	12 (0.2%)	
Normal	1284 (41.1%)	2520 (35.3%)	3249 (38.7%)		840 (29.1%)	1180 (18.3%)	1578 (24.0%)	
Overweight	1141 (36.6%)	2690 (37.7%)	3085 (36.8%)		1318 (45.6%)	3193 (49.4%)	3308 (50.4%)	
Obese	636 (20.4%)	1873 (26.2%)	1956 (23.3%)		715 (24.7%)	2073 (32.1%)	1672 (25.4%)	

	Women				Men			
	Current smoker	**Past smoker**	**Never smoked**	**p-value**	**Current smoker**	**Past smoker**	**Never smoked**	**p-value**
	N=3121	**N=7143**	**N=8388**		**N=2890**	**N=6459**	**N=6570**	
Alcohol consumption†				<0.001				<0.001
Abstainer	144 (4.6%)	218 (3.1%)	809 (9.6%)		76 (2.6%)	146 (2.3%)	465 (7.1%)	
Former drinker	428 (13.7%)	613 (8.6%)	892 (10.6%)		291 (10.1%)	528 (8.2%)	462 (7.0%)	
Occasional drinker	876 (28.1%)	1642 (23.0%)	2581 (30.8%)		721 (24.9%)	1132 (17.5%)	1694 (25.8%)	
Regular drinker	1040 (33.3%)	2880 (40.3%)	3045 (36.3%)		898 (31.1%)	2501 (38.7%)	2566 (39.1%)	
Habitual drinker	633 (20.3%)	1790 (25.1%)	1061 (12.6%)		904 (31.3%)	2152 (33.3%)	1383 (21.1%)	
Fruit and vegetable consumption				<0.001				<0.001
<5 servings	1736 (55.6%)	2539 (35.5%)	2978 (35.5%)		2120 (73.4%)	3938 (61.0%)	3884 (59.1%)	
5+ servings	1385 (44.4%)	4604 (64.5%)	5410 (64.5%)		770 (26.6%)	2521 (39.0%)	2686 (40.9%)	
Physical activity				<0.001				0.023
Low	810 (26.0%)	1546 (21.6%)	1750 (20.9%)		602 (20.8%)	1208 (18.7%)	1242 (18.9%)	
Moderate	1150 (36.8%)	2815 (39.4%)	3435 (41.0%)		865 (29.9%)	2030 (31.4%)	2145 (32.6%)	
High	1161 (37.2%)	2782 (38.9%)	3203 (38.2%)		1423 (49.2%)	3221 (49.9%)	3183 (48.4%)	
Sleep				<0.001				<0.001
<7 hrs	721 (23.1%)	1273 (17.8%)	1553 (18.5%)		784 (27.1%)	1376 (21.3%)	1471 (22.4%)	
7-9 hrs	2016 (64.6%)	5027 (70.4%)	5933 (70.7%)		1846 (63.9%)	4502 (69.7%)	4662 (71.0%)	
9+ hrs	384 (12.3%)	843 (11.8%)	902 (10.8%)		260 (9.0%)	581 (9.0%)	437 (6.7%)	

†Abstainer: has never drunk alcohol, former: has drunk alcohol before but not over the past 12 months, occasional: drank ≤2–3 times/month over the past 12 months, regular: drank ≥ once/week but ≤2–3 times/week, habitual drinkers: drank ≥ 4–5 times/week.

Chapter 5: Discussion

5.1 Summary of findings in comparison with literature

This study is among the first in Canada to investigate the relationship between mental health disorders and cancer risk. Furthermore, it is one of the first studies to investigate the mediating effects of several different health behaviours in the relationship between mental health disorders and cancer risk. While mental health and cancer have been studied in populations outside of Canada, results have been inconsistent and acknowledgement of the effect of health behaviours has been limited (2,3,25,183,184,227).

Using longitudinal data from the CARTaGENE cohort in Quebec, this study assessed the relationship between mental health disorders and subsequent cancer risk. The study captured baseline depression status using three distinct definitions, and in addition assessed anxiety, amd co-morbid depression and anxiety as exposures. Since both mental health disorders and cancer risk are associated with health behaviours such as smoking, alcohol consumption, diet, and physical activity, a mediation analysis was performed to assess the potential mediating effect of health behaviours in this relationship. This chapter reviews the key findings of the study with comparison to previous literature, discuss strengths and limitations, potential implications of the research, and future directions for this area.

5.1.1 Research Question 1: Assessing the relationship between mental health disorders and cancer risk

5.1.1.1 All cancer risk

For all cancer risk, nearly all hazard ratios were above 1.0, indicating an increased risk for most mental health disorders exposures, although few associations reached statistical

significance. The relationship between comorbid anxiety and depression and all cancer risk was statistically significant in women (HR =1.29, 95% CI: 1.00, 1.66), as was depression (PHQ-9, antidepressant use, or self-report of physician diagnosis) in men (HR = 1.16, 95% CI: 1.02, 1.32) with adjustment for age (Model 1). With adjustment of additional covariables however, statistical significance for both relationships were attenuated. As noted, although most associations were not statistically significant, hazard ratios tended to be higher among women, with the exception of depression defined by antidepressant use and PHQ-9, antidepressant use, or self-report of physician diagnosis, where hazard ratios were higher for men. Furthermore, hazard ratios were higher for comorbid anxiety and depression compared to when anxiety and depression were assessed individually.

Previous evidence on depression and all cancer risk is inconsistent. Gross et al. conducted a longitudinal study with up to 24 years of follow-up, and found that there was a significant positive association between depression (as defined by DSM-3 criteria) and all cancer risk (HR = 1.9, 95% CI: 1.2, 3.0) (4). However, the Gross et al. study did not adjust for any health behaviours other than smoking, and hence there is potential for unmeasured confounding in this finding (4). Consistent with our study, O'Neill et al. found that associations between depression and all cancer risk were not significant, and similarly found that risk estimates were higher in women than men (3). The O'Neill et al. study reported that they adjusted for history of smoking (ever/never) and educational attainment, but that this adjustment did not significantly change the models, so they only included unadjusted risk estimates in their publication. The present study found that adjustment for smoking status considerably changed risk estimates. It is possible that the definition of smoking status used by O'Neill et al. (ever/never smoked) did not capture

smoking status as accurately as the present study, which used a more detailed assessment of smoking history (current/former/never smoker) (3).

A meta-analysis of 51 cohort studies by Wang et al. found a pooled estimate of RR = 1.13 (95% CI: 1.06-1.19) for depression and anxiety and all cancer risk (25). However, a limitation of the Wang et al. study was that depression and anxiety were assessed as one exposure and as such, could not determine potential differential effects of depression and anxiety (25). Given the biological differences between depression and anxiety, it is likely that assessing these as separate exposures elucidates this connection more clearly, as done in the present study. Similar to our study, Liang et al. found a non-significant association between anxiety and all cancer risk (HR = 1.01, 95% CI: 0.95, 1.07) (183). O'Neill et al. assessed several types of anxiety disorders and found that panic disorder and phobias were associated with increased risk of subsequent self-reported cancer, but risk estimates for anxiety as assessed by the GAD were not significant (3). O'Neill et al. also demonstrated that risk of self-reported cancer was greater if a person had more than one mental health disorder. A dose-response was observed with increased mental health disorder comorbidities, indicating that risk of cancer increased with the number of individual mental health disorder diagnoses (3). This is similar to findings in the present study, where hazard ratios for comorbid anxiety and depression were higher than the individual estimates for depression and anxiety.

5.1.1.2 Prostate cancer risk

Prostate cancer was the second cancer outcome to be assessed in its relationship with mental health disorder. Nearly all hazard ratios were below 1.0, indicating a non-significant inverse association between mental health disorder and prostate cancer incidence. The exception

was for risk estimates for depression defined by antidepressant use, and the combined variable of PHQ-9, antidepressant use, or self-report of physician diagnosis, which both had non-significant hazard ratios of 1.03, respectively in fully adjusted models.

The relationship between mental health disorder and prostate cancer risk in the literature is conflicting and depends on the operationalization of mental health disorder. Gross et al. found a positive association between single-episode major depression and prostate cancer (HR = 6.88, 95% CI: 1.98, 23.90), but no association with history of major depression (4). However, it should be noted that the number of cases was extremely small (n = 7), and these results should be interpreted with caution. A cohort study in Korea found inconsistent results within their study. In a dose-response analysis, mild depression was significantly associated with subsequent prostate cancer risk, while moderate and severe depression were not (228). In a separate assessment of minor and major depression, only minor depression was significantly associated with increased prostate cancer risk (228). These studies may suggest that mild forms of depression are associated with prostate cancer risk. The present study assessed all mental health exposures as a binary variable (yes/no). If there was a significant relationship between prostate cancer and more mild forms of mental health disorders, it was not captured by this study.

There are few studies investigating the relationship between prostate cancer incidence and anxiety. Two population-based studies in Taiwan found significant positive relationships between anxiety and prostate cancer risk (183,184). Shen et al. found a standardized incidence ratio (SIR) of 2.17 with a 95% CI of 1.56-2.93 for anxiety and prostate cancer risk, versus those without anxiety (184). In an analysis similar to that of the present study, Liang et al. used Cox regression modelling and reported a HR of 1.32 (95% CI 1.02-1.72) for anxiety after adjusting for urbanization, hypertension, diabetes, and hyperlipidemia (183). Of note, these studies did not

adjust for health behaviours, while the present study did, which may account for some of the inconsistencies. Furthermore, this could also reflect inter-national differences in screening and detection of prostate cancer.

5.1.1.3 Lung cancer risk

The last cancer outcome that was assessed was lung cancer. Although most relationships had a hazard ratio above 1.0, indicating an increased risk, there were no statistically significant relationships observed for any mental health exposure in male participants. Similar to all cancer risk, hazard ratios were higher for comorbid anxiety and depression compared to anxiety and depression individually. Hazard ratios were consistently higher in women compared to men for all mental health exposures in all three levels of adjustment.

A study by Trudel-Fitzgerald et al. investigated the relationship between depression and lung cancer risk in a cohort of women (195). Among n=1,009 cases of lung cancer they found that women with the highest versus lowest level of depression symptoms had an increased lung cancer risk (195). The authors also assessed depression status at intervals during the follow-up period, as well as chronicity of depressive symptoms. They found that the association between depression and lung cancer risk was similar or stronger when assessing depression in this manner, suggesting that lung cancer risk increases with longevity and/or severity of depression (195). In contrast, Gross et al. did not find any reliable associations between lung cancer and depression, however they did not stratify risk estimates by sex (4). Few studies assessing the relationship between mental health disorders and cancer have stratified for sex, with general exceptions for sex-specific cancers such as breast and prostate cancer. Although few results

reached significance in the present study, there was a consistent difference in hazard ratios between men and women, with women having generally higher estimates.

Similar to prostate cancer, evidence surrounding the relationship between anxiety and lung cancer is slim. Goldacre et al. observed that lung cancer was more common in those with anxiety (RR = 1.29, 95% CI: 1.12-1.48) than in those without (229), and Shen et al. found a significant positive association between anxiety and lung cancer risk in men (SIR = 1.77, 95% CI: 1.33-2.30) (184). However, in another cohort study, Liang et al. did not find a significant association between anxiety and lung cancer (183). Of note, unlike the present study, Liang et al. did not adjust for health behaviours or stratify by sex (183). Our results found a significant positive relationship between anxiety and lung cancer for women, but not men, indicating that future studies should aim to stratify by sex when assessing this relationship.

Across all three cancer outcomes there were conflicting findings between the present study and existing literature. There were few studies to draw comparisons to, including studies from different countries with different cancer incidences and screening practices, different lifestyle behaviours and assessment of lifestyle behaviours, varying methods of ascertaining cancer status (e.g., self-report and cancer registry) and exposure status (e.g., DSM criteria, questionnaire scores, and administrative health databases). The conflicting findings among mental health disorders and cancer outcomes explored in this study compared to the literature may also be explained by the heterogeneity of cancer types among cases, within this study and in previous studies.

5.1.2 Research Question 2: Assessing the role of lifestyle-related behaviours in the relationship between mental health disorders and cancer risk

The present study indicates that the relationship between depression (PHQ-9), anxiety (GAD-7), and co-morbid depression and anxiety on lung cancer incidence in women was partially mediated by smoking status by a proportion of 27%, 18%, and 26%, respectively. Smoking status also mediated 17% the relationship between depression (PHQ-9, antidepressant use, or self-report of physician diagnosis) and all cancer incidence in men. Although smoking was the only health behaviour that significantly mediated the relationship between mental health disorders and cancer risk, there was a strong association between smoking status and other health behaviours (alcohol consumption, fruit and vegetable consumption, sleep, BMI, and physical activity).

The results of the mediation analysis are consistent with the findings of Trudel-Fitzgerald et al., who found that in the Nurses' Health Study, lifetime pack-years of smoking mediated 38% of the overall association between depressive symptoms and lung cancer risk in women (195). To our knowledge, there is no comparable study that assessed this relationship in a cohort with men. A study by Burns et al. assessed the extent to which smoking mediated the relationship between mental health difficulties and smoking-related diseases (194). Both mental health difficulties and smoking-related diseases encompassed several exposures and outcomes. Mental health difficulties were defined as any one of the following: self-reported emotional, nervous, or psychiatric problems, self-reported alcohol or substance use, psychiatric medication use (anxiolytics, antidepressants, or antipsychotics), or a positive result from the Center for Epidemiologic Studies Depression Scale, or the Hospital Anxiety and Depression Scale (194). Smoking-related diseases included cancers, respiratory diseases, and cardiovascular disease (1,2)(194). The authors found that smoking had no significant mediating role in this relationship,

contrary to the results in the present study and the study by Trudel-Fitzgerald et al. (195). The results found by Trudel-Fitzgerald et al. and the present study present stronger evidence supporting the mediating effect of lifestyle behaviours, as they were both looking at a single exposure and single outcome, compared to the Burns et al. study which grouped them together (194,195). However, given the limited number of studies in the literature assessing this relationship, additional research is warranted.

The findings from the current study clarify some of the mechanisms involved in the relationship between mental health disorders and cancer risk. This is meaningful given that both mental health disorders and cancer are significant public health burdens, and the pathways between these two illnesses is unclear. These findings contribute to the literature elucidating the mechanistic pathways between mental health disorders and cancer risk. However, as smoking explained less than a third of the associations in the present study, there are still other unknown pathways that warrant investigation. Furthermore, similar to the results for the first research question, this mediation analysis found that there were differences between men and women. Disparities were observed in both the number and magnitude of significant mediating relationships between men and women, with smoking mediating a higher proportion of the relationship in women (depression on lung cancer, 27%; anxiety on lung cancer, 18%; co-morbidity on lung cancer, 26%) compared to men (depression on all cancer, 17%).

There are potential etiological differences in mental health disorders between men and women, that may explain some of the differences observed for results between men and women in this study. Evidence in the literature has shown that depression in men and women can present differently and be triggered by different factors. Women more often present with internalizing symptoms and men with externalizing symptoms (230). Externalizing symptoms are more

frequently associated with unhealthy lifestyle behaviours such as smoking and alcohol consumption (231,232). However, Dawson et al. demonstrated that the odds of lifetime alcohol dependence associated with internalizing and externalizing symptoms was significantly greater for women than men (233). A similar disparity has been observed for internalizing and externalizing symptoms and cannabis smoking, with odds of cannabis use being significantly higher in females (234). These findings suggest that mental health disorder symptoms may manifest differently on unhealthy health behaviours in men and women. The present study found that smoking status mediated a higher proportion of the relationship between mental health disorders and cancer risk in women compared to men. Future research should assess how the sex and gender disparity in lifestyle behaviours observed with mental health disorder symptoms may affect subsequent pathological pathways.

Interestingly, there is research to suggest that depression between women and men differs beyond prevalence and symptomology. Women experience specific forms of depression-related illness, including premenstrual dysphoric disorder, postpartum depression and postmenopausal depression and anxiety. These forms of depression are hypothesized to be attributable to changes in hormone levels, and thus may be associated with different biological pathways than other depressive disorders (235,236). The current study did not differentiate between depression subtypes that may have been associated with changes in hormones, nor have any other studies in the literature. However, there is a substantial body of evidence linking hormone factors such as menarche, menopause, and hormone replacement therapy on cancer risk (237–239). These factors have largely been linked to breast cancer, which was not assessed in this study, but should perhaps be evaluated in future research.

There are additional sex-specific biological differences that have been observed in mental health disorders. A systematic review on sex-specific pathology in major depressive disorder found that women presented with higher levels of inflammatory markers and there was a stronger correlation between levels of some inflammatory markers and the severity of symptoms (240). For example, Kohler-Forsberg et al. found a significant positive association between C-reactive protein (CRP) levels and depressive symptom severity among women but not among men (241). Birur et al. found that IL-1β and tumor necrosis factor (TNF)-α were positively correlated with this score in depressed females, but not males (242). These chronic inflammation markers CRP, IL-1β and TNF-α have been consistently associated with increased cancer risk, suggesting that there may be a shared pathophysiological link between mental health disorders and cancer risk in women, that may not appear in men (243,244). Given the biological differences in mental health disorders between men and women, and the differential risks between men and women observed in the present study, future research should stratify analyses by sex. Furthermore, investigation into the shared biological pathways between mental health disorders and cancer, and how they differ between sexes is warranted.

5.1.2.1 Results in the context of the Bradford-Hill criteria

The Bradford-Hill criteria is a tool to assess the potential causal relationship between mental health disorders and cancer risk (222). The nine criteria: effect size, consistency of findings, specificity of association, temporality of effect, dose-response relationship, plausibility, coherence between epidemiological and laboratory findings, experimental evidence, and analogy can be applied to the literature reviewed and the results presented in the above sections (222).

Each of these criteria will be briefly reviewed in turn for an additional perspective of causality beyond that provided by the mediation analysis.

1. **Effect size**

This criterion examines the strength of the association between the exposure and the outcome. Results from the present study and previous literature indicate that if there is a true positive association, it is relatively small. A systematic review and meta-analysis of 25 studies with a pooled sample of 1,469,179 participants and 89,716 incident cases of cancer assessed the association between depression and incident cancer risk (2). They found that depression was significantly associated with overall cancer risk (RR = 1.15, 95% CI: 1.09-1.22), liver cancer (RR = 1.20, 95% CI: 1.01-1.43) and lung cancer (RR = 1.33, 95% CI: 1.04-1.72) (2). Subgroup analysis of studies in North America showed a summary relative risk for all cancers (RR = 1.30, 95% CI: 1.15-1.48) (2). The general effect size observed in the present literature may change as our understanding of the biological mechanisms between mental health disorders and cancer improves and additional research is conducted.

2. **Consistency of findings**

The second criterion examines whether the observed association has been repeatedly observed by different persons, in different places, circumstances and times (222). While the topic of mental health disorders and cancer risk has been studied in many different geographic areas, findings have been inconsistent, as discussed in length in above sections.

3. **Specificity of association**

Hill notes that if, as in his example, the association is limited to specific workers and to particular sites and types of disease and there is no association between the work and other modes of dying, then clearly that is a strong argument in favour of causation (222). In this case,

we could draw evidence of causality if the association with cancer was limited to people with specific mental health disorders. However, mental health disorders constitute a wide spectrum of morbidities with many individual and overlapping psychological, biological, and physical differences. For this reason, it is of interest to study different dimensions of mental health disorders and subtypes of cancer. Examining these specific definitions could determine whether generality of exposure and outcome definitions in previous literature could account for inconsistent findings. However, at present it is difficult to specify the association when both the exposure and outcome represent broad categories of medical conditions.

4. Temporality of effect

The understanding of temporality in the assessment of cause-effect relationships critical. Strong evidence demonstrates that cancer survivors and people with cancer diagnoses are more likely to have a mental health disorder than a healthy individual (245–247). Therefore, the temporal nature of this relationship is a key issue that should be addressed. The design of a longitudinal study, like the present study, allows researchers to better assess the temporal sequence of an exposure and outcome. Many other studies that have found positive associations between mental health disorders and cancer have utilized a longitudinal study design to address the issue of reverse causality (2,24,25). However, while the present study also excluded participants who had a diagnosis of cancer in the first six months, the potential for reverse causality cannot be fully eliminated.

5. Dose-response relationship

This criterion generally refers to a biological gradient, and whether there is a linear relationship between units of exposure and rate or risk of the outcome. In this case, there are limitations to defining the severity of a mental health disorder. Severity of symptoms,

determined by a validated measure such as the PHQ-9, is a useful measure. However, the PHQ-9 and GAD-7 are limited to assessing symptomology in the most recent two weeks. Chronicity of symptoms could potentially serve as a better measure of severity, as could treatment resistance, both of which are more difficult to capture objectively and quantitatively. Limitations aside, Trudel-Fitzgerald et al. found that among n=1,009 cases of lung cancer women with the highest versus lowest level of depression symptoms had an increased lung cancer risk, which could suggest a dose-response relationship (195). Chang et al. also found a positive dose-response relationship between depression symptoms and prostate cancer, however not all risk estimates reached statistical significance (228). Alternative definitions of mental health disorder severity could be explored in the future to further explore this criterion.

6. Plausibility

This step seeks to determine whether a causation is biologically plausible. However, Hill notes that this criterion is limited by the biological and medical knowledge of the present day (222). Given the current understanding of the underlying physiological processes in both mental health disorders and cancer, we could cautiously say that this association is biologically plausible. However, the exact pathways that connect these two morbidities is still unclear.

7. Coherence between epidemiological and laboratory findings

It is hypothesized that there could be shared biological pathways between mental health disorders and cancer. Meta-analyses have found that severe mental illnesses such as schizophrenia, bipolar disorder, and major depressive disorder are associated with systemic inflammation, peripheral inflammatory markers, and create oxidative stress—leading to a cellular environment optimal for malignant growth (27–29).

Clinical studies have also observed biological differences in mental health disorders between men and women (235,236,241,242). For example, the inflammatory markers CRP, IL-1β and TNF-α have been consistently associated with increased cancer risk and have associated with depression in women but not men (241,242). This suggests that there may be a shared pathophysiological link between mental health disorders and cancer risk in women, that may not appear in men. The present study observed that smoking status mediated the associations between mental health disorders and risk of all cancers combined and lung cancer, by larger proportions in women than in men. Whether the abovementioned pathophysiological pathways interact with smoking status is presently unclear but may be a focus of future research.

8. Experimental evidence

In this case, it is not possible to assess this criterion. Hypothetically, this criterion would assess whether the frequency of the associated events is affected by preventive action (i.e., reduced mental health prevalence). However, this cannot be controlled for experimentally.

9. Analogy

Hill states that in some circumstances it would be fair to judge by analogy (222). For example, given the effects of thalidomide and rubella we would be able to accept slighter but similar evidence with another drug or disease in pregnancy (222). In this case, it is difficult to find an appropriate comparison. Parallels could be drawn with other morbidities such as cardiovascular disease or diabetes and their relationship to cancer. However, these comparisons are limited. For example, the permanence of diabetes cannot be compared to the occasionally fluctuating nature of a mental health disorder such as depression. As our understanding of this topic grows, in the future it may be possible to draw parallels between different mental health

disorders such as bipolar disorder and depression for evidence of causality. However, presently there is not sufficient evidence to draw meaningful analogies.

In summary, it could be argued that some of the abovementioned criteria – such as effect size, temporality, dose-response, and coherence – are met in the discussion of the cause-effect relationship between mental health disorders and cancer risk. However, there are other criteria that require further research, or are not relevant in this case. While there are no formal tests of significance to assess the criteria as they stand, the Bradford-Hill criteria serve as a useful guideline to frame and discuss the potential causal relationship between mental health disorders and cancer. They could also serve to identify gaps in the literature and strengths and limitations of previous research to inform future studies.

5.2 Strengths and limitations

The CARTaGENE cohort recruited participants residing in metropolitan areas that represented a total of 55.7% of the Quebec population (Montreal, Quebec, Sherbrooke, and Saguenay) (47). This represents the majority of the Quebec population; however, it is limited to urban areas which may limit its generalizability to individuals living in rural areas. The current study categorized ethnicity as "white" and "non-white". Furthermore, within the CARTaGENE cohort there was a significant underrepresentation of Indigenous and Asian ethnicities compared to the Canadian population, which limits generalizability to these population groups (241). Although the voluntary nature of the CARTaGENE cohort study resulted in a more affluent and educated sample compared to the Canadian population, there was reasonable heterogeneity in many other sociodemographic variables and health-related outcomes which supports generalizability to other Canadian provinces and other large populations (248).

This study also benefitted from several key methodological strengths. Importantly, this was a large prospective study with a follow-up of up to nine years with linked administrative data. Validation of cancer diagnoses thorough administrative health databases was also a strength. Incident cancers were determined from the provincial cancer registry until 2010. After 2010, incident cancers were defined from the hospitalization and medication data. Previous studies in the literature have relied on self-reported, however the present study made use of administrative health data which is more comprehensive and reliable. Furthermore, the large sample size facilitated the ascertainment of a substantial number of cases.

Data on mental health disorders was collected at baseline, along with information about health behaviours. This is a particular advantage, as previous studies have seldom included health behaviours in their analyses and many studies have used case-control designs, which can be limited by selection bias. Furthermore, several variables on mental health were collected. For depression specifically, antidepressant use was available, along with PHQ-9 scores, and prior lifetime diagnosis by a physician. Although information on duration was not captured, this allowed for a comprehensive assessment of depressions status at baseline, and alternative conceptualizations of depression in the analysis. Although this was overall a strength of the study, there were some limitations for these alternative conceptualizations of mental health. Agreement between self-reported diagnosis of depression and administrative health data was relatively low with a kappa statistic of 0.45 (95% CI: 0.43-0.47) (200). Furthermore, although the majority of antidepressant medications prescribed in Quebec are for treatment of depression (55.2%), there is still a large proportion that are prescribed for alternative indications (201). This could have introduced nondifferential misclassification to the study. When there is a

dichotomous exposure, as was the case in the present study, this results in a bias towards the null value.

Another limitation of this study was the missingness of the GAD-7 and PHQ-9 individual items. Both questionnaires are composites of individual questions, and if the full questionnaire had not been completed by a participant, responses to individual questions were omitted from the data set. The full scores could not be imputed without the individual components, and so individuals without full scores were excluded (n = 2,509). This likely caused bias in the estimates of the parameters, as it is unlikely that these scores were missing completely at random (MCAR) (249,250). Another important limitation was that, although individuals with an incident cancer in the first six months of follow-up were excluded, it is possible that participants had asymptomatic or early stages of cancer that were not captured at baseline. Thus, the possibility of reverse causality cannot be eliminated. Another limitation was also a short overall follow-up time, which given the long latency of most cancers, might not have accurately captured the association between mental health disorders and cancer incidence.

As with all observational research, unmeasured or residual confounding remains possible. Multiple relevant covariates that may be common prior causes of mental health disorders and cancer were controlled for, yet some were limited. For example, there was not enough data to assess lifetime pack-years or family history of prostate and lung cancer, so smoking status and family history of cancer were used in their place. Lastly, the study intended to exclude the non-melanoma skin cancer cases as they are non-fatal and treatment is relatively minor compared to other cancers. However, data on cancer subtypes other than lung and prostate cancer was not available from CARTaGENE. Furthermore, lung cancer can generally be classified into the subtypes small-cell and non-small cell lung cancer, as they are distinct diseases with different

histology. For the mediation analysis, it was of interest to assess these subtypes separately, but this data was not available.

5.3 Study implications

This study further sheds light on the complexity of the relationship between mental health disorders, cancer risk, and lifestyle behaviours and has implications for cancer prevention strategies and policies. Cancer rates are projected to increase in coming decades, and it is estimated that a considerable fraction of cancer cases can be prevented through modifiable risk factors (11,78). Although the net 5-year survival rate for prostate cancer is quite high at 93%, individuals who survive prostate cancer experience poor long-term quality of life, life satisfaction, and psychological adjustment after prostate cancer (49,251). Given that is the one of the most commonly diagnosed cancers in Canada, it is associated with a significant clinical and economic burden, which can be reduced by identifying risk factors (7,252). The current study did not identify any significant associations between mental health disorders and prostate cancer. However, as discussed previously, further research is warranted.

The present study observed positive associations between mental health disorders and lung cancer, where smoking status mediated a significant proportion of this relationship. Furthermore, previous research has identified that individuals with mental health disorders engage in unhealthy lifestyle behaviours at higher rates than the general population (33,35,154,155,161,173,175,253,254). The present study confirmed these findings. In Canada, the net 5-year survival rate for lung cancer is very low at 22% among females, and 15% among males (255). Thus, it is imperative that risk factors, particularly those associated with smoking, are identified. However, while smoking status is a modifiable risk factor, mental health disorders

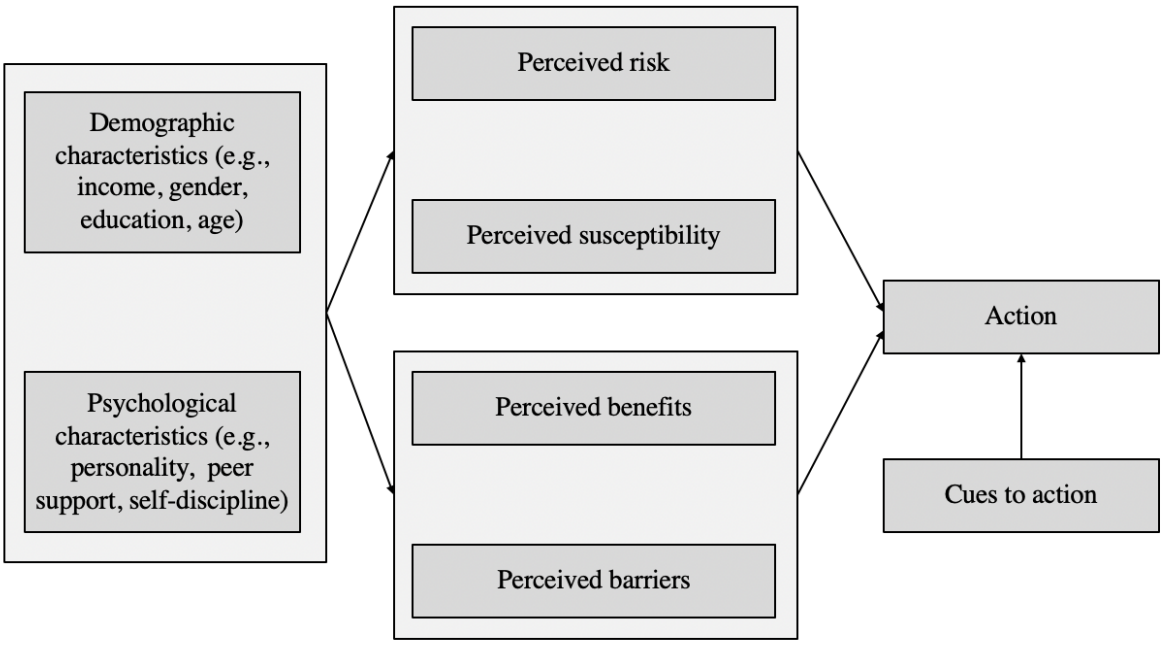
may also require attention as an independent risk factor for cancer. Parallels can be drawn with other morbidities, such as cardiovascular disease and diabetes, that have been associated with increased cancer risk (31,66,68,69,71). Since decreasing incidence of cardiovascular disease and diabetes is already a high public health priority, focusing on reducing these morbidities would not be an effective solution for decreasing cancer incidence. Therefore, in instances where illnesses such as cardiovascular disease, diabetes, and mental health disorders increase risk of cancer, focus may instead be put on encouraging the adoption of a cancer prevention lifestyle.

5.3.1 Health Belief Model

Understanding research in the context of a framework such as the Health Belief Model (HBM) is a useful way to explore its contribution to the literature, as well as its potential implications. The HBM was initially developed by social psychologists to explain hesitancy of people to participate in programs to prevent and detect disease (**Figure 5.1**) (256,257).

The HBM proposes that people are most likely to take preventative action if they perceive that there are fewer costs than benefits to engaging in it. A central aspect of the Health Belief Model is that behavior change interventions are more effective if they address an individual's specific perceptions about susceptibility, benefits, and barriers. Interventions focusing on this model involve risk calculation and prediction, as well as personalized advice and education.

Figure 5.1 The Health Belief Model, adapted from Becker, 1974



This study can be interpreted as contributing to literature that addresses how people with mental health disorders perceive their risk of developing cancer. It can also address the perceived benefits of reducing cancer risk behaviours such as smoking cessation among people with mental health disorders. In the context of the HBM, future directions for research on this topic would include addressing the other concepts within the model such as cues to action. This could include communicating the susceptibility of cancer risk to people with mental health disorders and the benefits of smoking cessation. It would also include addressing the other two key constructs in the model – perceived severity of the disease, and perceived barriers.

In Canada, cancer is generally perceived as a severe and serious disease (258). However, the perceived barriers to adopting a cancer prevention lifestyle such as smoking cessation, adopting a healthier diet, and engaging in regular physical activity among Canadians are high. Newsom et al. found that 66.7% of older Canadians did not believe that they should do anything

to improve their health (259). Among those who did believe they should improve their health, only 59.6% reported any intention to do so in the next year (259). Participants cited lack of willpower and time, stress, and cost as barriers to engaging in health behaviours (259). Another study on Canadians' perceptions of diet and health found that consumers believe that nutrition is one of the most important factors for maintaining health, however the majority reported difficulty finding healthy and affordable foods (260). Knowledge translation and health promotion initiatives should emphasize the severity of cancer and its subsequent impact on quality of life, and the comparatively low barriers of adopting a cancer prevention lifestyle.

5.3.2 Knowledge translation and public policy

Ho et al. stated that knowledge translation includes the application of research findings to at least three areas of action: the practices of health professionals, policymaking by health authorities and governments; and implementation of strategies to enable health professionals and policy makers to work together to put policies into practice. In the context of the first area of action set forth by Ho et al., the present study may encourage health professionals to suggest health behaviour change in individuals with mental health disorders, with the aim of decreasing risk of adverse health outcomes such as cancer. Although many risk estimates for the relationship between mental health disorders and cancer did not reach significance, the findings from the mediation analysis indicated that smoking status partially mediates the relationship between mental health disorders and cancer. Furthermore, a cancer prevention lifestyle encourages smoking cessation, lower alcohol consumption, better diet quality, and more physical activity, which have many benefits beyond cancer prevention (12). Thus, integrating greater

support for health behaviour change into mental health care may be beneficial for overall health as well as cancer prevention.

Smoking in particular should be a focus for healthcare professionals. A systematic review and meta-analysis found that individuals with mental health disorders do not receive adequate smoking cessation advice, even though research indicates that individuals with poor mental health have greater need for these services (261). Health professionals could prioritize screenings and assessments for lifestyle factors in patients presenting with mental health disorders such as depression and anxiety, with emphasis on smoking behaviours. Where applicable, referrals and recommendations to support adoption of healthy behaviours could also then be made. Incorporating these practices into mental health care could ultimately improve the disparities in cancer prevention behaviours between individuals with mental health disorders and those without.

The second level of practice identified by Ho et al. was policymaking by health authorities and governments (262). The Canadian Partnership Against Cancer has highlighted smoking cessation as a top priority for cancer prevention (263,264). Thus, determining demographic groups that are more likely to engage in smoking behaviours is a key strategy for informing policy and planning interventions. Canada's Tobacco Strategy currently acknowledges that tobacco use is often linked to health and social inequities and has highlighted LGBTQ+, young adults, and Indigenous peoples as demographics with higher rates of tobacco use (265). Our results and others also suggest individuals with mental health disorders may be a population who would benefit from support for cancer prevention behaviour change (35,154,155). Policies and public health interventions on a local, provincial, and national level can work to facilitate adoption of cancer prevention lifestyle changes such as smoking cessation, lower alcohol

consumption, increased physical activity, and improved diet quality. Based on the results of this study, it is possible that women require additional support to engage in cancer prevention behaviours, as reflected by the higher risk estimates for cancer risk and higher mediating effects of smoking status for women.

The last level of knowledge translation described by Ho et al. was implementation of strategies to enable health professionals and policy makers to work together to put policies into practice (262). In theory, evidence-based policy making is a sound strategy, however it is not always effective (266–268). Evidence illustrating the disparities in healthy lifestyle behaviours and chronic diseases between people with and without mental health disorders has existed for several years (21,154,155,167,173,175,177,253). However, in Canada there are still significant disparities (35,269). Solutions that should be applied are employing knowledge brokers (translational scientists), promoting dialogue between researchers and policymakers, and building effective inter-disciplinary teams (268,270,271).

5.4 Future directions for research

Cancer is a large and complex group of diseases with a wide range of etiologies, progression patterns, and symptoms (272). Therefore, where there are subtype-specific risk factors, assessing all cancer types collectively as one outcome in epidemiological studies may attenuate the effect. For example, cancer subtypes can be further classified by histology such as non-small cell lung cancer and small cell lung cancer, which have distinct etiologies. It is possible that mental health disorders affect only certain cancer subtypes, and this effect is attenuated in the risk estimates by the subtypes that are not affected by mental health disorders. However, this presents a challenge for research such as the present study, as cancer cases

documented in the CARTaGENE database are not classified by these histological differences. Furthermore, ascertaining a number of cases to achieve sufficient statistical power when assessing several mental health exposures is difficult in a provincial cohort at this stage of follow-up. Future research could explore the risk for different cancer subtypes.

In addition, depression and anxiety themselves both represent groups of distinct illnesses. While the current study was able to capture depression using more comprehensive methods than previous studies, anxiety was assessed based solely on GAD-7 scores. There were also some dimensions of mental health that were not able to be measured in the current study such as chronicity, severity, treatment resistance, neurochemical changes, and inflammation.

Although advancing quite rapidly in recent decades, research on the neurobiology of depression and anxiety is still in early stages. Some evidence suggests that, like cancer, there are differential biological subtypes of mental disorders, even when symptomology or clinical features are similar (273,274). Analysis of neurotrophic factors in different anxiety disorders found a significant decrease in brain-derived neurotrophic factor (BDNF) in females with GAD, and males with phobias, but not any other subtypes (275). Biochemical studies indicate that there might be depression subtypes with and without disturbed neurotransmitter levels, and another study suggested there may be an inflammatory subtype (276–278). Neuroimaging studies have also found evidence for depression groups with structural and connectivity differences (274,279,280).

It is possible that biological subtypes of mental health disorders have differential associations with subsequent cancer risk. Thus, assessing depression and anxiety by symptomology and medication use alone, as done in the present study, may not have been sufficient to capture these differences. An individual's unique environmental, genetic, and

psychological dimensions of their mental health disorders may be stronger determinants of their cancer risk and could be a focus of future research in this area.

Other cancer outcomes, such as mortality and survival, should be studied in future research for their association to mental health disorders and health behaviours. Like cancer incidence, there is a reasonable body of evidence suggesting a positive association between mental health disorders and other cancer outcomes. A meta-analysis of 76 studies (n = 176,863) investigating the relationship between depression and cancer mortality found that depression diagnosis and higher levels of depressive symptoms predicted elevated mortality (281). This was true in studies that assessed depression before cancer diagnosis as well as in studies that assessed depression following cancer diagnosis (281). The authors noted that surprisingly few studies assessed health-related behaviours as confounders or mediators, similar to the meta-analysis investigating depression and cancer incidence by Jia et al. (2,281). Based on observations from previous literature and results from the present study, future research investigating this relationship should aim to stratify by sex, assess modifiable health behaviours, and explore alternative conceptualizations of mental health.

Future studies should also investigate cancers that have larger attributable risks with preventable lifestyle behaviours and have a high public health burden such as breast, colorectal, stomach, liver, and esophageal cancers (11). Some of the mediation factors assessed in this study, such as physical activity, are more strongly associated with these other cancer subtypes and mediation effects may be differential. Furthermore, given the association between smoking status and the other health behaviours assessed as mediators, it is possible that assessing the mediators independently did not fully disentangle this relationship. Future analyses could include

multiple mediation, to assess the joint mediation effect between mental health disorders and cancer incidence, as well as assessing these effects by strata of smoking status.

While the Baron and Kenny method is the dominant strategy to analyze statistical mediation within health and social sciences, there are limitations to this technique (223,282). Firstly, the first Baron and Kenny criteria indicated that there must be a significant relationship between X and Y (224). However, several statisticians have argued that under certain circumstances (e.g., temporal distance between X and Y, as was the case in the present study), a mediator variable may be exercising its effect even when no significant relationship between X and Y is found. The present study only assessed relationships for mediation for mental health exposures and cancer outcomes that were significant. Furthermore, Pardo et al. found that small variations in data (that are perfectly acceptable due to random sampling) can change a mediation conclusion into a non-mediation one, and vice versa (282).

Gene-based mediation analysis is an emerging statistical technique that could effectively elucidate the connection between mental health disorders and cancer incidence. The theory behind the technique is that the relationship between an exposure and outcome is partially mediated by intermediate molecular processes, i.e., gene expression (283). It could, for example, clarify why some individuals do not develop cancer after a significant history of poor health behaviours or mental health disorders, and others do. Fang et al. applied this technique to investigate genes whose methylation levels act as important mediators in the relationship between alcohol consumption and epithelial ovarian cancer (284). Using a gene-based high-dimensional mediation analysis they identified six genes that mediate the drinking effect on epithelial ovarian cancer risk (*ZFYVE19*, *KRAS*, *FAM167B*, *MAN2C1*, *RASSF4*, and *TFPT),* all of which have been associated with immune function and cancer (284). Luo et al. developed a

gene-based mediation analysis procedure for survival models that has applications to the present study (285). Their mediation analysis found three novel epigenetic markers linking smoking and survival of lung cancer patients (285). While the biological and genetic underpinnings of mental health disorders, and sex-specific mental health disorders, are still unclear, this technique could help further elucidate the mechanisms between mental health disorders and cancer risk.

5.5 Conclusion

This study is one of the first to investigate the relationship between mental health disorders and cancer risk with multiple conceptualizations of depression, and a comprehensive assessment of the mediating effects of several health behaviours in this relationship. The study demonstrated a modest positive association between mental health disorders exposures and overall and lung cancer risk. However, only anxiety was significantly associated with an increased risk of lung cancer in women (HR = 1.67, 95% CI: 1.01-2.76) with full adjustment. In order to fully elucidate the relationship between mental health disorders and cancer risk, further studies should be conducted prioritizing sex stratification, assessment of health behaviours, and alternative conceptualizations of mental health.

The mediation analysis found that anxiety, co-morbidity, and depression in women with lung cancer, and depression in men with all cancers were partially mediated by smoking. Policies and interventions supporting behaviour change such as smoking cessation for individuals with mental health disorders should be prioritized, particularly among women since they had greater risk. Understanding the barriers in place for health behaviour change for people with mental health disorders may help support these initiatives.

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Appendices

Appendix A

Appendix A.1

This table presents the cut-offs in the IPAQ scoring protocol to categorize physical activity.

Physical activity categories	**Criteria**
Low	• No activity is reported *OR* • Some activity is reported but not enough to meet Categories "moderate" or "high".
Moderate	Any one of the three criteria below: • 3 or more days of vigorous activity of at least 20 minutes per day *OR* • 5 or more days of moderate-intensity activity and/or walking of at least 30 minutes per day *OR* • 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-minutes/week.
High	Any one of the two criteria below: • Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week *OR* • 7 or more days of any combination of walking, moderate- or vigorous-intensity activities accumulating at least 3000 MET-minutes/week

Appendix A.2

This table presents the number and percentage of missing data for variables in the final analytic sample.

Variables	Missingness N (%)	Variables	Missingness N (%)
Dependent variables		**Covariates**	
All cancers	0 (0)	Age	7 (0.02)
Prostate cancer	0 (0)	Sex	0 (0)
Lung cancer	0 (0)	Education	128 (0.37)
Independent variables		Income	2889 (8.36)
PHQ-9	0 (0)	Ethnicity	567 (1.64)
GAD-7	0 (0)	Smoking status	103 (0.30)
Depression occurrence	65 (0.19)	Alcohol consumption	929 (2.69)
Antidepressant use	0 (0)	Physical activity	2495 (7.21)
		Body mass index (BMI)	4781 (13.83)
		Sleep	92 (0.27)
		Fruit and vegetable consumption	448 (1.30)
		Self-perceived health	74 (0.21)
		Myocardial infarction	118 (0.34)
		Diabetes	157 (0.45)
		COPD	16 (0.46)