Cancer in the Context of Severe Mental Illness in New Zealand

An Epidemiological Study

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ABSTRACT

Background

Experience of severe mental illness is associated with poor physical health and premature death. This issue has received little research attention in New Zealand. This thesis explores the burden of cancer amongst people with severe mental illness in New Zealand.

Aims

This thesis aims to answer four questions:

1. Is cancer an important cause of morbidity and mortality among adults living with severe mental illness in New Zealand?
2. Is cancer contributing to differences in health outcomes between people with severe mental illness and others in the population?
3. What are the factors that are contributing to any differences in cancer outcomes between people with severe mental illness and others in the population?
4. Does the relationship between mental illness and cancer vary by mental health diagnosis or cancer type?

Methods

Recent contact with secondary mental health services was used as a proxy for experience of severe mental illness. Anonymised national data on secondary mental health service contacts for adults aged 18-64 (2001-2010) were linked to cancer registrations and mortality records (2006-2010).

Annual cancer incidence and mortality rates among people in contact with mental health services in the five years prior to cancer diagnosis/death were estimated, and standardised for comparison with annual rates for the New Zealand population.

People diagnosed with breast and colorectal cancers in 2006-2010 were identified. Cancer-specific survival was compared for recent mental health service users and nonusers using Cox regression. The contribution of cancer stage at diagnosis, deprivation and physical comorbidity to survival differences were explored for people with diagnoses of schizophrenia and bipolar disorder (Group A) and others in contact with mental health services (Group B).

Results

Nearly two thousand (1876) cancers occurred over five years among people with a history of recent mental health service use. The standardised incidence of cancer was similar in this

group and the general population [SIR 1.03 (95% CI 0.98-1.08)], while lung cancer was more common [SIR 1.98 (1.73-2.26)] and prostate cancer less common [SIR 0.66 (0.54-0.8)]. Mortality from all cancers combined was higher among people in recent contact with mental health services compared to the general population [SMR 2.21(2.07-2.37)].

Of 8762 and 4022 people with breast and colorectal cancer respectively, 440 (breast) and 190 (colorectal) had recent contact with mental health services. After adjusting for demographic confounders, the risk of death from breast cancer was increased for Group A [Hazard Ratio (HR) 2.55 (1.49–4.35)] and B [HR 1.62 (1.09–2.39)], and from colorectal cancer for Group A [HR 2.92 (1.75–4.87)], compared to others in the population. Later stage at diagnosis contributed to survival differences for Group A, and comorbidity contributed for both groups. Fully adjusted HR estimates were breast: Group A 1.65 (0.96–2.84), B 1.41 (0.95–2.09); colorectal: Group A 1.89 (1.12–3.17), B 1.25 (0.89–1.75)].

Conclusions

Cancer diagnosis overall was equally common, and the risk of lung cancer was higher, among people with severe mental illness compared to the general population, while cancer mortality was more than doubled. Commonly used methods can, however, result in biased underestimation of cancer incidence. Survival disparities between people with mental illness and others in the population were evident for both breast and colorectal cancers, and related to the high burden of comorbid physical illness, and late stage at cancer diagnosis (for Group A only). Interventions to reduce tobacco use and improve cancer detection and care have the potential to improve physical health in those with experience of mental illness.

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STATEMENT OF PARTICIPATION

This study was conceived and designed by me for my PhD thesis. I cleaned and analysed the data, with bio statistical support from Dr James Stanley. The code for scoring comorbidity was adapted from code written by Dr Jason Gurney for the C3 study of comorbidity and cancer led by Professor Diana Sarfati. The interpretation of the data is also mine, with support and input from all of my supervisors.

I have published two papers from the work contained in this thesis (included as appendices), co-authored with my supervisors. I was responsible for the study design and analysis, and the first draft of each paper. My co-authors contributed to the interpretation of findings and to drafting the final papers. Anonymous reviewers also provided useful comments which have influenced my thinking.

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Chapter One: **INTRODUCTION**

1.1 THESIS PURPOSE

Experience of mental illness has been associated with physical health problems, and premature mortality, for many centuries. In the asylums of the 19th century, tuberculosis and other infectious diseases were rife, while today, diabetes and heart disease are common among those under the care of community mental health services. The health concerns of the day are writ large in this population. And, despite major changes to psychiatric care in the past century, the relative difference between the mortality of those using psychiatric services and that of the general population has not diminished.

This study explores the pathways by which experience of mental illness is associated with unequal health outcomes in contemporary New Zealand. It focuses on cancer, and the pathways leading to cancer outcomes. Cancer is a major cause of premature mortality and the leading cause of death in New Zealand (Ministry of Health, 2014a). Amongst those with experience of mental illness, cancer is also an important cause of death. In fact, after heart disease, cancer is the most common cause of death in those with schizophrenia (Bushe and Hodgson, 2010). Cancer is also an important contributor to the shortened life expectancy of those with severe mental illness relative to the rest of the population (Piatt et al., 2010). Worldwide, cancer incidence is increasing (Ferlay et al., 2013). However, while survival from cancer is improving in the general population (Ministry of Health, 2012a), there is evidence to suggest that cancer survival amongst those with diagnosed mental illness may not be improving in the same way (Lawrence et al., 2000a). Understanding cancer in the context of mental illness is therefore important to the overall project of improving physical health in those with mental illness. And yet, while the occurrence of mental illness in people with a diagnosis of cancer has been the subject of considerable research interest, the occurrence of cancer in the context of mental illness is much less well researched, and has been identified as an important area for future research endeavours (Purushotham et al., 2013).

This thesis examines cancer in the context of prior mental illness in the New Zealand setting. Firstly, it sets out to explore whether there are in fact inequalities in cancer burden associated with a history of mental illness in New Zealand. It then focuses on the mechanisms behind disparities in cancer survival, as an area in which international research indicates substantial differences between those with mental illness and others, and also the part of cancer burden likely to be most amenable to intervention.

This thesis concentrates on the experience of people in contact with mental health services. This is a group who have had experience of mental illness disruptive enough to lead to contact with public specialist (secondary or tertiary) mental health services, whether voluntary or involuntary. This group is referred to as experiencing severe mental illness, to distinguish from the much larger group in the population experiencing mental health problems which are managed by individuals, their families, and primary care services.

Two studies were undertaken, linking routine health records on mental health service use, cancer diagnosis, health care receipt, and mortality. The first study examined cancer burden in a cohort of adults in contact with mental health services between 2001 and 2010, compared to the general New Zealand population. The second study examined survival after diagnosis with breast or colorectal cancers between 2006 and 2010, comparing people with a history of mental health service contact in the five years before cancer diagnosis with those without such a history.

1.1.1 Thesis aims

This thesis aims to answer four questions:

5. Is cancer an important cause of morbidity and mortality among adults living with severe mental illness in New Zealand?
6. Is cancer contributing to differences in health outcomes between people with severe mental illness and others in the population?

7. What are the factors that are contributing to any differences in cancer outcomes between people with severe mental illness and others in the population?
8. Does the relationship between mental illness and cancer vary by mental health diagnosis or cancer type?

In order to answer these questions, the following research objectives were set:

- To link routine data on mental health service use, cancer diagnosis and mortality, in order to estimate rates of cancer diagnosis and cancer death in people in current or recent contact with mental health services.
- To use standardisation methods to compare cancer incidence and cancer mortality rates amongst adults in current or recent contact with mental health services with rates in the general population, examining all cancers combined and separately examining four common cancers (breast, colorectal, lung and prostate) .
- To use survival analysis methods to compare cancer-specific survival after diagnosis with two common cancers (breast and colorectal cancers) between those with contact with mental health services in the five years prior to cancer diagnosis and those with no recent history of contact with mental health services.
- To use regression methods to estimate the contribution of potential confounding or mediating factors to differences in cancer survival between those with and without a history of recent mental health service use.
- To use these methods to separately examine cancer outcomes for people with a diagnosis of schizophrenia or bipolar disorder.

1.2 THESIS OUTLINE

This section presents an outline of the content of each chapter in the thesis.

Chapter Two: Background provides background to the thesis in three areas. Firstly, the current state of knowledge on the physical health of people with experience of mental illness is reviewed, and the importance of further work in this

area is outlined. Secondly, the study of cancer in the context of mental illness, as an example of a physical health problem, is discussed. Thirdly, a brief overview of the New Zealand context is provided in particular regarding health and health services in the areas of mental health and cancer.

Chapter Three: Literature review provides a more detailed exploration of the literature concerning cancer in the context of mental illness. This is explored in four areas: cancer incidence, cancer mortality, cancer survival, and the possible factors contributing to cancer survival. In each of these areas, the landscape of the literature is described, and particular methodological and contextual factors important for interpretation are discussed. For cancer incidence, a novel framework for classifying studies is used to explore the reasons for apparently contradictory study findings. For cancer incidence and mortality, selected population based studies are reviewed. For cancer survival, a more comprehensive approach is taken, and all available studies are included in the review.

Chapter Four: Study One presents the methods and results for the first study, examining cancer incidence and mortality in a cohort of adults aged 20 to 64 in contact with mental health services in New Zealand. The methods for identifying the cohort and linking to cancer registrations and deaths are discussed. The methods for comparing cancer incidence and mortality with the general population are described, based on the findings of the literature review. Results of descriptive analysis of the cohort of mental health service users are presented. Cancer incidence and mortality are presented for all cancers combined and then for specific common cancers. Sensitivity analyses are used to explore the implications of the methods used.

Chapter Five: Study Two presents the methods and results of breast and colorectal cancer survival analyses, comparing people identified as having contact with mental health services in the five years before their cancer diagnosis with those without. The methods for identifying breast and colorectal cancer cohorts, and identifying those with and without past mental health service contact, are described. Survival analysis methods and methods for identifying and measuring possible mediating and confounding factors are then described. Descriptive analysis of cancer survival cohorts is presented for each cancer. Kaplan Meier survival curves and Cox

proportional hazards regression models describing survival differences between groups are then presented. Sensitivity analyses are used to examine the impact of analysis decisions including the factors included in models and the survival analysis method itself.

Chapter Six: Discussion of methods describes the strengths and limitations of study design and conduct for the two studies presented. The role of chance, bias and confounding in explaining the study results, and the generalizability of findings, are discussed. Major methodological issues are identified, and their implications for interpretation of study findings discussed. Recommendations are made to improve the validity and generalizability of future studies of this type.

Chapter Seven: Discussion of results reviews the main study findings and discusses their implications. The study results are put into the context of existing literature and possible reasons for similar or different findings are explored.

Chapter Eight: Implications and conclusions discusses the implications of study findings for researchers, policy makers, clinicians and mental health service users. This final chapter then presents some brief conclusions.

1.3 SUPPLEMENTARY MATERIAL

Two papers have been published from the material in this PhD, and these are presented as appendices to the thesis. Each paper was co-authored with my supervisors.

The first paper, entitled *Premature mortality in adults using New Zealand psychiatric services* was published in May 2014 in the New Zealand Medical Journal (see Appendix Three, page 307). This paper presents mortality rates from natural and external causes for adults using psychiatric services compared to the general New Zealand population. When I began the work of this PhD, it became clear that no epidemiological information on the health status of those accessing mental health services in New Zealand was available. Therefore, my first step was to make use of the data obtained for this PhD to generate estimates of mortality in this population.

This analysis found that men and women using mental health services in New Zealand have more than twice the mortality rate of the total population [combined SMR 2.14 (95% CI 2.09–2.19)], indicating that physical health inequalities are a substantial issue in New Zealand, as they are internationally. The work described in the paper is not presented elsewhere in this thesis. However, it provides useful background and is referred to at various points in the thesis.

The second paper, entitled *Cancer survival in the context of mental illness: A national cohort study*, was published in General Hospital Psychiatry in November 2015 (see Appendix Four, page 318). This paper presents the results of the second study of the PhD, investigating survival after breast and colorectal cancer diagnosis in those with a history of recent mental health service use compared to others in the population. Chapter Five provides a more detailed coverage of the methods and results of this study.

Chapter Two: BACKGROUND: MENTAL HEALTH AND PHYSICAL ILLNESS AND THE NEW ZEALAND SETTING FOR THIS STUDY

2.1 INTRODUCTION

This chapter provides the context for the thesis. It is divided into four sections.

The first section describes the broad area of research exploring the physical health of people with severe mental illness. The history and current state of knowledge on the physical health of people with experience of mental illness, in particular severe mental illness, are outlined. The literature on the causes of poor physical health in people with mental illness is explored, including the role of factors at the individual, provider and system levels, and the role of stigma and discrimination across all three levels.

The second section considers how the study of cancer in the context of mental illness fits into this broad area, and why using cancer as an example may provide useful insights.

The third section provides an overview of the New Zealand setting for this research, providing background on the New Zealand population, the health system, and the specific areas of cancer and mental health.

The fourth section summarises the context outlined in this chapter.

2.2 MENTAL ILLNESS AND PHYSICAL COMORBIDITY

2.2.1 The association of mental illness with physical illness

Mental illness is common. The lifetime prevalence of depression is estimated at 20-30%, (Kessler et al., 2005; Jenkins et al., 2003) while the lifetime prevalence of schizophrenia and bipolar disorder is estimated at 3% (Perala et al., 2007). Mental disorders are also major contributors to loss of quality of life (or disability). The most recent update of World Health Organisations' Global Burden of Disease study

found that mental and substance use disorders were responsible for more than 250 million years of life lived with disability globally in 2013, 40% of the burden of non-communicable diseases (Vos et al., 2015). Major depression and anxiety are the most common mental disorders, with an estimated 253 million prevalent cases of depression and 266 million prevalent cases of anxiety in 2013, and are also the greatest contributors to disability, ranked 2nd and 9th in the top 25 causes (Vos et al., 2015). In New Zealand, major depression and anxiety ranked 2nd and 4th respectively as causes of disability. Schizophrenia and bipolar disorder, while less common (49 and 24 million prevalent cases in 2013 respectively), are major contributors to the global burden of disability (ranked 11th and 17th).

Mental illness is also associated with physical illness. Mental illness, in particular depression, is common in people with chronic physical health problems such as diabetes and heart disease (Nouwen et al., 2010; Kessler et al., 2003). Physical health problems, including diabetes and cardiovascular disease, are common in people with experience of mental illness. There is evidence to suggest that depression is an independent risk factor for cardiovascular disease (Van der Kooy et al., 2007). Schizophrenia is associated with an increased risk of obesity, diabetes, hypertension, cardiovascular disease, dental disease, and numerous other conditions (Leucht et al., 2007). Moreover, the co-occurrence of physical and mental conditions complicates the treatment and worsens the prognosis for both conditions (Doherty and Gaughran, 2014). The links also go beyond co-occurrence. Mental and physical illnesses share common risk factors, such as early life adversity (Gluckman and Hanson, 2004; Goldberg and Goodyer, 2014). Developing theories of integrated psychological and physiological systems suggest that mental and physical health are closely and complexly related (Korff, 2009).

This thesis deals with physical health problems occurring in the context of mental illness. The focus is on severe mental illness, such as schizophrenia, and also includes other mental health problems that are disruptive enough of a person's life to require specialist mental health care. Experience of severe mental illness has long been known to be associated with a high burden of co-occurring physical health problems and shortened life expectancy. Infectious diseases, particularly

tuberculosis, were very common in the psychiatric institutions of the 19th century (Wright et al., 2013). Mortality was also very high: in 1841 it was estimated that those living in the asylums in England apparently providing the "best" care still had three times the mortality rate of the general population, while those in other asylums fared far worse (Farr, 1841).

In recent years, psychiatrists have again highlighted the "scandal" of shortened lives and physical illness amongst those in psychiatric care (Thornicroft, 2011; Gray, 2012). Current estimates have put the life expectancy of those with severe mental illness at around 12 years less than the general population in the United Kingdom, (Chang et al., 2011) while in the United States the life expectancy gap between those using mental health services and the general population has been estimated at 25 years (Manderscheid, 2009). Natural causes (as opposed to suicide and other violent causes of death) are the most important factors in reduced life expectancy for those with mental illness (Brown et al., 2000; Colton and Manderscheid, 2006; Fagiolini and Goracci, 2009). In the developed world, chronic diseases such as heart disease and cancer are major contributors to premature mortality, while in developing countries infectious diseases such as tuberculosis continue to be major causes of death for people with mental illness (Sartorius, 2007a).

Importantly, there is evidence that the physical health of those receiving psychiatric care is not improving at the same rate as the general population. For example, in the United States, the life expectancy disparity for those using mental health services appears to have worsened between 1986 and 2006 (Manderscheid, 2009). In Sweden, excess mortality in people with schizophrenia, particularly from natural causes such as cardiovascular disease, increased markedly over the twenty year period from 1973 to 1995 (Osby et al., 2000). It is likely that this relative worsening in mortality rates is related to the life lengthening effects of improvements in care for physical health conditions not being shared by those with mental illness (Doherty and Gaughran, 2014).

2.2.2 Why is mental illness associated with poor physical health outcomes?

The literature on the physical health of people with experience of mental illness suggests multiple pathways by which poor physical health outcomes occur. For example, a paper written for the New Zealand Mental Health Foundation in 2004 entitled "Our Physical Health, Who Cares?" laid out four reasons for unequal physical health outcomes: exposure to risk factors, iatrogenic illness (specifically the effects of psychiatric medication), lack of clear responsibility for physical health care, and discrimination (Handiside, 2004). Other similar lists of factors have been proposed by researchers and commentators in this area. Osborn (2001) identified lifestyle risk factors, medication, and inadequate physical health care due to overshadowing, communication difficulties and the stigma of mental illness, as being key factors in the poor physical health of psychiatric patients. Other work has suggested that contributing factors can be identified at the patient, service provider and system level, and that the stigma associated with mental illness impacts on health outcomes via factors at all these levels (Irwin et al., 2014). Usually, these lists are used as ways of organising the literature on potential pathways, or as ways of identifying the types of pathway which may be contributing to disparities in health outcomes. There has been little empirical exploration of the role of these factors in unequal outcomes. A few studies have tried to do this. For example, a review of the link between deficits in cardiovascular care and mortality rates in people with schizophrenia concluded that, although a causal link could not be confirmed, "indirect evidence supports the observation that deficits in quality of care are contributing to higher than expected mortality in those with severe mental illness and schizophrenia" (Mitchell and Lord, 2010). This section explores the evidence for some of the potential pathways.

Exposure to risk factors

Smoking is common among people with severe mental illness. Estimates from the United Kingdom and the United States suggest that up to two thirds of people with severe mental illness are cigarette smokers (Lasser et al., 2000). A meta-analysis of

42 studies examining the association between schizophrenia and smoking estimated an average smoking prevalence of 62% (de Leon and Diaz, 2005). Moreover, smoking declines seen in the general population have not been paralleled in people with mental illness (Cook et al., 2014; Tobias et al., 2008). In New Zealand, people using mental health services have some of the highest rates of cigarette smoking, and those who smoke tend to smoke more(Tobias et al., 2008; Wheeler et al., 2013). High rates of smoking are associated with multiple physical health problems, including cancer, heart disease, and stroke, and so high smoking rates will be contributing to reduced life expectancy and the high burden of physical illness. However, smoking rates themselves are determined by other factors further up the pathway leading to unequal health outcomes. The normalisation and acceptance of smoking among those using mental health services, as well as the use of cigarettes to promote adherence to mental health care recommendations, mean that any intervention to reduce tobacco consumption must address the culture of mental health services (Lawn, 2004; Royal College of Physicians and Royal College of Psychiatrists, 2013).

Poor diet and physical inactivity are also more common among people with severe mental illness than the general population (Scott and Happell, 2011). For example, a study of 56 people with serious mental illness using mental health services in Dunedin, New Zealand, found levels of food insecurity approximately double that reported by the general population, with 25% of the group interviewed unable to afford to eat properly, 29% eating smaller meals, and 41% eating less than they would like because of affordability issues (Lee et al., 2000). A more recent survey of 404 adults in contact with mental health services in Auckland, New Zealand, found that this group were significantly less likely to report adequate fruit and vegetable consumption, and to be physically active, than the general population (Wheeler et al., 2013). Again, diet and physical activity have multiple impacts on physical health. The reasons for unhealthy diets and lack of physical activity are likely to be complex. Lack of financial resources, reduced motivation associated with the effects of mental illness itself, psychiatric medication causing sedation and increased appetite, and the sometimes restrictive nature of psychiatric care limiting

opportunities for exercise and dietary choices may all be playing a part (Stanley and Laugharne, 2014).

The use of alcohol and other drugs is also more common amongst those using mental health services, although not universally so. For example, a recent New Zealand study found that those using mental health services were more likely to report being abstinent from alcohol than the general population (42% vs 16%) but those who did drink were more likely to drink heavily (Wheeler et al., 2013). However, the particular health issues associated with these drugs (such as alcoholic liver disease, Hepatitis C and HIV, and overdose) are not major contributors to the disparities in physical health associated with mental illness overall (Lawrence et al., 2010).

Social deprivation is also a risk factor for physical illness, with a large literature detailing the impact of social deprivation on a wide range of health conditions (Marmot and Wilkinson, 2009). Social deprivation is associated with mental illness, as both a contributing factor to the development of mental illness, and as a consequence of the societal repercussions of mental illness leading to downward social mobility (Saraceno et al., 2005; Gilman et al., 2002; Dohrenwend et al., 1992). The mechanisms by which mental health problems can lead to poverty include the disruptive effect of mental illness and its associated stigma on education and employment, and are more commonly associated with more severe mental illness including schizophrenia (Saraceno et al., 2005). However, although deprivation is closely associated with mental illness, deprivation alone cannot explain the poor health outcomes associated with mental illness. Studies that have adjusted for differences in socioeconomic status have still found differences in physical health outcomes, including cancer survival and all-cause mortality (Kisely et al., 2005; Chang et al., 2014).

Medications prescribed to treat mental health problems commonly also have effects on other bodily systems, and these detrimental effects have been implicated in worsening the physical health of people taking them. Anti-psychotic medications, in particular olanzapine and clozapine, but also others to varying degrees, are associated with weight gain and abnormalities in glucose and lipid metabolism, leading to an increased risk of obesity, diabetes and cardiovascular disease (De Hert

et al., 2012). In spite of this, studies in many countries have found that most patients taking anti-psychotic medication do not receive adequate monitoring of their cardio-metabolic health (Mitchell et al., 2012). Medication used to treat depression can also impact on cardio metabolic health (Sowden and Huffman, 2009). There is also evidence that improved mental health, including that obtained with potentially harmful medications, has a positive impact on physical health including on life expectancy, as well as the important quality of life gains from improved mental health (Tiihonen et al.). Therefore, any attempt to reduce the harms to physical health from medication needs to be weighed against the potential harms of not having access to medication.

Health service factors

Diagnostic overshadowing, or the obscuring of physical health conditions by mental ones, can delay diagnosis of medical conditions (Shefer et al., 2014; Happell et al., 2012b; Jones et al., 2008). People with experience of mental illness report not having physical complaints taken seriously by health providers (McCabe and Leas, 2008; Chadwick et al., 2012), and having their credibility and accuracy questioned (Mesidor et al., 2011). A recent study of emergency department staff in four UK hospitals found that the majority of those interviewed recalled cases of psychiatric disorder leading to misdiagnosis or delays in diagnosis in treatment of physical health conditions, some of which resulted in deaths and permanent damage to health (Shefer et al., 2014). Diagnostic overshadowing can therefore impact on health outcomes and contribute to health inequalities.

The impact of mental illness itself may complicate the diagnosis and management of physical conditions. Cognitive impairment and impaired decision-making capacity have been cited as barriers to physical health care in people with severe mental illness (Farasatpour et al., 2013; Hashimoto et al., 2009; Inagaki et al., 2006). However, neither cognitive impairment nor impaired decision making are universally associated with severe mental illness (Owen et al., 2008; Krabbendam et al., 2005; Bowie et al., 2010; Okai et al., 2007). Decision making capacity therefore needs to be assessed specifically in relation to particular decisions to be made by each patient, rather than presumed on the basis of diagnosis or previous capacity

(Howard et al., 2010). In New Zealand, the Protection of Personal and Property Rights Act 1988 states that a person must be presumed to be competent and have the capacity to understand and make decisions, unless a formal assessment is made to the contrary (1988). Moreover, there is evidence to suggest that even where capacity is assessed as lacking, with extra support capacity, it can improve (Carpenter et al., 2000). Presumption of incapacity has been associated with withholding of life sustaining treatment (Hanson et al., 1994), and so the decision about capacity is a crucial one, which may be implicated in unequal treatment and unequal outcomes.

Lack of clear responsibility for the physical health care of people with mental illness can lead to people falling in the gaps between psychiatric and primary care, with each assuming the care for the physical health of the patient is something that the other is doing (Chadwick et al., 2012; Robson and Gray, 2007). Confusion about responsibility for physical care is also found in New Zealand (Lee et al., 2000; Handiside, 2004). Surveys of mental health nursing staff in Australia and the United Kingdom have found that mental health nurses do not necessarily feel competent to provide physical health care, despite general nursing training (Happell et al., 2012c; Blythe and White, 2012). Likewise surveys of general practitioners have shown a degree of discomfort in caring for people with mental health problems (Robson and Gray, 2007; Happell et al., 2012a).

The disconnect between care for the mind and care for the body is entrenched in the Western health care system, with separation in training, and physical and organisational separation of care facilities (Holt, 2011). In recent decades there has been some coming together of services. For example, in New Zealand the large, geographically separate, psychiatric hospitals have been closed down and smaller inpatient facilities opened on the grounds of general hospitals (although still mostly in separate buildings). More holistic models of health are also being incorporated into health care education and (more slowly) into practice. For example, the indigenous Māori model Te Whare Tapa Wha (Durie, 1985), which incorporates physical (tinana), mental (hinengaro), spiritual (wairua) and family (whanua) aspects of health, is widely recognised in New Zealand health education, although its incorporation into health care practice is far from complete. The growth of

indigenous health care services in New Zealand has also been a move towards more holistic care (Durie, 2011). On the other hand, the funding and the health information systems for mental care in New Zealand, as well as many other aspects, remain separate from the physical health care system.

Stigma and Discrimination

Finally, stigma and discrimination are important determinants of unequal outcomes associated with mental illness. Several authors have pointed out that the stigma of mental illness and its associated discrimination are important drivers of unequal health outcomes (Pope, 2011; Lawrence et al., 2001; Disability Rights Commission, 2006). Just as ethnic and socioeconomic health inequalities can be seen as human rights issues related in large part to discrimination, health care inequalities for people with mental illness can be seen in the same way.

Stigma relating to mental illness occurs at the public or societal level, and comprises the reactions of the general public to a group based on stigma associated with that group. Three components of stigma are commonly identified: stereotype, consisting of negative beliefs about a group such as incompetence and dangerousness; prejudice, consisting of agreement with those beliefs and a negative emotional reaction such as fear; and discrimination, the behavioural response to prejudice such as withholding help. Stigma can also be internalised as self-stigma, whereby people with experience of mental illness internalise the stereotypes, prejudice and discriminatory attitudes, leading to low self-efficacy, avoidance of situations where discrimination may occur such as applying for jobs, and not seeking mental health help (Rüsch et al., 2005).

Internationally and locally, research has demonstrated that discrimination is commonly experienced by people with mental illness in almost every sphere of life – in employment, in housing, in access to recreational and social services, and also in access to and quality of health care services (Peterson et al., 2011; Mitchell et al., 2009). Discrimination on the basis of mental health status can impact on health through its impact on education and employment opportunities and therefore access to resources, as well as through its association with harmful health behaviours

(Pascoe and Smart Richman, 2009). There is also evidence that comorbid physical illness increases stigma and discrimination faced by those with mental illness (Bahm and Forchuk, 2009) .

The stigma of mental illness pervades the health system, and it has been suggested that general societal efforts to reduce the stigma of mental illness such as New Zealand's Like Minds Like Mine campaign should have the health sector as a priority audience (Sartorius, 2007b). A 1996 survey by the UK mental health charity MIND of 778 users of mental health services found that 50% of people surveyed reported discrimination by non-psychiatric health care services (Read and Baker, 1996). In a similar survey by the New Zealand Mental Health Foundation in 2003 of 785 users of mental health services, 23% reported experiencing discrimination by general health services while 34% reported discrimination by mental health services (Peterson et al., 2007). Those with experience of mental illness have expressed concerns about the way their physical health is cared for (or not cared for) by health providers, including highlighting not being taken seriously and not being treated with respect by health providers as barriers to accessing physical health care (Chadwick et al., 2012).

Moreover, a history of mental illness is associated with not getting indicated preventive care and treatment for physical health problems (McGinty et al., 2015; Lawrence and Kisely, 2010). A recent systematic review examining the quality of care provided to people with mental illness or substance abuse, compared to the general population, found that the majority of studies demonstrated disparities in the quality of physical health care delivered, despite higher rates of health care access. A meta-analysis of studies examining revascularisation procedures after myocardial infarction in people with mental illness found a 14% lower rate of invasive interventions (and a 47% lower rate for people with a diagnosis of schizophrenia) and an 11% increase in mortality in the year following the cardiac event (Mitchell and Lawrence, 2011). Another systematic review of receipt of preventive care, including cancer screening, found that amongst 61 comparisons in the reviewed studies, 27 found that the quality of preventive and screening services provided to those with mental illness was lower than that provided to those without mental

illness, 10 suggested higher quality care was provided, and 24 had inconclusive findings (Lord et al., 2010).The majority of the studies finding higher quality care focused on people with depression, while inferior care was more apparent in those with schizophrenia. It is not possible to directly attribute these differences in treatment receipt to discrimination on the part of the health system. However, there is evidence to suggest that, all other things being equal (including similar presentation and similar burden of comorbid illness), a mental illness diagnosis is associated with not getting indicated treatment and having a worse outcome (Mitchell and Lawrence, 2011; Mitchell and Lord, 2010; Lawrence and Kisely, 2010).

A wide variety of factors therefore contribute to the poor physical health of people with severe mental illness. Factors related to health behaviours, the care provided for mental illness and other health conditions, the structure of the health system, and even the structure of society, are all implicated.

2.3 CANCER AS AN EXAMPLE

Much of the literature on physical health and mental illness focuses on mortality and cardiovascular disease. Cancer has been less of a focus, although there is evidence that disparities also exist for people with mental illness in cancer mortality and cancer survival (Chang et al., 2014; Lawrence et al., 2000a; Kisely et al., 2015). The existing literature on cancer in the context of mental illness is discussed in depth in the next chapter. This section focuses on the ways in which the study of cancer might provide a useful perspective on the possible causes of and solutions to physical health disparities associated with mental illness.

The availability of reliable information is a practical reason for choosing to investigate cancer. Unlike other disorders, there is compulsory reporting of cancer diagnosis to a national database in New Zealand, the New Zealand Cancer Registry. It is therefore possible to identify all cases of cancer in the population with reasonable certainty. These cases of cancer can then be matched to other health information data sets, to determine history of mental health service contact and mortality after cancer diagnosis. It is, therefore, possible on a national level to

examine cancer burden in people with a history of mental health service use compared to the rest of the population. Moreover, because date of diagnosis is recorded, it is possible to look at outcomes after diagnosis, including cancer survival. The factors that influence outcomes can also be examined, including the stage at which cancer is diagnosed. The relative contribution of such factors to survival differences can be estimated.

Research examining ethnic and socioeconomic cancer inequalities is well established, and its methods can be used. New Zealand research into ethnic and socioeconomic inequalities has investigated factors associated with cancer incidence, such as tobacco use and cancer screening receipt, and factors associated with cancer survival including cancer stage at diagnosis, the presence of comorbid illness, and health service factors (Hill et al., 2010; Blakely et al., 2011; Soeberg et al., 2015). Similar methods and data sources can be used to investigate the relationship between mental illness and cancer.

There is also research examining the impact of comorbid illness on cancer. It is well established in the cancer literature that the presence of comorbid illness impacts on the diagnosis of cancer and its subsequent management, and therefore on cancer prognosis (Sarfati et al., 2009; Bradley et al., 2014). However, this work has tended to focus on comorbid physical rather than mental illness, and so there is the opportunity to investigate how and why mental illness might be similar or different to other comorbidities in this regard. For example, it has been demonstrated that comorbid illness can impact on cancer diagnosis in different ways depending on the severity of comorbid illness (Fleming et al., 2005). While more severe illness might overshadow cancer, less severe illness might lead to early cancer diagnosis through the increased surveillance associated with frequent contact with health services. Whether this is the case for comorbid mental illness is unclear.

Examining cancer in the context of mental illness may reveal different patterns from those found by research into cardiovascular disease or other conditions. Cancer is treated almost entirely by specialist services, unlike other common conditions such as heart disease and diabetes, which are mainly managed in primary care. Much cancer treatment is guideline or protocol driven. It may therefore be that cancer

treatment is more uniformly provided, and that inequalities between groups, such as between people with prior mental illness and others, are less apparent in cancer than in other areas of health care where more provider discretion is present. On the other hand, the complex and intensive nature of cancer management may present additional barriers to people with mental illness, compared to care provided in the community by a general practitioner.

Cancer services, and their allied support agencies, also have a culture of holistic care, perhaps more so than other health services. There is recognition of the stresses of cancer, and the need for social and psychological support for those undergoing treatment. Cancer services also frequently have relationships with consultant liaison mental health services, to provide support for their patients. It may be that cancer services are more aware of, and used to, dealing with mental health problems, and therefore better equipped to care for those with pre-existing mental illness.

Finally, there is a considerable literature suggesting that cancer occurs less commonly in people with experience of mental illness, particularly schizophrenia, than in the rest of the population (Catts et al., 2008; Tabares-Seisdedos and Rubenstein, 2013; Bushe and Hodgson, 2010). In this study, an important first step will be to establish whether cancer is, in fact, an important health condition in the context of severe mental illness in New Zealand, and therefore whether it is a useful example through which to explore the disparities in physical health and life expectancy associated with mental illness.

Cancer in the context of mental illness was used in this thesis as an example to explore the health inequalities associated with mental illness. It is recognised that what happens in cancer care will not necessarily be the same as what happens in other parts of the health system, but that we can, none the less, learn about the health and health care of people with mental illness in New Zealand by examining cancer outcomes.

2.4 THE NEW ZEALAND CONTEXT

2.4.1 The country and its people

New Zealand is a country with 4.4 million inhabitants, spread across three islands in the South Pacific. The population is predominantly urban, with one half of the population concentrated in four major urban centres (Statistics New Zealand, 2015b). Maori are the indigenous people of New Zealand, and make up 14% of the current population (Statistics New Zealand, 2014). New Zealand has a British colonial history dating back two centuries, and 70% of the population are of European descent. The Treaty of Waitangi, signed by Māori and the British Crown in 1840, is the founding document of New Zealand and sets out the foundations for the relationship between Māori and the Crown, including all subsequent settlers. Other major ethnic groups are the indigenous peoples of other Pacific Islands, in particular Samoa, Tonga and the Cook Islands, many of whom were born in New Zealand, who make up approximately 7% of the population. Ten per cent of the population are of Asian descent, including South Asian and South East Asian, and both first generation and established migrants (Statistics New Zealand, 2014).

New Zealand has an aging population profile, similar to other developed countries, but a much younger age distribution in Māori and Pacific ethnic groups. Based on current death rates, life expectancy at birth in New Zealand is 83.2 years for females and 79.5 years for males (Statistics New Zealand, 2015a). Life expectancy is, however, lower in Māori and Pacific populations. Life expectancy at birth is 77.1 years for Māori females and 73.0 years for Māori males, 78.7 years for Pacific females and 74.5 years for Pacific males.

2.4.2 Health services in New Zealand

New Zealand has a publicly funded national health service, which was established in 1938 and provides universal coverage. There is also a small private health sector. The public health system is structured around 20 District Health Boards (DHBs), which are funded based on a weighted funding formula to provide care to a geographically defined population. DHBs operate government-owned hospitals and

health centres, provide community services, and purchase services from non-government and private providers. DHBs are responsible for setting priorities and funding services for their population, which results in some geographical differences in the services provided. There is also a publicly funded no-fault Accident Compensation Corporation, which funds accident and injury care in the public and private sectors.

Primary care in New Zealand is provided by general practitioners (GPs), working with practice nurses and allied health professionals in community clinics. GPs are usually independent self-employed practitioners who are paid through a mixture of upfront patient co-payments and a government subsidy paid through Primary Health Organisations (PHOs), of which there are currently 46 across the country. PHOs are community-governed organisations, which were set up in 2001 to improve access and reduce the cost barriers to primary care, and are funded by DHBs on a capitation basis to provide care including health promotion and services for people with chronic conditions to their enrolled population. Almost all New Zealanders (94%) are enrolled with a PHO (Ministry of Health, 2016). Patient co-payments in primary care are heavily subsidised to improve access, but continue to present a barrier to seeking care for some (Jatrana and Crampton, 2009).

Secondary and tertiary (specialist) care is provided mainly by public hospitals in the main centres and specialist outpatient services. Public secondary and tertiary care is free at the point of access. Primary care practitioners act as gate keepers, with referrals required to access secondary care (with the exception of emergency care).

About one third of New Zealanders have private health insurance, but the insurance sector only accounts for approximately 5% of health expenditure, mainly on primary care co-payments, elective surgery in private hospitals, and private outpatient consultations (Gauld, 2015). Private care is also funded by individuals out of household budgets. Many specialist doctors work in both the public and private sector, mainly providing private clinic services, but also care in a small number of private hospitals. All emergency and intensive care services are provided by public hospitals.

2.4.3 Mental health and mental illness in New Zealand

As in other developed nations, mental health problems are a major contributor to the burden of disease in New Zealand. The New Zealand Mental Health Survey Te Rau Hinengaro conducted in 2003-2004 found that 40% of the population had met the criteria for a mental disorder at some time in their life, while 21% had had experiences meeting these criteria in the past twelve months (Oakley Browne et al., 2006). The lifetime prevalence of mental disorder in New Zealand at that time was estimated to be 47%.

The burden of mental illness is not evenly distributed in the population. The Mental Health Survey showed that people of Māori ethnicity more commonly met the criteria for mental disorder, although were less likely to access health services for mental health problems (Baxter et al., 2006). Māori are overrepresented in hospitalisations for mental disorder and in suicide statistics (Robson and Harris, 2007). People living in more deprived areas were also more likely to have a diagnosable mental illness (Oakley Browne et al., 2006).

Mental health care in New Zealand is provided mainly in primary care by general practitioners. There is also limited access to publicly funded psychological treatments. Public secondary mental health services are funded to cater for the 2-3% of the population with the highest mental health needs (Wilson, 2000). As in other countries, New Zealand went through a process of deinstitutionalisation in the 1970s and 1980s, with the number of psychiatric beds reduced from over 10,000 to less than 2,000 over two decades (Mental Health Commission, 1998). The majority of public mental health care is now provided in the community. A much reduced number of inpatient beds are available and are mostly used for short stays. Secondary mental health care is provided by DHBs to approximately 125,000 people annually, mainly in major centres (Ministry of Health, 2014b). Community services are also provided by Non-Government Organisations.

While most psychiatric care is provided by public services, there are some private mental health services in New Zealand. These are mainly community services, where psychiatrists provide care for those generally not meeting the high severity criteria

for public care. There is also a very small private psychiatric inpatient sector, however many of the patients treated by these services are publicly funded. There is minimal coverage for mental illness from private health insurers (Wilson, 2000).

The legislative framework for mental health care in New Zealand is provided by the Mental Health (Compulsory Assessment and Treatment) Act (1992). This Act defines the circumstances in which a person may be subject to compulsory psychiatric assessment and treatment. It also makes the rights of people undergoing such treatment explicit, and provides a system for protection of those rights. Compulsory treatment can be in inpatient settings or under Community Treatment Orders (CTOs).

The consumer movement, the social and political movement of people with experience of mental illness that has sought to change society's treatment of and approach to mental illness, has been relatively strong in New Zealand. Accounts of the experience of psychiatric care such as Mary O'Hagan's "Stopovers on my way home from Mars" (O'Hagan, 1993) were influential in bringing the consumer voice to the attention of mental health services and the New Zealand public in the 1980s and 1990s. The Aotearoa Network of Psychiatric Survivors (ANOPS) was set up in 1989 to foster a collective voice for people with lived experience of mental illness. From the 1990s there has been a growing recognition of the need to actively and formally seek consumer input into mental health policy. The 1997 National Mental Health Strategy included a goal to "improve the responsiveness of mental health services to consumers" (Ministry of Health, 1997). The national programme to counter stigma and discrimination, "Like Minds Like Mine", which has run since 1996, has had a very strong thread of consumer leadership and capacity building.

The physical health of people with experience of mental illness has not been a major policy or research focus in New Zealand. In a 2004 discussion paper for the Mental Health Commission entitled "Our Physical Health, Who Cares?", it was noted that, despite improving service users' health being an objective of the "New Zealand Health Strategy" (released in 2000), "the issue of service users' physical health… appears not to have registered with policy makers or researchers" (Handiside, 2004: p.6). Over the intervening decade there has been some recognition in policy

documents: the Mental Health Commission's "Blueprint II" identifies the physical health of those with severe mental illness as a priority for action (Mental Health Commission, 2012), and the Ministry of Health's current mental health service development plan, "Rising to the Challenge", has better integration of primary and secondary care as one of its goals (Ministry of Health, 2012b). There have also been numerous initiatives at a local level aimed at better integrating mental health services with primary care and ensuring that the physical health needs of those cared for by secondary mental health services are met. In 2014 the Equally Well Collaborative was set up, bringing together the NGO and public sectors, with a focus on improving the physical health of people with experience of mental illness (Te Pou, 2015). This initiative seeks to bring together those working at a local level to share ideas and create momentum for action at a national level.

However, there has been little research investigating the physical health burden associated with severe mental illness in New Zealand. Several small non-representative studies have investigated the prevalence of risk factors for physical illness amongst adults in contact with mental health services (Lee et al., 2000; Wheeler et al., 2013). But, despite the existence of linkable health service databases, the issue of the physical health of those in contact with mental health services has not previously been investigated on a national scale.

2.4.4 Cancer in New Zealand

Cancer has recently overtaken cardiovascular disease as the leading cause of death for New Zealanders. In 2011, 21,050 cases of cancer were diagnosed and 8900 people died from cancer (Ministry of Health, 2014a). The most common cancers to be diagnosed in New Zealand are colorectal, lung, breast and prostate cancers. The most common causes of cancer death are lung, colorectal and breast cancers.

Cancer is not a single disease, but many different diseases with different aetiologies and prognoses. While some risk factors such as tobacco and alcohol consumption are associated with multiple different cancers, other cancers have specific hormonal or infectious aetiologies. Prognosis varies widely between cancers, with some such as testicular cancer having a very high cure rate, while others such as lung cancer are

much less treatable. None the less, cancer mortality has fallen markedly in recent decades, in New Zealand as in other developed countries, due to improvements in diagnosis and treatment (Jemal et al., 2010).

The burden of cancer is not spread evenly through the population. Cancer is a disease of old age, with 60% of cancers in New Zealand diagnosed over the age of 65 (Ministry of Health, 2014a). Cancer incidence, mortality and survival are socially patterned. In New Zealand as in other places, cancer incidence varies by ethnicity and socioeconomic position. Many cancers, including those related to tobacco consumption and to chronic infections (such as Hepatitis B), are more common in the indigenous population of New Zealand and in more socioeconomically deprived groups (Blakely et al., 2011). Cancer survival disparities by ethnicity and socioeconomic status have been documented (Hill et al., 2010; Soeberg et al., 2015).

New Zealand has two population based organised screening programmes for cancer which are publicly funded and offer free screening. Cervical screening was established in 1990, with women aged 20 to 70 offered screening every three years. The programme has achieved good coverage, with 95% of eligible women enrolled. The programme has had a demonstrable impact on cervical cancer incidence and survival, and on inequalities in the burden of cervical cancer (Blakely et al., 2011). Breast cancer screening was launched in 1998, and offers mammograms to women every 2 years between the ages of 45 and 69. Approximately 70% of eligible women are up to date with screening, although coverage for Māori women is somewhat lower (National Screening Unit, 2015). Although New Zealand has one of the highest rates of colorectal cancer in the world, there is currently no national screening programme for colorectal cancer.

Other cancers are detected through ad hoc screening, that is, screening that does not seek to systematically identify and invite a population to be screened, but rather occurs because of an individual seeking the test out, or a practitioner offering the test to patients he or she sees. In particular, this occurs with prostate cancer in New Zealand. Because prostate cancer screening picks up cancers which would not have caused a problem in the patient's lifetime and been diagnosed clinically, prostate cancer screening increases the recorded incidence of prostate cancer. There has been

a marked increase in prostate cancer incidence over the past two decades in New Zealand, with increasing uptake of prostate cancer screening (Blakely et al., 2011). Prostate cancer screening, and therefore prostate cancer diagnosis, is much more common in people with higher incomes and people of European ethnicity (Blakely et al., 2011).

Cancer treatment in New Zealand mostly occurs in public hospital settings. Four regional cancer networks coordinate cancer care and cancer control activities. Increasingly, there is also private provision of surgery for cancer, particularly in larger centres, and recently some private providers have extended into providing radiotherapy and chemotherapy services.

2.5 CONCLUSIONS: THE CONTEXT FOR THIS THESIS

This thesis examines cancer burden in the context of severe mental illness in New Zealand. Cancer is used as an example for exploring the causes of physical health inequalities in people in contact with mental health services, for the reasons presented earlier

The reasons for inequalities in health outcomes among people with severe mental illness are multiple and complex. Factors including health behaviours, access to and quality of health care, and health system design issues are all implicated, as is the pervasive effect of the stigma and discrimination associated with mental illness. These factors will be considered in exploring the example of cancer.

The New Zealand context is similar to that of other developed Western nations, with a relatively wealthy population, predominantly of European descent, and an organised and relatively well funded health system with specialist mental health and cancer care services. However, the New Zealand situation is also unique. New Zealand has a publicly funded health care system, with co-payments for general practice but no charge for secondary services, and a small private health sector. Mental health care in New Zealand is predominantly provided in the community, similar to the model used in other countries such as the United Kingdom. The mental health consumer movement has had a relatively strong voice in New Zealand's

mental health sector, a factor which may impact on treatment within the wider health sector. New Zealand is an ethnically diverse country, with a strong indigenous population, and a Treaty relationship between indigenous New Zealanders and subsequent settlers. Moreover, very little is known about the physical health of people in contact with mental health services in New Zealand, despite the availability of linked anonymised routine health data.

Therefore, this thesis examines cancer in the context of mental illness as identified through contact with specialist mental health services. It seeks to establish whether disparities in health status are present in the New Zealand context, and the causes of those disparities.

Chapter Three: **LITERATURE REVIEW: WHAT DO WE ALREADY KNOW ABOUT CANCER IN THE CONTEXT OF MENTAL ILLNESS?**

3.1 INTRODUCTION

This chapter reviews the current state of knowledge with respect to cancer in the context of mental illness. It starts by briefly exploring the landscape of literature dealing with the co-occurrence of mental health problems and cancer, and how the literature focusing on cancer *following* mental illness fits into this landscape. It then examines four areas of the literature in depth: firstly, cancer incidence in people with history of mental illness; secondly, cancer mortality in this group; thirdly, cancer survival; and finally research exploring the determinants of cancer survival. It finishes with a summary of the current state of knowledge and the way in which the current study will build on that knowledge.

3.2 METHODS

Five separate but interconnected reviews were carried out to inform this thesis. Narrative synthesis was used to present the results of each review.

Scoping review

The first review conducted was a scoping review, which sought to identify the breadth and major areas of focus of the epidemiological literature on cancer burden in the context of mental illness. The initial database searches focused on identifying the intersection of cancer and mental health research, while recognising that a large proportion of this research focuses on mental illness in the context of prior cancer rather than the other way around. Major databases were therefore searched for articles with key words relating to both mental illness and cancer. Psych Info, Ovid Medline, CINAHL, Google Scholar and Web of Science were searched, with strategies adapted for each database. Initial searches were unrestricted by time, to capture historical as well as current literature. Where possible, alerts were set up to rerun searches regularly.

For example the following strategy was used to search OVID Medline:

Search terms related to mental illness (combined with OR): schizophrenia, severe mental illness, psychosis, depression, bipolar disorder, personality disorder, mental disorder.

Search terms relating to cancer (combined with OR): Neoplasms, cancer, breast neoplasm, colorectal neoplasm, lung neoplasm.

These two searches were then combined with AND to give the intersection.

Additional searches were run combining more specific terms added to the above terms with AND: "incidence", "mortality", "survival", "screening", "stage at diagnosis".

These searches returned very large numbers of results, very few of which were directly relevant to cancer in the context of mental illness. This area of research spans disciplines, and indexing of key words is inconsistent, and so it is not straightforward to identify material using key word searches. There is also no clear way to separate papers examining cancer in the context of mental illness from those examining mental illness in the context of cancer through the search strategy. Therefore, the titles (and abstracts where indicated) of a large number of papers identified in searches were scanned for relevant studies, with a focus on studies from 1996 onwards. Additional methods were also used to ensure that relevant material was identified. The references of identified papers were checked and included where relevant. Subsequent citations of papers of particular relevance were also searched using Google Scholar, and citation alerts set up for relevant papers. Major authors in the area were identified and searches done in Medline and Google Scholar to identify their other papers. The University websites of these authors were also checked.

Further searches sought to investigate specific areas deemed relevant to the pathways by which mental illness relates to cancer outcomes, combining other terms with the mental illness search terms: "smoking", "stigma" or "discrimination", and "quality of care".

Table 1 OVID Medline Search Strategy example

Medline Search Strategy	No. results(Rerun 5/11/15)
1. Depressive Disorder/ or Schizophrenia/ or Mental Disorders/ or Mental Health Services/ or mental illness.mp. or Bipolar Disorder/ or Psychotic Disorders/ or severe mental illness.mp. or BPAD.mp. or Personality Disorders/	338581
2. Survival Analysis/ or Survival/	112143
3. 1 and 2	793
4. Comorbidity/	78037
5. 1 and 4	15929
6. Neoplasms/	324547
7. 1 and 6	1801
8. Neoplasms/ or cancer.mp or Breast Neoplasms/ or Colorectal Neoplasms/ or Lung Neoplasms/	1406455
9. 8 and 1	3362
10. Smoking/ or Smoking Cessation/	138565
11. 1 and 10	2585
12. cancer incidence.mp.	12743
13. Neoplasms/mo [Mortality]	14943
14. 1 and 12	36
15. 1 and 2 and 8	33
16. 1 and 13	120
17. 5 and 6	194
18. discrimination.mp or stigma.mp or Social Stigma/	113880
19. 1 and 18	4770
20. "Quality of Health Care"/ or quality of care.mp. or Quality Assurance, Health Care/	129594
21. 1 and 20	3730
21. Health Status/ or physical health.mp.	72343
22. 1 and 21	110
23. limit 9 to ("all adult (19 plus years)" and English and humans and last 15 years)	990
24. limit 23 (review articles)	58
25. limit 7 to (review articles and English and humans and last 15 years))	285

Table 1 gives the Medline search strategy and numbers as an example. This was not a linear search, but instead consisted of multiple connected searches aimed at identifying different parts of the literature of interest and refining the very large initial numbers of results. Methods such as restricting to reviews and reviewing the reference lists of these reviews were also used in order to ensure that key pieces of literature were identified.

Four further reviews followed from the initial scoping review, exploring in more depth particular areas identified in the first review. These reviews covered cancer incidence, cancer mortality, cancer survival, and the determinants of cancer survival, all in the context of mental illness. In the areas of cancer incidence and cancer survival, systematic methods were used to identify all available published studies fitting specified criteria, although in neither case was a formal systematic review felt to be warranted. The searches conducted in these areas are discussed in more detail below. For the areas of cancer mortality and the determinants of cancer survival, searches were conducted to identify review articles and key studies, including reviews of reference lists and citation searches.

Cancer incidence

Initial searches of the cancer incidence literature identified a large number of studies, multiple narrative reviews, and two systematic reviews with meta-analyses focusing on cancer incidence in people with schizophrenia (Catts et al., 2008; Catalá-López et al., 2014). Because of the existing systematic reviews, a decision was taken not to pursue a full systematic review in this area. However attempts were made to identify all available studies which provided estimates of cancer incidence in people with experience of mental illness, through searches combining terms for mental illness, terms for cancer, and terms for incidence or risk (as specified above for the Medline database) and through reference list and citation searches. Within this literature it became clear that a synthesis of outcomes from these studies (cancer incidence estimates) was problematic because of heterogeneity, particularly in the definition of the exposed population. A critical review was therefore performed, focusing on the different methods used and the biases arising from these studies. This review was restricted to population-based cohort studies published from 2000 to 2014 which

identified a group with mental illness and a comparison population and followed this group over time (retrospectively or prospectively) to identify incident cases of cancer. Because this review focused on the different methods used to identify those with mental illness in cohort studies, case-control studies were not included. In practice, only a single population-based case control study examining the risk of cancer in people with mental illness was identified (Hippisley-Cox et al., 2007). Case control studies do not provide estimates of disease incidence, and so are also less suited to examining this area.

Cancer survival

As cancer survival was a major focus for this thesis, attempts were made to systematically identify all the relevant literature. Studies were included if they compared case fatality or survival after cancer diagnosis between a group with mental illness (identified at or prior to cancer diagnosis) and a comparison group without mental illness. Initial searches performed in 2011, using search terms for mental illness, for cancer, and for survival/case-fatality, as well as reference list and citation searches, identified only three studies. Rerunning of searches and citation alerts resulted in the identification of a further ten studies published up to December 2015.

3.3 THE STUDY OF CANCER IN THE CONTEXT OF MENTAL ILLNESS

3.3.1 The co-occurrence of cancer and mental illness

A recent review of research covering the intersection between mental health and cancer (Purushotham et al., 2013) used Web of Science to search for articles published between 2002 and 2012. They found 1463 papers dealing with the dual presence of mental illness and cancer, amounting to 0.26% of all cancer research and 0.51% of all mental health research over the ten-year period. When these titles were manually reviewed, 80% of the relevant papers focused on mental health problems subsequent to cancer rather than the reverse. Very little research focusing on cancer occurring in the context of pre-existing mental illness was found, and the authors identified this as an important research need.

Research into the implications of the co-occurrence of mental disorders and cancer has been increasing over time. A similar search on Web of Science, looking at the intersection between the research topics "cancer" and "mental disorder", returned 2,052 publications for the period 1995 to 2015, with an increase in the number of papers published year on year, from 28 in 1995, to 88 in 2005 and 215 in 2015 (search performed 21/01/16) (see Figure 1). This increase does not necessarily indicate an increase in empirical studies published, but may also relate to an increase in commentary about the co-occurrence of mental illness and cancer.

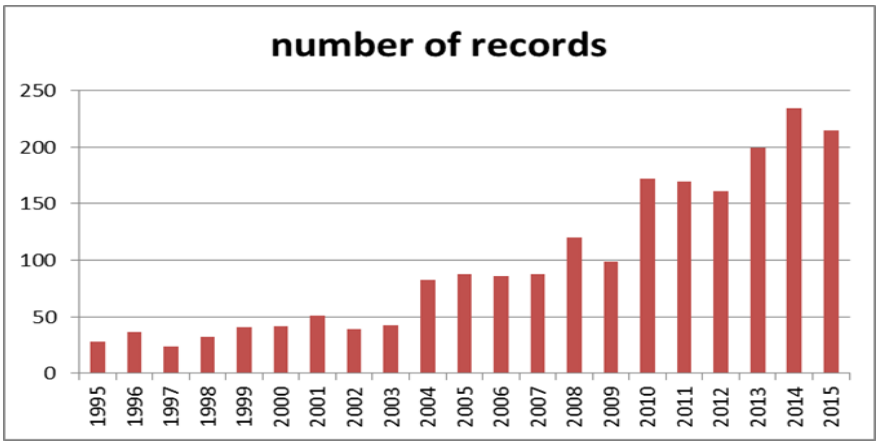

Figure 1 Number of records returned by Web of Science for the intersection of the search topics "cancer" and "mental disorder", by year

As noted above, most work at the intersection of cancer and mental disorder focuses on psychosocial adaption following cancer diagnosis, including the prevalence of problems and the role of services. However, there is also a growing body of epidemiological and health services research, which considers the impact of prior mental illness on cancer burden and cancer care. This body of research is the focus of this review.

Within the area of cancer in the context of prior mental illness, the majority of research has focused on cancer incidence and mortality. This research has been driven by epidemiological and biological curiosity about the apparently low burden of cancer, particularly in people diagnosed with schizophrenia. It is only over the past two decades (and mainly in the past few years) that another branch of research in this area has begun to develop, driven by concern for health inequalities related to experience of mental illness, and focusing on cancer case-fatality and cancer survival.

This literature review focuses on epidemiological studies in both these areas, and considers possible explanations for study findings, including differences between people with experience of mental illness and others in the population, and factors related to study design.

3.3.2 Disentangling cancer incidence, mortality and survival

Cancer burden can be measured through cancer incidence (the frequency of cancer diagnosis in the population), cancer mortality (the frequency of deaths attributed to cancer in the population), and cancer survival (the length of time survived following cancer diagnosis). Each approach identifies a different aspect of the impact of cancer on the population. Whilst there is overlap, different factors influence each of these aspects of cancer burden. Therefore, differences between population groups in each of these measures will be related to different mechanisms and will respond to different types of intervention.

Cancer incidence is the rate of cancer diagnosis in a population; that is, the number of new cases of cancer occurring over a certain period of time (usually a year) in a

population at risk. Cancer incidence depends on the pattern of both risk and protective factors for cancer in the population. These factors vary for individual cancers. For example, tobacco smoking is the main risk factor for lung cancer, while the main risk factors for breast cancer are reproductive ones. There are therefore differences in the patterns of cancer incidence for any given population group. For example, smoking is usually more common in deprived groups, resulting in higher rates of lung cancer amongst these groups. In contrast, women in deprived groups may have more children earlier, and so breast cancer rates may be lowest in deprived groups.

For some cancers, the health services by which cancers are detected also influence incidence. For example, for breast and prostate cancers, screening tests can pick up cancers which would never have caused a clinical problem and been diagnosed without the test. Thus, those who undergo screening have a seemingly higher incidence than those who do not. In contrast, cervical and colorectal screening can reduce the incidence of these cancers, by picking up cancer precursors that can be treated. Therefore, access to health services can have a differential effect on cancer incidence by the type of cancer.

Cancer survival is measured as the proportion of people surviving for a given period of time after cancer diagnosis, or the average length of time between cancer diagnosis and death. Cancer survival depends on the type and aggressiveness of the cancer, how early it is diagnosed, how well an individual is when cancer is diagnosed, and on the way that cancer is treated following diagnosis. Variation in cancer survival between groups can also relate to differences in any of these factors. Cancer survival varies by cancer type. For some cancers, such as breast cancer, the majority of people diagnosed will survive for five years beyond diagnosis, while for other cancers, such as lung cancer, survival for five years beyond diagnosis is uncommon. Inequalities in cancer survival also vary by cancer type (Soeberg et al., 2012).

Cancer mortality is the rate of deaths attributed to cancer in a population. Cancer mortality depends on both cancer incidence and cancer survival; that is, on both the factors that influence the occurrence of cancer and the factors that influence its

prognosis. It also depends on competing causes of death. Cancer is mostly a disease of old age, and so populations with high rates of diseases such as diabetes, which cause death at earlier ages, may have relatively low crude cancer mortality rates.

Each of these aspects provides useful information on the burden of cancer in a population. Cancer incidence provides information on how commonly people in the population experience cancer and the incidence of individual cancers can give pointers to the risk and protective factors which are influencing how commonly cancer occurs. Cancer survival provides information on what happens to members of a population once cancer is diagnosed, and inequalities in cancer survival point to the need for improvements in cancer diagnosis and treatment. Cancer mortality provides information on the magnitude of the impact of cancer on the population, or how commonly people in that population die from cancer. However, cancer mortality is a combined measure affected by incidence and survival, as well as by competing causes of death. Therefore, it is much more difficult to interpret and find ways to intervene on mortality differences between groups than for differences in either incidence or survival. This review focuses on cancer incidence and survival. The results of studies of cancer mortality are also briefly reviewed, and the utility of mortality studies is discussed.

3.4 CANCER INCIDENCE

3.4.1 Overview of cancer incidence findings for all cancers combined

In 1909 the Board of Control of the Commissioners in Lunacy for England and Wales suggested that 'the insane' (those in psychiatric care) might be protected from cancer (Commissioners in Lunacy for England and Wales, 1909). Early studies seemed to show unexpectedly low rates of cancer in people in hospital care for psychiatric illness, in particular people with schizophrenia (Scheflen, 1951). However, these studies were mostly based on proportional mortality rates (the proportion of deaths due to cancer) as information on incident cases of cancer was not available. These studies did not take into account the high rates of premature mortality from other causes in this population, leading to low rates of death attributable to cancer, and so the results are difficult to interpret. Subsequent studies have examined cancer incidence in people with diagnosed mental illness, and have found varying results. Some studies seem to support this protective effect hypothesis, with lower cancer incidence found in people with schizophrenia (Barak et al., 2005; Chou et al., 2011; Grinshpoon et al., 2005) and other mental disorders (Kisely et al., 2015) compared to the general population. Other studies have found similar or even higher rates when comparing people with experience of mental illness (including schizophrenia) and the general population (Hung et al., 2014; McGinty et al., 2012; Carney et al., 2004; Dalton et al., 2008a; Osborn et al., 2013; Lichtermann et al., 2001).

Only two published systematic reviews and meta-analyses have considered the incidence of all cancers combined in people with schizophrenia (Catts et al., 2008; Catalá-López et al., 2014). There is considerable overlap between these reviews, with eight studies included in both meta-analyses, and eight additional studies in the more recent review. The studies included in the reviews produced a wide variety of estimates of cancer incidence, from much reduced to much elevated. When the results of multiple studies were analysed together, both reviews found similar overall cancer incidence in people with schizophrenia and the general population (SIR 1.05

[0.95-1.15] (Catts et al., 2008); SIR 0.98 [0.9-1.07] (Catalá-López et al., 2014)). However, despite finding a similar overall incidence, both reviews concluded that cancer incidence is lower than *expected* in people with schizophrenia, and that this may indicate a protective effect of schizophrenia. This is concluded on the basis that high rates of smoking among people with schizophrenia would be expected to lead to higher cancer incidence amongst this group than the general population.

Findings of an apparently low or lower than expected cancer incidence in people with mental illness, and in particular schizophrenia, have given rise to a variety of hypotheses regarding possible mechanisms by which people with mental illness may be protected from developing cancer. Factors related to the physical and social environment implicated in the apparently low incidence of cancer include the possible protective effects of the institutional environment or other behavioural factors associated with schizophrenia (Gulbinat et al., 1992). Other environmental factors, such as smoking rates and reproductive patterns will also influence the incidence of cancer among people with schizophrenia. Pharmacological explanations for low cancer incidence include possible protective effects of phenothiazines (Gil-Ad et al., 2004). On the other hand, it has been suggested that atypical anti-psychotics may *increase* the risk of breast cancer (Azoulay et al., 2011). Biochemical and genetic explanations for an association between schizophrenia and a low risk of cancer have also been put forward (Wang et al., 2011; Ferentinos and Dikeos, 2012). For example, it has been suggested that the tumour suppressor gene p53 (which is associated with a reduced risk of cancer) is involved in the aetiology of schizophrenia (Park et al., 2004; Yang et al., 2004).

A small number of studies have had sufficient power to consider the relationship between more than one psychiatric diagnosis and cancer incidence. For the most part, these studies have found little difference between diagnostic groups. Moreover, variations by diagnosis have not been consistent, with the exception of increased cancer incidence in people with alcohol misuse disorders. For example, in a recent Australian study (Kisely et al., 2013), estimates of relative cancer incidence for most psychiatric diagnoses did not differ significantly from the general population. The exceptions to this were a raised risk of cancer in people with alcohol and drug

disorders and “other psychoses”, and a decreased risk of cancer in men with affective psychoses and adjustment disorders. Another study by the same authors (Kisely et al., 2015) found that cancer incidence was increased in people with alcohol and drug disorders [SIR 1.29 (95%CI 1.17-1.41)] and affective psychoses [SIR 1.15 (1.02-1.28)] compared to people without mental disorders, while people with “other mental disorders” had a reduced incidence of cancer [SIR 0.78 (0.72-0.83)]. These findings suggest that the factors associated with the incidence of cancer in those with experience of mental illness do not, in general, relate to specific disorders, with the exception of the role of alcohol in increasing the risk of cancer.

There have been a number of studies of family members of those with schizophrenia, driven by the idea that schizophrenia is associated with genetic protection from cancer, which would be shared by family members. Study results have been mixed, but the majority have found a low incidence of cancer in parents and siblings of those with schizophrenia (Catts et al., 2008). However, these studies are likely to be subject to bias. Survivorship bias can occur, because the ‘exposed’ group of parents and siblings need to have survived long enough for their child or sibling to have developed schizophrenia, while the unexposed comparison group are a general population group who may or may not have adult children or siblings. This bias could produce spuriously low rates of cancer in the group who are required to have not died of cancer prior to their family member’s schizophrenia diagnosis. Similarly, the comparison of parents of people with schizophrenia with people in the general population (including non-parents), can lead to a seeming protective effect, when in fact what is being measured is cancer incidence in those who were healthy enough to have children. It is therefore important to ensure an appropriate comparison population that is also subject to the same constraints. A Danish study, which directly compared cancer rates in the parents of people with schizophrenia with cancer rates in other parents, found no difference in cancer incidence (Dalton et al., 2004). The evidence provided by these studies of a genetic basis for low cancer risk in people with schizophrenia should, therefore, be treated with caution.

Many studies of cancer incidence in people with experience of severe mental illness have been undertaken, with a wide variety of findings ranging from a higher to a

lower incidence of cancer associated with mental illness. These studies have been conducted in many countries, including the United Kingdom (Goldacre et al., 2005), the United States (McGinty et al., 2012), Sweden (Ji et al., 2013), Denmark (Dalton et al., 2006), Australia (Kisely et al., 2015), Japan (Saku et al., 1995), and Taiwan (Hung et al., 2014). They have also been undertaken over a variety of time periods, from the early 20th to the early 21st centuries. According to some commentators, the current consensus is that the incidence of cancer in people with schizophrenia and other mental illnesses is not significantly different to that of the general population (Lawrence et al., 2015). However, the idea that mental illness, and in particular schizophrenia, is somehow protective against cancer still has currency (Catts et al., 2008; Catalá-López et al., 2014). The relationship between cancer and prior mental illness is therefore still debated. Examining the reasons for the apparently contradictory findings of different studies may help to elucidate the relationship and perhaps settle the debate.

3.4.2 Possible explanations for different findings

One possible reason for the differences in study findings is that these are real differences, explained by differing patterns of cancer risk factors over time and place. Both the health system context and the distribution of behavioural risk factors change over time, and vary between places. In the case of severe mental illness, the two are intricately entwined. Those under psychiatric care in New Zealand or the United Kingdom in the early twentieth century tended to live very restricted lives in institutions, while today, community care means that many fewer restrictions are placed on those under psychiatric care. Smoking rates, currently very high amongst users of mental health services in most countries, may in fact have previously been lower than general population rates at the time when mental illness was associated with prolonged institutional care and restrictions on access to tobacco. The way the health system operates also impacts on the likelihood of cancer diagnosis. There may be systematic differences in the likelihood of diagnosis between those with and without particularly severe mental illness, and such differences are likely to vary over time and place. For example, women with schizophrenia may be more likely to have a breast lump come to the attention of health providers because they are in

frequent contact with health services, but may be less likely to have their cancer diagnosed if such services pay scant attention to physical health (as they may have historically).

Undoubtedly, there will be differences over time and place that need to be considered when comparing results from cancer incidence studies. However, contemporary studies continue to find variable results, even in the same country. For example, two recent studies by different research teams from Taiwan have estimated the incidence of cancer in men with schizophrenia. One found a reduced incidence of cancer in these men [SIR 0.67 (95% CI 0.66-0.72)] (Lin et al., 2013a), and the other found no difference in the incidence of cancer compared to the general population [SIR 1.02 (0.9-1.16)] (Lin et al., 2013b), despite both investigating the same population over approximately the same period, albeit using slightly different methods. This suggests that differences are due to other factors than variation by time and place.

Another possible explanation is that these differences are an artefact of studying cancer as a combined entity, and that studies of individual cancers will be more consistent. Many studies, especially historically, have looked at the rates of all cancers combined, particularly focusing on people with schizophrenia. Studying the incidence of all cancers combined may seem surprising from a cancer epidemiology point of view, as aetiology and risk factors vary enormously between cancers. While some risk factors such as smoking are common to many cancers, major cancers such as breast and colorectal cancer have very different aetiologies and population incidence patterns, and so it makes little sense to consider them together. The reasons for examining all cancers together are likely to be two-fold. Firstly, studies that have used small and often relatively young institutional samples (as many early studies did) will identify too few cancers to consider specific cancers individually. Secondly, interest in a shared biological mechanism between schizophrenia and cancer has likely also encouraged this examination of cancer as a single entity (Wang et al., 2011) (Ponizovsky et al., 2011). However, considering all cancers together in this way ignores the aetiological differences between cancers, and any

finding of a pattern in all cancers combined will be driven by differences in common cancers.

Where all cancers are combined, differences in the age and sex of the population under study will affect which cancers are most common, and therefore the cancers that are having the most impact on the combined cancer incidence. For example, if the population is relatively young and female, breast cancer will be an important driver of the overall cancer incidence, while if the population is relatively old and male, prostate cancer will play much more of a role. The risk factors for these two cancers are very different, and the expected incidence in people with experience of mental illness is also very different. For example, low parity in women with mental illness may drive high breast cancer rates, while lack of access to physical health care (and prostate cancer screening) may result in low rates of diagnosed prostate cancer. By combining all cancers, competing underlying patterns can be masked. It is therefore important to disentangle the effects of individual cancers within the total incidence. However, although there is increased consistency when cancers are considered separately, there are still contradictory results. For example, a recent systematic review included studies finding the incidence of lung cancer in people with schizophrenia to be both higher and lower than in the general population (Catalá-López et al., 2014), and similarly variable findings have been noted for breast cancer (Bushe et al., 2009).

The way in which the population with mental illness under study is identified may also affect the results of studies of cancer incidence. Some studies have focused only on people admitted to hospital with schizophrenia (for example (BarChana et al., 2008)), while others have also included those under outpatient care (for example (Barak et al., 2005)), and still others have included people with a schizophrenia diagnosis managed in primary care (Grinshpoon et al., 2006; Ji et al., 2013). Some studies have been restricted to people with a diagnosis of schizophrenia specifically, and excluded related conditions such as schizoaffective disorder and other non-affective psychoses (for example (Chou et al., 2011)), while others have been less restrictive (for example (Lichtermann et al., 2001), in some cases including all people in contact with psychiatric services (Lawrence et al., 2000a; Osborn et al.,

2013). If there was a biological or genetic basis for the relationship between schizophrenia or other mental illness and cancer, then it might be expected that studies which were more restricted would find a clearer and more consistent relationship. One study has tried to look for differences between familial and sporadic cases of schizophrenia, on the basis that inherited cases will have a stronger genetic component and therefore perhaps more strongly exhibit a genetic protective effect for cancer (Gal et al., 2012). In fact, this study did not find a difference between these two groups in terms of cancer incidence. Nor is there evidence that there is any kind of dose response relationship, with more restrictive studies finding a stronger relationship between schizophrenia/mental illness and cancer which is diluted out in studies which are more inclusive. In fact, there are studies restricted to those with a diagnosis of schizophrenia which have found a raised risk of cancer compared to the general population (Lin et al., 2013b), and other studies including all those using mental health services which have found a reduced risk of cancer (Osborn et al., 2013). Therefore, although differences in the definition of the population with mental illness included may be affecting study findings, other factors must also have a role in explaining contradictory findings.

Recent reviews of cancer incidence in the context of mental illness (mostly schizophrenia) have highlighted methodological differences as important in explaining the great variation in cancer incidence between studies (Hodgson et al., 2010; Howard et al., 2010; Bushe and Hodgson, 2010). Early studies looking at cancer in mental illness used small institutional samples, and so were underpowered. These studies were also plagued by problems such as missing cancer diagnoses (as access to routine physical care in such settings was often poor), length of follow up being limited by time as an inpatient, and the young age of the population examined. In contrast, more recent population based studies have used routine data sources such as cancer and death registration systems and health service records, giving much fuller ascertainment of cancers and deaths over a wider age range. These studies are generally retrospective, and so do not require costly follow up of individuals. However, the length of follow-up time available is limited by the time since the databases used were established.

A recent systematic review of breast cancer in schizophrenia (Bushe et al., 2009) found that the variation in study findings (some reporting higher incidence, others lower) could at least in part be explained by the differences between the age of the populations studied and the follow up time. Higher relative rates were found in older populations with longer follow up, but not in younger groups or studies with shorter follow up. However, these differences in results by the age of the population examined may be specific to breast cancer. Pre- and post-menopausal breast cancers have different risk factors, with factors such as obesity having a protective effect against pre-menopausal cancers but a predisposing effect to post-menopausal cancers (Carmichael and Bates, 2004). This difference may be important in explaining the findings of higher rates amongst older women with schizophrenia but not younger women. Conversely, a recent study which explored changes in the relative cancer incidence with age for a population with schizophrenia found that older members of the cohort in fact had a relatively lower incidence of cancer than the general population, while the younger members of the cohort had a similar incidence of cancer to the general population (Lin et al., 2013a) – the reverse of the pattern suggested by Bushe and Hodgson. A more detailed exploration of the methodological differences between studies is required.

Whitley and colleagues examined the effect of different analytic strategies on cancer incidence estimates using data from a cohort of 1 million Swedish men (Whitley et al., 2012). They identified the problem of the precise timing of cancer and mental illness onset being unknown, with neither the diagnosis date of cancer nor of mental illness necessarily indicating the onset of the condition. This results in the potential for misclassification of mental illness status at the time of cancer diagnosis. In order to deal with this problem, the study explored the impacts of three different ways of treating cancers diagnosed before diagnosis of mental illness, on the basis that the common approach of excluding these cancers may be over-compensating for the problem of reverse causation (the possibility that cancer or cancer diagnosis is the cause of a mental illness). The first study design excluded all people with cancers diagnosed prior to mental illness diagnosis, and found a low relative incidence of cancer among people with mental illness compared to those without such a history [HR 0.72 (95%CI 0.67–0.78)]. The second design included all cancers diagnosed

before or after mental illness diagnosis, and found a higher relative incidence of cancer compared to people without a history of mental illness [HR 1.14 (1.07-1.22)]. A third method, which assigned person-time prior to mental illness diagnosis as unexposed, but did not exclude people with prior cancer from the whole study, resulted in a slightly increased relative incidence of cancer in people with mental illness diagnoses (similar to the results from the second method).

Whitely and colleagues then reviewed previous studies, categorising them into studies that had excluded people with prior cancer, and studies that were not explicit about this exclusion. They demonstrated that studies reporting this exclusion found a low incidence of cancer, while studies not reporting the exclusion found the incidence of cancer to be either similar to the general population or slightly increased. They concluded that exclusion of this group is an overly conservative approach to estimating cancer incidence, and go on to show that even random exclusions of a proportion of the study population can lead to underestimates of cancer incidence. However, the specific biases that are driving the differing results found by different methods were not explored.

Selection and misclassification biases may explain the differences in study findings. Selection bias in a cohort study occurs when the selection of the study cohort is not representative of the population from which it is drawn in terms of the relationship between the exposure and the outcome, or when different criteria are applied to the selection of the exposed and unexposed cohorts. Most of the studies looking at cancer incidence in the context of mental illness select a cohort of people with mental illness and then compare this cohort to the general population. The problem arises when the selection criteria for the exposed population do not match the selection criteria for the unexposed population. For example, when selection into the exposed cohort (having a mental illness) requires that a person has not previously experienced the outcome (cancer diagnosis) then this result will be biased if selection into the unexposed cohort at risk (people without a mental illness) does not also have a similar requirement (no previous cancer). In this case, the exposed cohort is required to be invulnerable to cancer (to never have had cancer), while the unexposed cohort is not. Misclassification bias on the other hand can occur when

someone is classified as being exposed (in this case, having a mental illness) when they in fact are not (for example, they have a cancer manifesting with psychiatric symptoms, such as a neurological malignancy). It can also occur when someone with cancer diagnosis prior to mental illness diagnosis is classified as unexposed despite their pre-existing symptoms of mental illness. Both of these biases can impact on the results of studies exploring the relationship between mental illness and cancer incidence.

3.4.3 A typology of cancer incidence studies

This section examines these biases in detail. It presents a typology of study design types in order to explore whether differences in design may explain differences in findings. Examples of studies of each type are included to illustrate the impact of each different design.

In order to understand how these biases occur, it is useful to articulate the range of possible relationships between cancer and mental illness in an individual. Cancer and mental illness can occur in the same individual in any order, and can be related or unrelated events. Cancer diagnosis can occur before or after mental illness diagnosis; can precipitate mental illness; can cause a condition which appears to be a mental illness, but is in fact a manifestation of cancer; or can have no relationship to subsequent or preceding mental illness. Figure 2 shows the seven possible sequences of events in an individual.

In studies of the incidence of cancer in people with mental illness, the exposed population are people with experience of mental illness who are identified as such (diagnosed or come into contact with mental health services) at some point in time. There are four main ways of defining the exposed population in studies examining the relationship between mental illness and cancer incidence. Figure 3 sets out these four potential designs, building on the designs identified by Whitley (designs A to C), with the definition of the exposed population described in terms of the possible temporal sequencing of mental illness and cancer (the numbers refer to the sequences listed in Figure 2).

1. Diagnosed with mental illness and then diagnosed with cancer some time later (unrelated)
2. Diagnosed with mental illness and then diagnosed with cancer shortly afterwards (related)
3. Diagnosed with mental illness and no past or future cancer
4. Diagnosed with cancer and then diagnosed with mental illness some time later (unrelated)
5. Diagnosed with cancer and then diagnosed with mental illness shortly afterwards (related)
6. Diagnosed with cancer and no past or future mental illness

Figure 2 Possible sequences of cancer and mental illness in an individual

A **Exposed** group (group with mental illness) = **1+2+3** but not 4 or 5 (any mental Illness except after cancer). **Exclude 4+5** from analyses.

B **Exposed** group = **1+2+3+4+5** (i.e. any mental illness before or after cancer)

C **Exposed time** (time with mental illness) = **1+2+3**, time after mental illness diagnosis only. Time prior to mental illness diagnosis included as unexposed. 4+5 included as unexposed, and censored at cancer diagnosis.

D **Exposed time** (time with mental illness) = **1+2+3+4+5**, time after mental illness diagnosis only. Time prior to mental illness diagnosis excluded.

Figure 3 Possible study designs for examining cancer incidence in people with mental illness

The four designs are explained in detail below, with examples of studies of each type. Table 2 categorises recent studies into each of these four types.

Design A defines the exposed group (with mental illness) as all people in groups 1, 2 and 3 (all people with mental illness and subsequent cancer, and mental illness with no cancer at any time), and excludes people in groups 4 and 5 (with cancer diagnosis prior to mental illness diagnosis). It is important to note that these three types of individuals (groups 1, 2 and 3) cannot be distinguished from each other at the point of exposure definition (mental illness diagnosis) but they can be distinguished from groups 4 and 5, who are excluded. Selection bias will occur if the same exclusion of

people with prior cancer is not applied to the unexposed comparison cohort at the beginning of follow up time, as the exposed cohort are by definition invulnerable to cancer up to the time of mental illness diagnosis, and prior cancer is associated with the risk of subsequent cancer. This results in an apparently lower incidence of cancer in the exposed cohort. Many studies have excluded people with prior cancers from their exposed cohort, and because they have used general population cancer rates for comparison, this exclusion has not been able to be applied to the comparison population (for example, (Lawrence et al., 2000b; Grinshpoon et al., 2005; Lin et al., 2013a)).

An exception is a recent UK study (Osborn et al., 2013), which used a comparison cohort for which it was possible to also exclude people with prior cancer. The comparison cohort was identified from the same General Practice database as the exposed cohort (people with a diagnosis of serious mental illness (SMI)). People with cancer diagnosed prior to SMI diagnosis were excluded from the SMI cohort, and people with cancer entered into their clinical record within the first six months of enrolment with a general practice were also excluded, on the basis that these cancers were likely to be prevalent rather than incident. It is unclear whether this means that people were being excluded if they had cancer at the start of the study, or were more broadly excluded if they had had cancer at any time prior to the study (the second exclusion being comparable to the exclusion applied to the SMI group). It is notable that this study does not find a reduced incidence of cancer in people with mental illness compared to the general population (adjusted IRR 0.95; 95% confidence interval 0.85-1.06), in contrast to other studies using this method with a general population comparison.

Two other important factors impact on the number of people excluded from the exposed group because of prior cancer, and therefore the impact of the exclusion on the study results. Firstly, the age of the exposed cohort at the time of being categorised as exposed (i.e. mental illness diagnosis or first known contact with mental health services). The older people are at the time of classification, the more likely it is that they have had cancer prior to this point, and so the more people will be excluded because of prior cancer. Secondly, the period of time for which

information on cancer risk is available prior to mental illness diagnosis. The more information there is about cancer risk prior to mental illness diagnosis, the greater the potential for excluding people based on prior cancer. Therefore we would expect that studies including people who were older at the time of mental illness diagnosis and about whom we have a long period of historical data to determine if they had cancer in the past, would find a lower incidence of cancer associated with mental illness where this exclusion is used. For example, when Lin (2013a) compared cancer incidence in those using mental health services from a young age and those with first mental health service contact at an older age, the older group had a lower incidence of cancer than the younger group.

Design A, which excludes people with cancer diagnosis prior to mental illness, is one of the most commonly used, and the biases inherent in this design appear to explain the results of many recent studies which have found a low incidence of cancer associated with prior mental illness.

Design B defines the exposed group as anyone with a diagnosis of mental illness at any time (i.e. groups 1, 2, 3, 4, and 5), including mental illness diagnosed after cancer, and includes all cancers in the follow up time regardless of whether they occurred before or after diagnosis of mental illness. This method deals with the problem of invulnerability by including all cancers regardless of timing, and treats propensity to mental illness as a time invariant exposure (something which is present throughout the life course – in keeping with a genetic explanation of the link between mental illness and cancer).

However, this design will be subject to misclassification bias, because people who had mental illness caused by cancer (group 5) are included in the exposed group, and therefore results may overestimate the incidence. The degree of this bias will depend on the proportion of those with mental illness following cancer that have mental illness directly related to their cancer, which will depend in turn on the length of follow up time of the study. If the period of follow up is long, then only a small proportion of people with both mental illness and cancer will have had cancer diagnosis and mental illness diagnosis occur close together in time. However, where the follow up period is short, most of the people included as having mental illness

and cancer will have had the two events occur close together. For example, Pandiani (2006) used this method and found a much higher incidence of cancer in those with mental illness compared to the general population. This study included cancers before and after mental health service use, but only had a maximum of one year of follow up for each individual. Therefore, a large proportion of those with mental illness will be in group 2 and group 5 (those with mental illness diagnosis and cancer diagnosis in close proximity to each other). Inclusion of group 5, who have mental illness caused by cancer, will inflate the estimate because this group are only included as mental health service users as a consequence of their cancer diagnosis. The large proportion of the exposed population who are in group 2 (cancer diagnosis occurring shortly after mental illness diagnosis) will add to this misclassification problem. This is because some of those who had a mental illness diagnosis just before a cancer diagnosis will have had their cancer misdiagnosed as a psychiatric problem (and so should actually be in group 5) and will likewise appear to have a very high risk of cancer.

Design B is also subject to bias which works in the other direction and results in underestimates of cancer incidence. This is because this design creates a period of immortal time prior to mental illness diagnosis where cancer incidence is being assessed. That is, there is a period of time where cancer incidence is being assessed but it was impossible for people in the exposed cohort to develop cancer and die from it because if they did they would not have lived long enough to be diagnosed with mental illness and be allocated to the exposed cohort. This can lead to spurious low rates of those cancers that are often fatal, but less difference in cancers that have better survival prospects. This problem will be more marked for people diagnosed with mental illness at older ages, and more marked in studies for which a longer period of time for which cancer diagnoses are available prior to mental illness diagnosis. For example, Ji (2013) compared cancer incidence before and after mental illness diagnosis, and found a much lower incidence prior to schizophrenia diagnosis (SIR 0.40, 95% CI 0.38-0.43) than after schizophrenia diagnosis (SIR 1.00, 95%CI 0.97-1.03). There is some evidence that this low incidence prior to mental illness diagnosis is more marked in cancers with a higher case fatality rate. The SIR for testicular cancer (with a low case fatality rate) prior to schizophrenia diagnosis was

0.84, while the SIR for lung cancer (with a much higher case fatality rate) prior to schizophrenia diagnosis was 0.09.

Design B is therefore subject to two types of bias (misclassification and immortality bias) which influence estimates of cancer incidence in opposite directions. This makes results from this method very difficult to interpret.

Design C treats exposure (mental illness) as a time varying exposure, and defines the exposed period (person time) rather than the exposed group of people. Time prior to mental illness diagnosis is treated as unexposed, while time following diagnosis is treated as exposed. All cancers in the follow up period are included, but only those occurring following mental illness diagnosis count towards cancer incidence in the exposed group.

This design avoids the problem of immortal time outlined above. However, time may be misclassified as unexposed (no mental illness) when people may have as yet undiagnosed mental illness (because of the problem of the time delay between mental illness symptoms and diagnosis/service use). This misclassification is likely to be non-differential, because it is not related to the risk of the outcome (cancer), and so will bias the results towards the null.

In order to conduct a study using Design C, a comparison cohort is required (rather than general population comparison), as person time needs to be assigned to the comparison cohort. Because most studies of this type have used general population cancer rates for the comparison cohort, this design is not often feasible. The only examples of this design I was able to find were Scandinavian studies, which used population registers with complete person-time follow up for those with and without mental illness diagnoses (Whitley et al., 2012) or neuroleptic medication use (Dalton et al., 2006). Both of these studies found an increased risk of cancer associated with mental illness/medication for mental illness.

Design D also treats exposure (mental illness) as time varying. However, instead of assigning all person time prior to mental illness diagnosis to the unexposed cohort, this person-time is entirely excluded from the study (amongst those with a

subsequent mental illness diagnosis). Any cancers prior to mental illness diagnosis are therefore disregarded, but all people are kept in the study regardless of prior cancer. This method acknowledges that people may have had mental illness prior to diagnosis, or have a genetic predisposition to mental illness or detrimental behaviours associated with mental illness prior to diagnosis, but it is impossible to know who shared these risks but died before diagnosis could be made. There will be some misclassification (as with Design B), where cases of mental illness due to cancer are included in the exposed group (because prior cancers are ignored). However, the prior cancers in these individuals will not count towards the cancer incidence, and so bias will only occur if this group has an increased risk of subsequent cancer (which will be slight). This design is useful in situations where a direct comparison cohort is not available.

Almost all studies using this design have found a similar or increased risk of cancer associated with prior mental illness (see Table 2). For example, a UK study (Goldacre et al., 2005) followed a cohort of people from their first admission for schizophrenia for up to 36 years, compared to a comparison cohort admitted over the same period for unrelated conditions, with no exclusions for prior cancer. This study found no difference in the incidence of cancer between those with schizophrenia and the comparison cohort [adjusted RR 0.99 (95%CI 0.90-1.08)].

One study using Design D did, however, find a reduced incidence of cancer associated with schizophrenia. This Swedish study (Crump et al., 2013b) followed a prevalent cohort of people with diagnosed schizophrenia for seven years. This cohort was older than many other studies, with 33% of those included aged over 55 at the start of follow up. The finding of a lower estimate of cancer incidence for men with schizophrenia [age-adjusted HR 0.67] but not women [HR 1.04] may relate to the large proportion of male cancers at older ages which are prostate cancers (the distribution of cancers is not stated). This finding may therefore be due to the low rate of diagnosis of prostate cancer among those with mental illness (the pattern of prostate cancer in people with mental illness is discussed further in the next section).

None the less, studies of this design can still be subject to problems of misclassification. Kisely (2008) used this method with an incident cohort (followed

up from first diagnosis in primary or secondary care), and found an increased rate of cancer in those with a history of mental health problems. This is likely to be because the short follow up time from first diagnosis means that those in group 2 (people with cancer diagnosis shortly after mental illness diagnosis) are overrepresented, and this group will have a high risk of being misclassified as having mental illness prior to cancer (when in fact they have mental illness symptoms due to cancer).

Designs C and D will therefore produce the most robust estimates of cancer incidence in the context of mental illness. They remain vulnerable to all the other methodological issues noted depending on the age and length of follow up of the cohorts included. They do however avoid the problems of invulnerability and immortality bias which affect designs A and B respectively. It is notable that none of the studies which use methods C or D produced estimates of low relative cancer incidence in people with mental illness, with the exception of the estimate for men in the Swedish study mentioned above (Crump et al., 2013b). Studies of cancer incidence in the context of mental illness should therefore use designs C or D to produce the most valid results.

Table 2 Cancer incidence studies by study design (cohort studies since 2000)

Study design (exposure definition)	Potential bias	Relevant studies	Results (age and sex adjusted if available)	Age at mental illness (MI) diagnosis or start of f/u	N exposed cohort (cancers)	Cohort follow up (period over which exposure (mental illness) and outcome (cancer) identified)	comments
A. **Exposed** (group with MI) = **1+2+3** but not 4 or 5 (any MI except after cancer). **Exclude 4+5** from analyses.	Period of time invulnerable to cancer diagnosis in exposed group. Expect to get spuriously low rates of cancer in general because of this. More marked if diagnosed with mental illness at older ages, and if long period of overlap between mental illness accrual and cancer follow up time. Also subject to selection bias where mental illness diagnosis immediately prior to cancer diagnosis (2) is in fact misdiagnosed cancer.	(Whitley et al., 2012) (Sweden, schizophrenia) (method 1)	All cancers HR 0.88 (0.83-0.94) (men)	Mean age 31, max age 51	65,243 (904)	MI*: 1969-2004 Cancer: 1969-2004	Men only, general pop comparison
		(Lin et al., 2013a) (Taiwan, Schizophrenia)	All cancer SIR 0.92 (0.9-0.96), men SIR 0.67 (0.66-0.72), women SIR 1.20 (1.18-1.28)	Not stated (median about 35 from graph)	102,202 (1,734)	MI: 1995-2007 Cancer: 1995-2007	Lower SIR at older ages. Breast, cervix, uterine and ovarian all high. Lung, prostate, crc, liver low in men. General pop comparison.
		(Lawrence et al., 2000a) (Australia, WA, all MHS users)	Total cancer RR men 1.05 (1.02-1.09) Women 1.02 (0.98-1.05)	Not stated	172,932 (496)	MI: any contact 1966-1995, cancer 1982-1995	General population comparison, follow up from 1982 or first contact if later.
		(Chou et al., 2011) (Taiwan, schizophrenia)	Total cancer Men HR 0.5 (0.46-0.55) Women HR 0.81 (0.74-0.88)	Mean age 41	59,257 (1,145)	MI: Schizophrenia diagnosed prior to end of 1999, Cancer: cancer diagnosis 2000-2008 Cancers prior to the end of 1999 also identified for schizophrenia group only.	Used age and gender matched controls from health insurance database, may have also excluded from control group on basis of prior cancer? Prevalent cohort. Cancers and mi identified from catastrophic illness register) for both groups

Study design (exposure definition)	Potential bias	Relevant studies	Results (age and sex adjusted if available)	Age at mental illness (MI) diagnosis or start of f/u	N exposed cohort (cancers)	Cohort follow up (period over which exposure (mental illness) and outcome (cancer) identified)	comments
		(Grinshpoon et al., 2005) (Israel, schizophrenia)	Total cancer men SIR 0.86 (0.8-0.93) women SIR 0.91 (0.85-0.97)	15-45yrs Mean age 31	26,518 (1,435)	MI: schizophrenia plus hosp admission 1962-2001 cancer: 1962-2001	Significantly raised SIR for breast (women) and lung (men)
		(Osborn et al., 2013) (UK, SMI)	Major cancers SMI adj (age, sex, period, deprivation) IRR 0.98 (0.88-1.09)	Median age 44	20,632 (380)	MI: 1990 (or registration or complete data) - 2008 Cancer: 1990 (and 6 months after registration) - 2008	Comparison cohort from GP database – random sample of patients without SMI Excluded people with cancer diagnosis prior to SMI diagnosis, AND excluded people with cancer recorded in clinical notes at the start of follow up from comparison cohort. No major differences between schizophrenia and bipolar disorder.

Study design (exposure definition)	Potential bias	Relevant studies	Results (age and sex adjusted if available)	Age at mental illness (MI) diagnosis or start of f/u	N exposed cohort (cancers)	Cohort follow up (period over which exposure (mental illness) and outcome (cancer) identified)	comments
		(Lin et al., 2013b) (Taiwan, Schizophrenia, Bipolar)	Schizophrenia All cancers SIR 1.17 (1.08-1.28) Men SIR 1.02 (0.9-1.16) Women SIR 1.31(1.17-1.48) Bipolar All cancers SIR 1.29 (1.11-1.51) Men SIR 1.42 (1.14-1.77) Women SIR 1.17(0.94-1.46)	Schizophrenia Mean age 37 Bipolar Mean age 38.5	Schiz. 71,317 (1,129) Bipolar 20,657 (367)	MI: 1997-2009 Cancer 1995-2009	General pop comparison. Cancer diagnosis information from two different sources: Catastrophic illnesses register for exposed cohort vs cancer registry for general population. Therefore may not be incident cancers in the exposed cohort. SIR >20 in first year of follow up, suggesting cases concentrated at the beginning (prevalent cases?)
A.(2) **Exposed** (group with mi) = **1+3** but not 2 or 4 or 5 (any mi except after cancer, except if cancer in first year after mi diagnosis). **Exclude 4+5** from analyses.	As above, but excludes those with cancer diagnosed in the first year after first mental health service contact to avoid bias due to misdiagnosis of cancers as psychotic illness)	(Dalton et al., 2005) (Denmark, schizophrenia)	All cancer Men SIR 0.85 (0.78-0.93) Women SIR 1.03 (0.96-1.11)	Mean age 38 (men 34, women 42), max age >75	22,766 (1,394)	MI: 1969-1993 Cancer: 1969-1995 (cancers in first year of follow up excluded)	Lower SIR at older ages. Men: tobacco associated cancers and prostate significantly reduced. Women: breast significantly increased. General pop comparison, excludes 3

Study design (exposure definition)	**Potential bias**	**Relevant studies**	**Results (age and sex adjusted if available)**	**Age at mental illness (MI) diagnosis or start of f/u**	**N exposed cohort (cancers)**	**Cohort follow up (period over which exposure (mental illness) and outcome (cancer) identified)**	**comments**
B. **Exposed** group = **1+2+3+4+5** (i.e. any mi before or after cancer)	Have a period of immortal time where cancer incidence is being assessed. Expect to get spurious low rates of cancers which are often fatal, but less difference in cancers which are usually not fatal. This problem will be more marked for people diagnosed with MI at older ages, more marked the longer the look-back period prior to MI. Subject to bias due to reverse causation/ misclassification (2 and 5).	(Whitley et al., 2012) (Sweden, schizophrenia) (method 2) Men	All cancers men HR 1.28 (1.21-1.36)	Mean age 31	65,243 (1,314)	MI: 1969-2004 Cancer: 1969-2004	Men only, young population (only followed up to max age 51), direct comparison.
		(Ji et al., 2013) (Sweden, schizophrenia)	All cancers men SIR 0.63 (0.61-0.66), female SIR 0.94 (0.91-0.97)	Median age men 38, women 47	59,233 (6,137)	MI: 1965-2008 Ca: 1965-2008	SIRs before and after schizophrenia diagnosis presented: SIR all cancer before diagnosis 0.4 (0.38-0.43), after diagnosis 1.00 (0.97-1.03). Some evidence of pre-schizophrenia SIR variation by fatality of cancer
		(Pandiani et al., 2006) (US, SMI)	RR Cancer 2.5 (2.0-3.0) Men 2.6 (2.1-3.1), women 2.4 (1.7-3.1), higher RR for under 50s.	Not stated (37% aged over 50)	3,317 (54)	MI: one year for each year (1994-2001) Cancer: one year for each year (1994-2001)	For each year people with MHS use in that year with or without cancer diagnosis in the same year (presumably before or after). Immortal time therefore only a max of 364 days. Will also have problem of reverse causation (large proportion will be group 5) and misclassification (large proportion in group 2 – of

Study design (exposure definition)	**Potential bias**	**Relevant studies**	**Results (age and sex adjusted if available)**	**Age at mental illness (MI) diagnosis or start of f/u**	**N exposed cohort (cancers)**	**Cohort follow up (period over which exposure (mental illness) and outcome (cancer) identified)**	**comments**
							whom many may be misclassified) which will inflate estimate.
		(BarChana et al., 2008) (Israel, Bipolar)	SIR men 1.59 (1.01-2.17) Women 1.75 (1.31-2.18)	Not stated	2,121 (90)	MI: first admission BPAD 1980-2005 Cancer: 1960?-2005	Person years of exposure for index group: from birth to death/ca diagnosis/end 2005. (unclear if exposed cohort is "index" group)
C. **Exposed time** (time with MI) = **1+2+3**, time after MI diagnosis only. Time prior to MI diagnosis included as unexposed (on basis that there is something about the diagnosis/onset of MI which conveys risk). 4+5 included as unexposed (and then censored at ca diagnosis).	If include time as unexposed then may have misclassification i.e. people may already have mental illness but not yet diagnosed (group 5). Will bias towards the null.	(Whitley et al., 2012) Sweden (method 3)	All cancers HR 1.26 (1.18-1.35)	Mean age 31	65,243 (1,314)	MI: 1969-2004 Cancer: 1969-2004	
		(Dalton et al., 2006) (Denmark, neuroleptic medication use)	All sites SIR 1.15 (1.10-1.21)	Mean age at entry 58.7	25,264 (1,648)	Neuroleptic prescription: 1989-2002 Cancer: 1989-2002	People with prior cancer excluded from exposed and unexposed cohorts at start of follow up. Person time categorised as unexposed prior to neuroleptic prescription and exposed following second prescription.

Study design (exposure definition)	**Potential bias**	**Relevant studies**	**Results (age and sex adjusted if available)**	**Age at mental illness (MI) diagnosis or start of f/u**	**N exposed cohort (cancers)**	**Cohort follow up (period over which exposure (mental illness) and outcome (cancer) identified)**	**comments**
D. **Exposed time** (time with MI) = **1+2+3+4+5**, time after MI diagnosis only. Time prior to mi diagnosis excluded.		(Goldacre et al., 2005) (UK, schizophrenia)	Adj RR (adjusted for gender, age, time period) all cancer 0.99 (0.90-1.08)	Mean age at entry 40	9,649 (486)	MI: 1st admission for schizophrenia 1963-1999 Cancer: 1963-1999	Comparison cohort (identified first admissions to hospital with various medical and surgical conditions). Schizophrenia and other cohort followed up for cancer from first admission, no info on prior cancer.
		(Crump et al., 2013b) (Sweden, schizophrenia)	Adj RR (adj. age) All cancer Men 0.67 (0.59-0.77) Women 1.04 (0.92-1.17)	Max age >75	8,277 (487)	MI: schizophrenia documented 2001-2002 Cancer: 2003-2009	Prevalent cohort. Direct comparison cohort (all people age >=25 who had lived in Sweden for at least 2 years as at 1/1/2003).
		(McGinty et al., 2012) (US, Bipolar)	Total cancer SIR Men 1.5 (0.8-2.6) Women 3.0 (2.3-3.9)	Max age 64	1,002 (155)	MI: 1996-2004 Cancer: 1996-2004	
		(McGinty et al., 2012) (US, Schizophrenia)	Total cancer SIR Men 2.6 (2.0-3.4) Women 2.6 (2.1-3.2)	Max age 64	2,315 (75)	MI: 1996-2004 Cancer: 1996-2004	Cohort with or without schizophrenia identified from Medicaid contacts

Study design (exposure definition)	Potential bias	Relevant studies	Results (age and sex adjusted if available)	Age at mental illness (MI) diagnosis or start of f/u	N exposed cohort (cancers)	Cohort follow up (period over which exposure (mental illness) and outcome (cancer) identified)	comments
		(Kisely et al., 2008) (Canada (Nova Scotia), MHS contact or mental illness diagnosis in primary care)	Total cancer SIR Men 1.21 (1.18-1.24) Women 1.31 (1.27-1.34)	Not stated	247,344 (total cancer not stated, sum of individual cancers reported = 2553)	MI: 1st contact 1995-2001 Cancer: 1995-2001	Follow up from first contact for mental health problems, general population comparison Includes primary care, represents 25% of pop
		(Lichtermann et al., 2001) (Finland, Schizophrenia)	SIR all cancer 1.17 (1.09-1.25)	Not stated	26,996 (724)	MI: 1969-1991 Cancer: 1971-1996	
Unclear as to method used		(Barak et al., 2005) (Israel, Schizophrenia)	SIR all cancer 0.58 (0.48-0.69)	Mean age 49 (age during study not at diagnosis – prevalent cohort)	3326 (120)	MI: 1993-2003 Cancer: 1993-2003	Unclear if any exclusions made for prior cancers

*MI = Mental Illness, MHS = mental health services

3.4.4 Incidence of specific cancers

A number of studies have investigated the incidence of specific cancers in the context of mental illness. Such studies enable disentangling of the impact of the different cancers within the overall incidence of cancer in people with mental illness. Because each cancer has a different aetiology, examining cancers separately allows examination of the possible mechanisms of cancer incidence in this group. Consistent results across cancers could suggest common susceptibility or resistance. Consistent results among studies of *individual* cancers are suggestive of mechanisms specific to that cancer. For example, consistently low prostate cancer incidence rates may be related to less screening amongst those with a history of mental illness, similar to the pattern seen in other disadvantaged groups (Blakely et al., 2010). Consistently high rates of lung cancer are likely to be related to higher smoking rates in people using mental health services (Lawrence et al., 2009). This section reviews the current state of knowledge on the incidence of the more common cancers. Breast, lung, colorectal, and prostate cancers are discussed below.

Where cancers are examined separately, it is possible to adjust estimates of incidence for risk factors for that cancer. For example, lung cancer incidence estimates can be adjusted for smoking rates, or breast cancer incidence for parity or hormone replacement therapy (HRT) use. This adjustment allows exploration of the role of these risk factors in explaining the differences in the incidence of cancer between people with and without mental illness. This can be done either to understand the role of risk factors in mediating differences found (for example, how much of the increased incidence of lung cancer is explained by smoking rates?) or to remove confounding of the estimates of cancer incidence by these risk factors (for example, once confounding by smoking rates has been removed, is there an independent relationship between mental illness and lung cancer?). Adjustment for confounding by risk factors assumes that these risk factors are obscuring the underlying (possibly biological or genetic) relationship between mental illness and cancer. On the other hand, treating such factors as mediators allows exploration of the socially mediated relationship between mental illness and cancer. Depending on how risk factors are treated, the relationship between mental illness and cancer reported as the best

estimate may be the adjusted one (where risk factors are regarded as confounders) or the unadjusted one (where risk factors are regarded as mediators).

Many studies do not have access to information on these risk factors. However, where information is available, some studies of cancer incidence in mental illness present estimates adjusted for these risk factors. Care must therefore be taken in combining studies. In a review of cancer incidence in the context of neurological conditions including schizophrenia, estimates of lung cancer incidence from studies which did and did not adjust for smoking rates were combined (Catalá-López et al., 2014). This makes the overall estimate impossible to interpret.

The effect of adjustment for risk factors can tell us about the role of these factors in explaining differences (whether as confounders or mediators), but mismeasurement can result in false estimates of the impact of the risk factor. For example, studies which adjust for smoking rates in people with mental illness commonly use data from different sources than the source used for estimating cancer incidence (such as health surveys), and commonly use data about contemporary smoking rates to infer information on smoking patterns several decades prior to cancer (Catts et al., 2008). This mismeasurement potential needs to be considered in interpreting the results of adjusted studies.

The evidence for a raised rate of breast cancer in those with experience of severe mental illness is now reasonably consistent (Catts et al., 2008; Kisely et al., 2008). This is likely to be due to important risk factors such as reduced parity and post-menopausal obesity being prevalent amongst those with severe mental disorder. However, some studies have not found a raised risk of breast cancer associated with mental illness (Barak et al., 2008; Mortensen, 1994). A recent systematic review of breast cancer in schizophrenia found variation in breast cancer incidence ratios depending on the age group studied, with higher rates amongst older women with schizophrenia but not younger women (Bushe et al., 2009). This finding may relate to variation in the effect of breast cancer risk factors with age. Obesity reduces breast cancer risk prior to menopause but increases it afterwards (Carmichael and Bates, 2004). The effect of parity on breast cancer risk also varies with age, with nulliparous women having a lower risk of breast cancer than parous women before

age 40, but a higher risk subsequently (Kobayashi et al., 2012). It may also be related to cohort effects, that is, different patterns of risk factors such as parity in women in contact with mental health services in the past compared to recently. In one of the only studies to directly examine the role of reproductive factors, Dalton and colleagues (2006) looked at breast cancer risk in Danish women aged 16-64 with a history of taking antipsychotic medication (compared to women with no history of taking antipsychotics), adjusted for the use of hormone therapy, age at first birth, and number of children. However, this study did not find an increased risk of breast cancer in women on antipsychotic medication compared to other women (and adjustment for reproductive factors did not affect the estimate), and so does not provide evidence about the role of reproductive factors in explaining the higher risk of breast cancer among women with mental illness found in other studies. Another factor implicated in raised breast cancer rates is antipsychotic medications causing elevated prolactin levels, particularly with older anti-psychotics (Bostwick et al., 2009). However, observational studies have not demonstrated the expected differences in breast cancer risk when comparing those treated with typical and atypical antipsychotics, or comparing medications know to raise prolactin levels with those not known to do so (Azoulay et al., 2011).

Studies examining colorectal cancer incidence have in general found no difference in rates of cancer in those with experience of mental illness compared to the general population. A meta-analysis of four studies found a slightly reduced rate of colorectal cancer in those with schizophrenia compared to the general population (SIR 0.84, 95%CI 0.7-1.0) (Catts et al., 2008). Similarly, a recent Taiwanese study found no difference between colorectal cancer risk in those with schizophrenia or bipolar disorder compared to the general population (Lin et al., 2011).

The incidence of lung cancer in those with a mental illness diagnosis, and in particular schizophrenia, tends to be higher than for the general population. For example, a large Danish study found an increased risk of lung cancer associated with both schizophrenia (age adjusted IRR men 1.67, 95%CI 1.42-1.97; women 1.54, 1.31-1.81) and depression (age adjusted IRR men 1.45, 95%CI 1.29-1.62; women 1.67, 1.42-1.97), and this risk increased when adjusted for socioeconomic factors

(Dalton et al., 2008a). Several other recent studies have also found an increased rate of lung cancer associated with mental illness (Lichtermann et al., 2001; McGinty et al., 2012; Grinshpoon et al., 2005). However, other studies have found a low incidence of lung cancer associated with schizophrenia and other mental illness (Gulbinat et al., 1992; Hippisley-Cox et al., 2007).

The results of studies of lung cancer incidence amongst those with schizophrenia have led to suggestions of a protective effect of schizophrenia, either through the nature of the illness or through the nature of drug treatment, because lung cancer rates are thought to be lower than expected given smoking rates (Catts et al., 2008). In their systematic review Catts and colleagues found a standardised lung cancer incidence rate ratio from 4 studies of 1.31 (95%CI 1.01-1.71), but after adjusting for smoking prevalence in those with schizophrenia (using data drawn from sources separate from the original studies) they found that this estimate reduced to 0.69 (no confidence interval reported)(Catts et al., 2008). Adjustment for smoking rates was performed using the method proposed by Mortensen (1994) in a study of cancer in patients first admitted with schizophrenia between 1970 and 1987. This study used recent data (from 1988) on the proportion of people with schizophrenia who smoke compared to the general population, and the relative risk of cancer among smokers compared to non-smokers calculated by Doll and Peto (1981), to calculate the expected number of cancers in people with schizophrenia adjusted for smoking rates. Data from the *end* of the study period on the relative difference in the proportion of smokers among people with schizophrenia compared to the general population was therefore used to estimate the relative difference at the time relevant to lung cancer incidence (several decades prior to lung cancer diagnosis). Similarly, the Catts review (Catts et al., 2008) uses estimates of relative smoking prevalence from between 1984 and 2004 (de Leon and Diaz, 2005) to calculate the expected effect on lung cancer rates of differences in smoking prevalence between people with schizophrenia and the general population, for incident cancers diagnosed as far back as 1960 (Gulbinat et al., 1992).

The review goes on to suggest that their result (an SIR of 0.69 after adjusting for smoking) means that the high incidence of lung cancer found is in fact lower than

would be expected given the high rates of smoking. Such conclusions are problematic, as they assume that accurate information on relative smoking prevalence at the time relevant to lung cancer risk (i.e. several decades before cancer diagnosis) can be estimated from what is known about current rates of smoking in people with schizophrenia relative to the general population. In fact, smoking rates may vary in different ways for those under psychiatric care compared to the way they vary for the rest of the population. In the past, restrictions on behaviour were imposed by institutional care, while more recently being in institutional care has made smoking almost compulsory through the normative practices such as offering cigarettes as rewards for behavioural compliance. Moreover, the smoking epidemic has not evolved in parallel in men and women, or in different ethnic and socioeconomic population groups (Shaw et al., 2005). Therefore it is unreasonable to assume that the epidemic of smoking in people with schizophrenia has evolved in parallel to the general population. It is much more likely that historical smoking rates in people with schizophrenia are overestimated when the current relationship between smoking and schizophrenia (which is around double the rate of smoking in people with schizophrenia compared to the general population (de Leon and Diaz, 2005)) is assumed to have held true in the past. And so, in the absence of accurate historical records, it may be impossible to correctly adjust for smoking in lung cancer estimates, and attempts to adjust are likely to over adjust for differences in smoking rates.

In a review examining prostate cancer incidence amongst those with schizophrenia, Torrey (Torrey, 2006) identified five studies with age-standardized data on prostate cancer incidence, all of which had a lower standardized incidence ratio for prostate cancer, ranging from 0.49 to 0.76. The authors note possible explanations for this lower rate including ascertainment bias, genetic factors, and antipsychotic drug effects (either by being cancer protective or decreasing testosterone). Different rates of prostate cancer are found between socioeconomic groups in New Zealand (and elsewhere) and this is thought to relate principally to differences in screening practices, with wealthier men being more likely to be screened (Blakely et al., 2010). It is likely that men under psychiatric care also undergo less prostate cancer

screening and this (referred to above as ascertainment bias) will affect their relative rates of prostate cancer.

3.4.5 Cancer incidence conclusions

When methodological and other differences between studies are taken into consideration, total cancer incidence in people with experience of mental illness is predominantly found to be similar to cancer incidence in the general population. However, differences in the age distribution, follow-up period and the types of cancers most common in the population, as well as differences in the methods used to identify the population and estimate cancer incidence, will all influence the estimates of combined cancer incidence made. Any estimates of total cancer incidence in the context of severe mental illness must be interpreted with caution and the context carefully examined.

Methodological differences between studies seem to underlie the main differences in study results. Two principal biases seem to be responsible for findings of low incidence of cancer amongst those with a history of mental illness, namely invulnerability bias, where those with prior cancer are excluded from the group with mental illness, and immortality bias, where people have survived long enough (not died of cancer) to come into contact with mental health services. Studies with less vulnerability to these biases produce more consistent findings. Other sources of bias, in particular the impact of reverse causation (cancer leading to mental illness), also need to be considered when interpreting study results.

People with experience of mental illness seem to have a higher incidence of some cancers than the general population, in particular lung and breast cancers, and a lower incidence of other cancers, in particular prostate cancer. However, these results can be explained without recourse to genetic explanations. While there may still be some genetic relationship between schizophrenia and cancer, the current epidemiological evidence does not provide support for this hypothesis.

3.5 CANCER MORTALITY

3.5.1 Overview of cancer mortality findings

Cancer is a common cause of death for people with experience of mental illness, just as it is for the rest of the population (Bushe and Hodgson, 2010). Recent studies comparing rates of death from cancer in people with schizophrenia or other mental illness with general population rates have tended to find higher rates of cancer mortality in those with experience of mental illness (Nordentoft et al., 2013; Tran et al., 2009; Kisely et al., 2013). For example, a recent study from Nova Scotia estimated the increased risk of cancer mortality in people using mental health services compared to the general population at 72% for men and 59% for women (both significant increases) (Kisely et al., 2008). A systematic review of studies of mortality in people with schizophrenia found a mean standardised cancer mortality ratio (SMR) of 1.44 from seven studies, or an average of a 44% higher rate of cancer deaths in people with schizophrenia compared to the general population (Saha et al., 2007).

However, just as with cancer incidence, the results of studies comparing cancer mortality between those with and without a history of mental illness have been mixed. Some studies have found lower than expected cancer mortality in people with mental illness diagnoses (Costa et al., 1981; Cohen et al., 2002). Other studies have found similar rates of death from cancer to those found in the general population (Osborn et al., 2007; Saku et al., 1995; Joukamaa et al., 2001). And, as noted above, recent population based studies have tended to find higher rates of death from cancer (Nordentoft et al., 2013; Tran et al., 2009; Kisely et al., 2013; Kisely et al., 2015; Lawrence et al., 2000a). As with cancer incidence studies, methodological differences between studies, as well as changes over time and place, may be important in understanding the different results found. Particular issues relating to cancer mortality studies also need to be considered, such as the impact of including people with mental illness due to terminal cancer in the population at risk, and the impact of high rates of premature death from other causes.

3.5.2 Measures of cancer mortality

Cancer mortality studies involve estimation of the rate of deaths attributed to cancer in a population with a history of mental illness. This rate is then compared with the rate of deaths attributed to cancer in either the general population, or in a comparison population without mental illness. This ratio of rates is standardised by age and sex to ensure comparability to produce a standardised mortality ratio (SMR). This review focuses on studies which compare standardised cancer mortality rates in people with and without mental illness. However, before considering the results of studies using this measure further, it is important to mention two other measures that have also been used to compare cancer mortality in people with mental illness to cancer mortality in others in the population. It is useful to clarify these measures, as they cannot directly be compared with mortality rate ratios.

The first is proportionate mortality, or the proportion of all deaths in a population in a specific time-period that are due to cancer. Usually proportionate mortality is presented by age and sex to account for differences in the age and sex structure of the populations compared. Where information is available on deaths, but not on the denominator population (the people at risk), then this may be the only measure of cancer mortality available. Older studies of the incidence of cancer in people with schizophrenia tended to use this method, because of the lack of information on the age composition of the total population with schizophrenia (Pool, 1930; Costa et al., 1981; Gulbinat et al., 1992). Proportionate mortality provides information on how important cancer is as a cause of death for people with schizophrenia or other mental illness. However, comparison of proportional mortality rates can be misleading where the *overall* age-specific mortality rates of populations are different. People with schizophrenia and other severe mental illness have high rates of premature mortality from causes such as cardiovascular disease (Laursen et al., 2012), which results in a lower *proportion* of deaths being due to other causes such as cancer, even if the *rate* of death from cancer at a certain age is the same as for others in the population. Therefore, studies that have used proportionate mortality to compare people with and without mental illness will give misleadingly low estimates of the incidence of cancer.

A second measure used to assess cancer mortality in people with mental illness is cancer patient mortality (for example (Kisely et al., 2015)), which involves estimating the death rate in a population with cancer. Because some people with cancer will die from other causes, the rate of deaths in people known to have developed cancer over a year will not be the same as the rate of deaths from cancer in the population over a year. Moreover, the time between cancer diagnosis and death may be many years or even decades, and so the estimate of the annual death rate in a population with cancer will depend on the length of follow up time included. Cancer patient mortality can also be referred to as the cancer case-fatality rate. This measure is therefore more usefully considered with cancer survival, as unlike cancer mortality measured in the population, it is not influenced by differences in cancer incidence.

3.5.3 Interpreting cancer mortality findings

The majority of recent studies have found that mental illness is associated with an increase in standardised cancer mortality for all cancers combined. Mortality rates have been found to be raised in people with mental illness across different types of cancer and amongst both men and women (Kisely et al., 2008; Lawrence et al., 2000b). Cancer mortality rates have also been found to be raised in people with different psychiatric diagnoses including schizophrenia, affective disorders, and substance use disorders (Nordentoft et al., 2013; Lawrence et al., 2000b).

A finding of high cancer mortality in a population could be due to increased incidence of cancer, worse survival after cancer diagnosis, or both. Studies that examine cancer incidence and cancer mortality in the same population allow direct comparison. Studies from Australia and Canada have directly compared cancer incidence and cancer mortality in people in contact with mental health services, and found that relative cancer mortality is uniformly higher than relative cancer incidence (Kisely et al., 2013; Lawrence et al., 2000a; Kisely et al., 2008), indicating lower cancer survival (in the absence of a change in incidence over time).

However, interpretation of the results of studies examining mortality due to cancer in a population with mental illness requires considerable care. Mortality from cancer

will be influenced by competing causes of death, where high rates of other illness (historically infectious diseases, more recently diabetes and cardiovascular disease), and higher rates of suicide, mean that death rates from cancer may seem low because of high rates of premature death from other causes (Guan et al., 2012).

The choice of the denominator or population at risk is also important. Where all those in contact with mental health services are included in the population at risk, people who have come into contact with mental health services because of mental illness brought on by a cancer diagnosis will be included. This group will have a higher risk of dying from cancer than others in contact with mental health services, and so their inclusion will bias the results. Studies that focus on people with schizophrenia or bipolar disorder or other long term conditions will be less prone to such bias, as such conditions are not likely to be precipitated by a cancer diagnosis (although they may be exacerbated).

Unlike mortality studies, studies of cancer survival allow direct assessment of the impact of a history of mental illness on the risk of dying from cancer. It is possible to exclude people who only had contact with mental health services after cancer diagnosis, and to investigate the impact of using methods designed to account for competing causes of death. It is also possible to investigate the factors that may be leading to worse outcomes from cancer.

3.5.4 Cancer mortality conclusions

Cancer mortality has been found to be increased in people with a history of mental illness compared to the general population in many recent studies. Cancer mortality has also been found to be relatively higher than cancer incidence in this group, suggesting survival differences. Standardised cancer mortality rates are useful for understanding how relatively common death from cancer is amongst people using mental health services or people who have been diagnosed with particular psychiatric conditions. However, direct assessment of cancer survival is required in order to explore the factors that influence cancer outcomes in people with mental illness.

3.6 CANCER SURVIVAL

3.6.1 Cancer survival comparisons

A small number of studies have looked specifically at cancer survival in the context of mental illness, and their findings suggest that people with mental illness may have worse outcomes after diagnosis with cancer than those without mental illness. While, in general, the populations of developed countries such as New Zealand have benefited from improved treatment and increased survival from cancer over recent decades, this benefit has not been evenly distributed. In New Zealand there is evidence of ethnic and socioeconomic disparities in cancer survival for many cancers (Hill et al., 2010; Soeberg et al., 2015). The burden of mental illness is distributed unevenly, with a higher burden on those living in deprived situations and those of minority ethnicities, and so the cancer survival disparities seen in people with mental illness may be in part related to ethnic and socioeconomic factors. Those with mental illness and cancer may also fare worse because of factors related to mental illness such as higher rates of comorbid illness or discrimination in health care settings.

Table 3 sets out the results of studies examining cancer case-fatality or survival, comparing people with prior mental illness to those without. The oldest of these studies dates back to 2000. I was not able to find any prior studies that explicitly examined cancer survival in people with mental illness compared to people without a history of mental illness. There have, however, been many more studies of this type in the past five years, thanks to the increasing availability of population level linked routine databases which allow this kind of investigation, and perhaps also to an increasing recognition of the utility of this type of study.

Each study reported worse survival in people with prior mental illness compared to those without such a history, although in one study the difference did not reach statistical significance (O'Rourke et al., 2008). Findings have been consistent despite differences in the mental illness examined, the cancer examined, the age of the cohorts, the health system context, and the time between mental illness diagnosis and cancer. However, there were considerable differences in the estimated effect sizes. Some studies found only a slight survival disadvantage associated with mental

illness, while others found large survival differences. For example, in a study of survival after diagnosis with non-small cell lung cancer in the US Medicare system, people with schizophrenia had a 7% survival disadvantage compared to those without, after adjusting for sociodemographic factors, comorbidity and stage [all cause HR 1.07 (95% CI 1.01-1.13)] (Bergamo et al., 2014). In contrast, a recent Australian study found that the risk of death after cancer diagnosis is more than doubled in people with a history of mental health service use [all cause HR 2.27 (2.39-2.51)] (Kisely et al., 2015). This difference between lung and colorectal cancers may relate to the relative prognosis of each cancer, with other studies of the impact of comorbidity on cancer survival suggesting that the relative impact of comorbid conditions is less in cancers with worse prognosis (such as lung cancer) (Sarfati et al., 2014a). The majority of studies have estimated that mental illness is associated with a 20-40% survival disadvantage. These estimates have been adjusted for various potential confounding and mediating factors, which are discussed further below. Where possible, this section focuses on estimates adjusted for demographic confounders, to allow comparison between studies.

All the studies identified used mental illness diagnosis prior to cancer diagnosis to define the population at risk. Batty and colleagues (Batty et al., 2012b) also investigate the inclusion of psychiatric hospitalisation after cancer diagnosis, on the basis that not including these events in order to avoid cases of reverse causation (mental illness caused by cancer) may be overly conservative (Whitley et al., 2012). However, the inclusion of events post diagnosis (mental health events which occur during the follow up time) will result in bias, as the participants have to survive long enough post cancer diagnosis to use mental health services (immortality bias). This is a particular problem when the outcome is survival time. It is therefore unsurprising that the inclusion of these individuals in the psychiatric hospitalisation group resulted in a lower estimate of the hazard of dying from cancer for people with psychiatric hospitalisation compared to those without such a history (HR 1.30), than the result obtained by excluding this group (HR 1.59).

Time between mental illness diagnosis and cancer diagnosis varies considerably between studies. A short period between mental illness diagnosis and cancer

diagnosis can mean that people with mental illness due to cancer are included in the mental illness cohort. One study excluded people with depression diagnosis in the three months prior to cancer diagnosis, in order to exclude those who may have had depression secondary to cancer (given the possibility of pancreatic cancer presenting with symptoms of depression, and the difficulty in diagnosing pancreatic cancer) (Boyd et al., 2012). This study found a slight survival disadvantage associated with a history of prior depression, more pronounced in those with less advanced disease (HR 1.20 for loco regional disease, and HR 1.08 for distant disease). Three of the identified studies (Kisely et al., 2013; Dalton et al., 2007; Lawrence et al., 2000a) included people with a long history of mental illness, diagnosed up to 30 years prior to cancer diagnosis. Inclusion of people with a long prior history of mental illness will minimise the proportion of cancers that were diagnosed immediately after first mental illness diagnosis, minimising the potential for misclassification of the exposure. Other studies have only included people with mental illness documented in the period immediately prior to cancer diagnosis (Baillargeon et al., 2011; Goodwin et al., 2004), or recorded simultaneously (Chang et al., 2013). This appears to be mainly due to data availability rather than a deliberate restriction. However, it has the effect of increasing the proportion that may have cancer misdiagnosed as a mental illness. This group may have better survival than others with long-standing mental illness, or worse survival where psychiatric symptoms are a sign of advanced disease. Therefore, it is difficult to predict the effect of this bias on cancer survival estimates.

On the other hand, a long period between mental illness diagnosis and cancer diagnosis will mean that the people included in the group with mental illness may not have any symptoms of mental illness at the time of cancer diagnosis. This may mean that the effect of mental illness on cancer survival is underestimated, if the impact of mental illness on cancer survival is related to active symptoms of mental illness (such as symptoms of mental illness impacting on treatment receipt). However, other mechanisms by which mental illness impacts on cancer survival, such as socioeconomic status or the stigma of mental illness, may be less related to the symptoms of mental illness. Studies including people with a long history of mental illness have estimated the survival disadvantage associated with mental

illness at the lower end of the studies examined (see Table 3), which may reflect the inclusion of people who no longer have symptoms of mental illness. For example, one study of people with mental health service contact up to 19 years prior estimated the hazard ratio for all-cause mortality at 1.41 and the cancer-specific hazard ratio at 1.2 (Kisely et al., 2013). A mid-length period between mental illness diagnosis and cancer diagnosis would balance these two opposing problems.

Another important difference between studies is the definition of mental illness used. While some studies have focused on particular diagnoses, such as schizophrenia or depression, others have focused on having any recorded psychiatric diagnosis, or on contact with primary or secondary mental health services. Where studies have focused on more severe mental illness, such as schizophrenia, or on people using secondary mental health services, the proportion of the cancer cohort who are identified as having mental illness is generally very low. For example, in a study of cancer survival in South London, England, 7.7% of people with cancer diagnoses had a history of contact with mental health services, and 0.4% had a diagnosis of schizophrenia or bipolar disorder (Chang et al., 2014). In a study of oral cancer survival in Taiwan, 1.2% of those with oral cancer had a major mental illness deemed current at the time of cancer diagnosis (Chang et al., 2013). However, when people with common mental disorders are included, the proportion of those with cancer diagnoses can be much greater. For example, in a study from the United States of colon cancer survival in older people, 25.7% had a diagnosis of any mental disorder in the two years prior to colon cancer diagnosis (Baillargeon et al., 2011). Where a large proportion of the population is defined as having a mental disorder, then the likelihood of finding a difference between that group and those without such a history is much lower than when those with mental illness as defined only make up a few percent of the population with cancer examined. This is because the groups with and without mental illness are likely to be more similar when a greater proportion of the total population are defined as having a mental illness.

The health care setting will also influence study findings. Four studies linking United States cancer registration (SEER) data and Medicare claims have looked at survival from specific cancers (breast, lung, colorectal and pancreatic cancers), comparing

older adults with mental illness with those without (Boyd et al., 2012; Goodwin et al., 2004; Baillargeon et al., 2011; Bergamo et al., 2014). Two of these studies focused on depression, a third on schizophrenia, and the fourth looked at all mental illness diagnoses including dementia, as documented in medical records. These studies focus on people aged over 67, and may not be generalizable to people of younger ages. Studies in the Medicare setting resulted in some of the lowest estimates of differences in cancer survival when comparing those with and without mental illness (see Table 3). Medicare provides relatively comprehensive care, and so people with mental illness may do better there than in other health service settings in the United States. Studies in other health care settings and at younger ages are therefore important.

Several studies have considered cancer survival in people with mental illness in the context of universal free health care, and found survival disparities. A study in the context of the UK's National Health Service found that people with schizophrenia or bipolar disorder were 70% more likely to die following a cancer diagnosis, compared to people without any history of contact with mental health services (Chang et al., 2014). Similarly, studies in Scandinavian settings with universal free health care have also found survival disparities associated with a history of mental health problems (Batty et al., 2012b; Dalton et al., 2008b). Studies have also been conducted in Taiwan (Chang et al., 2013) and Australia (Kisely et al., 2013), both countries with near universal national health insurance systems, and in particular parts of the United States medical system where comprehensive care is provided by the state (namely Medicare and Veterans Affairs). I was not able to find any studies that examine cancer survival in people with mental illness who were not eligible for predominantly free health care. This may be because, without systems of comprehensive health care coverage, information on mental illness and cancer diagnoses at a population level is not available. For example, no comparative population based studies were found which included people with limited access to health care. Such a study might find far greater disparities in survival than the current studies.

3.6.2 Reasons for cancer survival disparities explored in the survival studies

Just as there are many factors influencing worse physical health in people with mental illness, there are a number of possible pathways to apparently worse cancer survival.

- **Confounding:** Differences in factors such as the age, sex, and ethnicity of those with experience of mental illness compared to those without may explain some differences seen in cancer survival.
- **Comorbidity:** The higher burden of physical illnesses such as diabetes, heart disease, and liver disease among those with mental illness compared to those without may influence survival both directly and through the likelihood of being offered and the ability to tolerate cancer treatments. This burden of physical illness is referred to as physical comorbidity (or simply as comorbidity).
- **Stage at diagnosis:** People with mental illness may be less likely to access primary care services, or their mental illness may overshadow their cancer symptoms when they do, resulting in cancers being diagnosed later with worse prognosis. People with mental illness may also be less likely to access cancer screening.
- **Treatment:** Health care quality, or the likelihood of receiving appropriate and timely treatment once diagnosed, may influence subsequent survival.

This section examines the role of these pathways, as explored in the survival studies set out in Table 3. The following section (3.7) examines these pathways in more detail, including the relevant literature beyond these survival studies.

There has been little examination of these possible pathways in the literature on cancer survival in the context of mental illness. However, in order to address differences in outcomes, it is important to understand the reasons for the differences seen. In epidemiological modelling, adjusting for these factors as confounders or

mediators allows an estimation of the degree to which these factors contribute to the differences found.

Table 3 shows the factors that the existing studies of cancer survival were able to adjust for in the right hand columns. All the studies adjusted for confounding by age, and by gender where the study is not restricted to one gender. Some of the studies also adjusted for additional confounding factors such as ethnicity and type of cancer (where multiple cancers were examined together), year of diagnosis and region. There was evidence of confounding particularly by demographic variables in many of the studies, although raw estimates were not always provided to allow for estimation of the degree of confounding. Socioeconomic factors such as income, marital status, and deprivation level were also treated as confounders in a number of analyses.

Cancer stage at diagnosis, comorbidity, and treatment, have also been examined in some of these studies. For the most part, the studies treat these factors as confounders of the relationship of interest between mental illness and cancer survival. However, factors such as the stage at which cancers are diagnosed and the treatment received may be important reasons for survival disparities seen. They may also be amenable to intervention. In order to design and prioritise interventions to reduce survival disparities, it is important to understand the contribution of individual factors to survival disparities. Therefore, it is useful to assess the independent effect of each pathway. The following paragraphs discuss the available information from survival studies. The following section 3.7 further explores the role of these factors and others in understanding survival disparities for this group.

Only one study adjusted separately for stage at diagnosis to examine its independent effect, and did not find that stage distribution made a significant contribution to survival disparities (Chang et al., 2014). Several other studies have examined the distribution of stage at diagnosis. One study found that people with depression were 13% more likely to present with distant or unstaged pancreatic cancer than those without a history of depression in the US Medicare population (Boyd et al., 2012). On the other hand, another study in the Medicare population found that a history of schizophrenia was associated with being more likely to present with early stage lung

cancer (Bergamo et al., 2014). Stage data were often limited (for example, limited to the presence of metastases or not (Kisely et al., 2013)) or substantially missing (for example, (Chang et al., 2014)), which may result in the underestimation of the effect of stage. The association between cancer stage and presence of mental illness may vary by cancer. Stage discrepancies may be more, or less, pronounced in cancers that are commonly diagnosed by screening, compared to cancers that are diagnosed in other clinical settings. Studies with good stage information, and powered to look at individual cancers rather than cancer as a combined entity, are therefore needed. From the existing studies, stage at diagnosis does not appear to be a major contributor to survival disparities.

Comorbidity is also important in understanding cancer survival disparities. The association between mental illness, particularly severe mental illness, and a high burden of comorbid physical illness, is well established (De Hert et al., 2011b; Scott and Happell, 2011; Woodhead et al., 2014). Studies of cancer survival differences between ethnic and socioeconomic groups suggest that the burden of comorbid conditions can be an important contributor to survival inequalities (Hill et al., 2010; West et al., 1996; Byers et al., 2008). None of the studies of cancer survival in the context of mental illness assessed the independent effect of comorbidity in explaining cancer survival inequalities in this context. Nevertheless, a number of the survival studies did adjust for the presence of comorbid physical illness at the time of cancer diagnosis as a confounder of the relationship between mental illness and cancer survival, along with other sociodemographic confounders (Batty et al., 2012b; Baillargeon et al., 2011). Survival disparities remained after adjusting for comorbidity together with other factors, suggesting that comorbidity is not the only factor explaining survival disparities. For example, a study of cancer survival in Swedish men with a history of psychiatric admissions estimated a 60% increased cancer-specific hazard of death in these men compared to men without a history of psychiatric admissions, after adjusting for differences in age, socioeconomic status, educational attainment, body mass index and comorbidities (Batty et al., 2012b).

Cancer treatment also contributes to cancer survival and cancer survival inequalities. Three studies of cancer survival in the context of mental illness assessed the

independent contribution of survival differences to cancer survival disparities, and found that treatment differences made a contribution to survival differences (Chang et al., 2013; Boyd et al., 2012; Bergamo et al., 2014). A study from Taiwan found that some of the disparity in survival after diagnosis with oral cancer in people with a diagnosis of "major mental illness" was explained by treatment differences: adjustment for treatment differences reduced the hazard ratio for death from 1.83 (95%CI 1.50-2.23) to 1.58 (1.30-1.93) (Chang et al., 2013). A study of pancreatic cancer survival in the US Medicare population found that approximately 27% of the association between depression and 2-year mortality after pancreatic cancer diagnosis was mediated by surgical resection (Boyd et al., 2012). Another Medicare study found that differences in treatment for lung cancer in patients with a history of schizophrenia reduced the increased hazard of death associated with schizophrenia from 1.07 (95%CI 1.01-1.13) to 1.02 (0.96-1.09) (Bergamo et al., 2014). A study of women with breast cancer treated as per protocol in Denmark, examined treatment type (Dalton et al., 2007). Women with depression or schizophrenia had a higher hazard of death than women without such a history after adjustment for multiple factors including treatment type. Overall, treatment differences appear to contribute to survival differences, but adjusting for treatment differences does not completely account for survival disparities.

In order to assess and compare the contribution of different factors to cancer survival disparities, it is important to examine systematically the possible factors and the evidence for their relationship with both mental illness and cancer survival. The next section discusses other literature that examines the association between these factors and mental illness, and at other types of research investigating the reasons for survival disparities.

3.6.3 Cancer survival conclusions

There is a small but growing evidence base suggesting that a history of mental illness is associated with worse outcomes after cancer diagnosis. Thirteen studies of cancer survival in people with prior mental illness were identified from the literature. These range across a variety of cancers, health service settings, and types of mental illness. Almost all found that a history of mental illness was associated with worse survival from cancer, after adjusting for demographic differences between those with and without mental illness. Those studies that did not find a significant difference were none the less suggestive of worse outcomes for those with mental illness.

Factors contributing to survival differences include differences in the stage at which cancers are diagnosed, the burden of comorbid physical illness associated with mental illness, and differences in treatment receipt. The existing literature provides limited and sometimes conflicting information about the importance of these factors in explaining survival differences associated with mental illness. A more thorough investigation of the role of each of these factors in survival disparities is needed.

Table 3 Studies of the impact of prior mental illness (MI) on cancer survival

Author, year	**Country**	**Cancer**	**Mental illness**	**N cancer (N mental illness)**	**Time between MI and cancer**	**Survival** (no mental illness = reference group)	**Model adjusted for**	**Additional models**	**Comments**
(Kisely et al., 2015)	Australia (Queensland)	All cancers	Mental Health Service (MHS) use	89,992 (3349)	0-5 years	All cause Hazard Ratio (HR) any MHS use: 2.27 [2.15-2.39] schizophrenia: 2.02 [1.61-2.53] Depression: 1.92 [1.59-2.31]	Age, sex, rurality, deprivation		
(Bergamo et al., 2014)	US (Medicare, national)	Non-small cell lung cancer	schizophrenia	96,702 (1,303)	Any prior record of schizophrenia (time frame not given)	All cause HR 1.07 (1.01-1.13)	Age, sex, marital status, ethnicity, income, comorbidity, stage	Additionally adjusted for stage appropriate treatment: HR 1.02 (0.96-1.09)	Limited to people over 66
(Chang et al., 2014)	UK (South London)	All cancers combined	MHS use + specific diagnosis	28,477 (2,206; 507 with specific diagnoses included in main analyses)	Any prior record of contact with mental health services, most 0-2 years prior	All cause HR SMI: 1.71 (1.44-2.06) Depression: 1.27 (1.07-1.49)	Age, sex, type of cancer, year of diagnosis, primary care trust, ethnicity, deprivation	Additionally adjusted for stage: SMI: 1.74 (1.44-2.10) Depression: 1.30 (1.11-1.54)	35% with missing stage excluded
(Kisely et al., 2013)	Australia (WA)	All cancers combined	MHS use	135,442 (6,568)	0-19 years	All cause HR 1.41 (1.36-1.46) Ca specific 1.2 (1.15-1.26)	Age, sex , deprivation, metastases at diagnosis	nil	

Author, year	**Country**	**Cancer**	**Mental illness**	**N cancer (N mental illness)**	**Time between MI and cancer**	**Survival** (no mental illness = reference group)	**Model adjusted for**	**Additional models**	**Comments**
(Chang et al., 2013)	Taiwan	Oral	MI diagnosis recorded at admission for cancer	16,687 (206)	simultaneous	All cause HR 1.83 (1.50-2.33)	Age, sex, region, urban/rural, deprivation, hospital characteristics, comorbidity	Additionally adjusted for treatment: HR 1.58 (1.30-1.93)	Age range <40 to >70
(Boyd et al., 2012)	US (Medicare)	Pancreatic	Depression recorded in notes 3-27 months prior to ca diagnosis	23,745 (1,868)	3-27 months	All cause Loco regional 1.20 (1.09-1.32) Distant 1.08 (1.01-1.14)	Age, sex, ethnicity, marital status, comorbidity,	Additionally adjusted for definitive treatment Loco regional: HR 1.14 (1.04-1.26) Distant 1.03 (0.97-1.09)	Limited to people over 67
(Batty et al., 2012a)	Sweden (national)	All cancers	Psychiatric admission prior to cancer diagnosis (main analysis)	16498 (941)	Not stated	Cancer specific HR 1.59 (1.39-1.83)	Age, deprivation, education, BMI, comorbidities	When age not included in model HR 2.13 (1.86-2.44)	Men only, including cancers which pre-dated admissions HR 1.30 (95%CI 1.15-1.47)
(Baillargeon et al., 2011)	US (Medicare)	Colon cancer	Any mental disorder diagnosis documented in 2 years prior	80,670 (20,699)	0-2 years	All cause HR 1.44, (1.41–1.47) Cancer specific HR 1.23 (1.19–1.27)	Age, sex, ethnicity, income, year of diagnosis, SEER region,	Additional adjusted for comorbidity, stage All cause HR 1.33, (1.31–1.36) Cancer specific HR 1.23 (1.19–1.27)	Limited to people over 67, highest HR for dementia and psychotic disorder

Author, year	**Country**	**Cancer**	**Mental illness**	**N cancer (N mental illness)**	**Time between MI and cancer**	**Survival** (no mental illness = reference group)	**Model adjusted for**	**Additional models**	**Comments**
(Chou et al., 2011)	Taiwan	All cancers	schizophrenia	5294 (1145)	0-9 years	All cause HR 1.36 (1.24-1.50)	Age, sex, urbanicity, comorbidity, income	nil	Max 9 years f/u
(O'Rourke et al., 2008)	US (VA, single hospital)	Oesophageal	DSMIV diagnosis recorded in notes, specific diagnoses examined incl. dementia	160 (52) (dementia n=7)	Not stated	5yr all cause survival not significantly different psychiatric illness vs none (25% vs 29.6% (p=0.5)); Dementia HR 2.98 (1.35-6.60)	Age, cancer type	Diagnosis delay, advanced stage, treatment Results?	VA population, 98% male, 98% white. Small numbers
(Dalton et al., 2007)	Denmark (national)	Breast (protocol treated)	Mental health service contact with diagnosis of depression or schizophrenia	25,897 (3% with depression, 1% with schizophrenia)	Over 65 years	Cancer specific HR Depression: 1.12(0.96-1.31) Schizophrenia: 1.20 (0.94-1.52)	Age, tumour factors, multiple measures of deprivation, comorbidity, treatment type	All cause HR Depression: 1.19 (1.06-1.32) Schizophrenia: 1.43 (1.21-1.70)	Restricted to women with treatable (not disseminated or inoperable) disease, treated as per protocol, women aged up to 70
(Goodwin et al., 2004)	US (Medicare)	Breast	Depression	24,696 (1,841)		Cancer-specific HR 1.42 (1.13-1.79)	Age, ethnicity, comorbidity, marital status, no. Dr visits, stage, SEER site	Restricted to women receiving definitive treatment HR 1.46 (1.05-2.03)	

Author, year	**Country**	**Cancer**	**Mental illness**	**N cancer (N mental illness)**	**Time between MI and cancer**	**Survival** (no mental illness = reference group)	**Model adjusted for**	**Additional models**	**Comments**
(Lawrence et al., 2000a)	Australia	All cancers, specific cancers	Contact with psychiatric services prior to cancer diagnosis	80,325 (6,442)	0 to 29 years prior	Case fatality ratio men: 1.25 (1.15-1.35) Women: 1.19 (1.10-1.29)	Demographic factors	Sig raised CFR for breast and ovarian cancers and malignant melanoma in men, for depression, alcohol and drug, and schizophrenia in women	

3.7 PATHWAYS FROM MENTAL ILLNESS TO CANCER OUTCOMES

While there has been limited exploration of reasons for the poor cancer outcomes associated with a history of mental illness, it is possible to build up a theoretical model of pathways from the available literature. It is important to identify and investigate mechanisms because it is by understanding why and how disparities occur that it is possible to address them.

Cancer survival disparities between ethnic and socioeconomic groups have been demonstrated in numerous locations including New Zealand. Work on understanding these disparities has shown that differences in stage at cancer diagnosis partly explain disparities between groups, and that other factors relating to the individual, the cancer itself and to its management are also important. Given the similarities in findings across different axes of disadvantage, it is likely that similar mechanisms are involved in the disparity seen between people with mental illness and others in the population.

Figure 4 shows a diagram of possible causal pathways linking mental illness to cancer survival. This section draws together evidence to support this model, and to nominate the pathways that are likely to be most important for further investigation.

The principal pathways identified are:

- Access to primary care and screening for timely cancer diagnosis
- Detrimental health behaviours, medication and the burden of comorbid conditions
- Access to and receipt of timely and appropriate cancer treatment
- Prior social causes, including the impact of social deprivation and stigma, acting across all these pathways

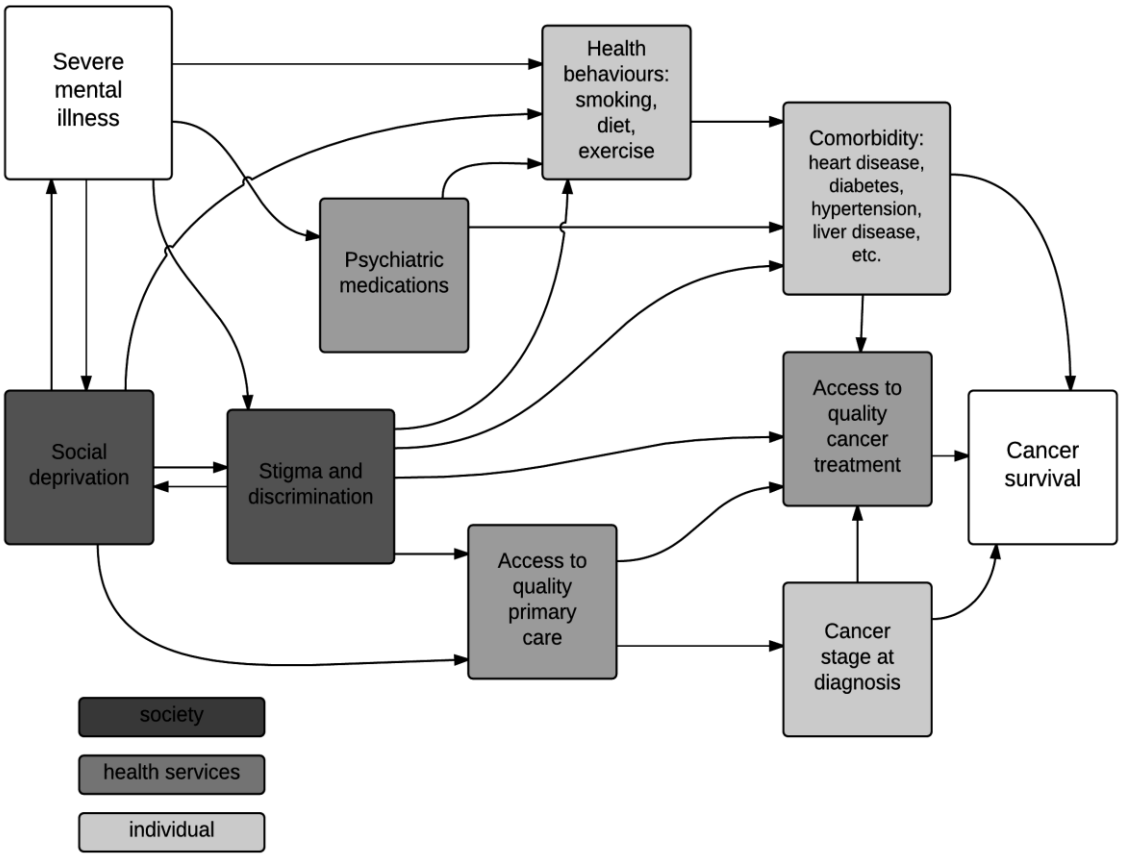

Figure 4 Pathways linking severe mental illness to cancer survival

3.7.1 Primary care and stage at diagnosis

While few studies have been able to examine the role of cancer stage at diagnosis in cancer survival disparities associated with mental illness, a wider group of studies have compared stage at cancer diagnosis between people with experience of mental illness and those without (Table 4). The majority of these studies have found no substantial difference in stage at diagnosis between people with a history of mental illness and others (Chang et al., 2014; Wadia et al., 2015; Goodwin et al., 2004; Kisely et al., 2013). Among those that have found a difference, some found mental illness associated with earlier diagnosis (Bergamo et al., 2014; Koroukian et al., 2015) while others found it associated with later diagnosis (Boyd et al., 2012; O'Rourke et al., 2008).

The literature on the impact of comorbid illness of any type on cancer diagnosis is informative when trying to interpret these apparently conflicting findings. Fleming (2005) describes two distinct relationships between comorbid illness and cancer

diagnosis: that of diagnostic overshadowing, whereby a comorbid condition obscures the cancer and results in later diagnosis, and surveillance, whereby the comorbid condition brings the individual into regular contact with health services resulting in more testing and vigilance and earlier diagnosis of cancer. While these ideas have generally been applied to chronic physical conditions such as diabetes, they apply equally to thinking about mental illness. A more severe comorbid condition may be more likely to overshadow, while a less severe one may result in more surveillance. Some cancers picked up by screening or observable clinical signs may be more amenable to surveillance, while cancers that are more insidious may be more easily overshadowed. The structure of the health system may also lend itself more readily to one than the other. For example, incentivised annual physical health checks may result in earlier cancer diagnosis, while a system driven entirely by presenting complaints may be more susceptible to overshadowing. Therefore, it is important to examine stage at diagnosis in different health system contexts, and within these contexts to compare different cancers and different severities of mental illness. If late cancer diagnosis is an important driver of poor cancer survival in people with mental illness, this will be important for targeting intervention.

The stage at which cancer is diagnosed is related to access to primary health care. There is some evidence of problems with access to primary care for people with severe mental illness, although this varies by health service setting. For example, work from the United States suggests that people with psychotic and major affective disorders are less likely to have a primary care physician and report more barriers to accessing primary care than others in the population (Bradford et al., 2008). A recent Dutch study found that people using mental health services were receiving inadequate primary care (van Hasselt et al., 2013). In contrast, work from Australia suggests that more than 80% of people with psychosis diagnoses are in regular (at least annual) contact with a general practitioner (Jablensky et al., 2000). Another Australian study found that people using mental health services are more likely to see a GP than those not using services (adjusted RR 1.62) across all diagnoses, although those who were also homeless had a very low rate of GP visits (adjusted RR 0.06) (Mai et al., 2010). Barriers to accessing physical health care identified by people with experience of mental illness include cost, difficulties navigating the

health system, the interpersonal and communication skills of providers, and not being taken seriously by providers(Chadwick et al., 2012). Delays in help seeking for cancer symptoms among those with mental illness have also been implicated in late diagnosis (O'Rourke et al., 2008; Inagaki et al., 2006; Nosarti et al., 2000).

Other work suggests that, even where primary care is accessed, the quality of primary care received by those with experience of mental illness is likely to be lower. For example, work from Australia and Sweden has found that potentially preventable hospitalisations are higher amongst people who have previously used mental health services (Mai et al., 2011) (Bjorkenstam et al., 2012). The problem of diagnostic overshadowing, or missed and incorrect diagnoses for physical health problems experienced by people with mental illness, is another quality of care issue which will impact on the stage at which cancer is diagnosed (Jones et al., 2008; Shefer et al., 2014). More generally, there is substantial evidence that severe mental illness is associated with lower quality physical health care (Lawrence and Kisely, 2010; Mitchell et al., 2009).

Three recent reviews have examined the evidence for cancer screening receipt among people with experience of mental illness (Lord et al., 2010; Mitchell et al., 2014; Aggarwal et al., 2013). All have concluded that there is substantial evidence that women with a history of mental illness (particularly severe mental illness) are less likely to receive breast and cervical screening (the focus of two of the reviews), with the evidence less clear for screening for other cancers. However, the results of individual studies have been mixed. In their 2010 review of cancer diagnosis in those with severe mental illness, Howard and colleagues (Howard et al., 2010) identified 12 studies that examined uptake of cancer screening by people with mental illness. The studies varied in quality, with more than half being small or unrepresentative. The studies examined different cancers (breast, colorectal, cervical and prostate) and a variety of types and severity of mental illness. Six found that those with a history of mental illness were less likely to be screened, while six found no difference between those with and without mental illness. The authors suggest this divergence in findings may be due to differences in disease severity between the “mental illness” groups in different studies, with those studies including more people with

psychosis or severe illness being more likely to find a difference in screening rates. They conclude that the balance of evidence suggests that those with severe mental illness are less likely than other groups to receive screening for a variety of cancers. This suggestion of lower screening rates for those with severe mental illness, but similar or higher rates for those with milder mental illness, fits with the hypotheses of overshadowing in severe mental illness and surveillance in less severe mental illness.

3.7.2 Comorbidity

Comorbidity, or the presence of other health conditions at the time of cancer diagnosis, is also an important predictor of cancer survival. As noted above, comorbid illness can influence the stage at which cancer is diagnosed, through overshadowing the cancer or through increasing surveillance for other health problems. Independent of this effect on stage, comorbid physical health conditions can also influence cancer survival, either directly, through the life shortening impact of the other condition, or through the influence of comorbid conditions on cancer treatment receipt. As noted previously, comorbid physical health conditions are known to be an important factor in cancer survival inequalities on ethnic and socioeconomic axes. For example, comorbid physical illness is an important driver of cancer survival disparities amongst Māori in New Zealand (Hill et al., 2010). Therefore, it is important to consider the role of comorbidity in exploring other cancer survival disparities.

There is a large literature on the relationship between mental illness and comorbid physical health conditions other than cancer. For example, mental illness is associated with an increased risk of cardiovascular disease, related to the effects of psychiatric medications and health behaviours in people with mental illness, as well as the quality of cardiovascular risk management in this population (De Hert et al., 2012; Newcomer and Hennekens, 2007; De Hert et al., 2011a). Similarly, a higher burden of obesity, diabetes, and chronic lung conditions associated with smoking is also found in people with a history of mental illness, particularly severe mental illness (Leucht et al., 2007; Blanchard, 2014). There is also evidence linking a higher

burden of these conditions to common mental disorders such as depression (Aragones et al., 2007; Whooley and Wong, 2013).

The presence of comorbid illness at the time of cancer diagnosis is associated with being less likely to receive curative treatment for cancer. A recent systematic review of the impact of comorbidity on cancer survival found that multiple studies of patients with colorectal, breast and lung cancers have demonstrated that the likelihood of surgical management for cancer steadily declines with presence of increasing comorbidity, regardless of the cancer site or the stage at which cancer was been diagnosed (Sogaard et al., 2013). The same review found that people with comorbid illnesses were also less likely to receive adjuvant chemotherapy, more likely to receive reduced doses of chemotherapy and less likely to complete courses of chemotherapy (Sogaard et al., 2013). In New Zealand, a study of colon cancer patients found that a level of high comorbidity was associated with being less likely to be offered chemotherapy among patients with stage III colon cancer (19% of those with a Charlson Score of ≥3 compared with 84% of those with a score of 0 were offered treatment) (Sarfati et al., 2009).

The reasons for being less likely to receive curative treatment are not entirely clear. Clinician concern over toxicity of treatment, patient preferences, lower quality of clinical cancer, and poor adherence to treatment have all been suggested as possible mechanisms (Sogaard et al., 2013). However, there are a number of studies which suggest that cancer treatment can be adhered to and have beneficial effects in the context of comorbid illness. A recent German cohort study of breast cancer treatment found that the presence of diabetes and depression were both associated with reduced rates of discontinuation of tamoxifen (Hadji et al., 2013). The New Zealand study of colon cancer mentioned above found that adjuvant chemotherapy was associated with a 60% reduction in excess mortality for those with a Charlson score ≥ 3, indicating that this treatment offered benefit despite high levels of comorbid illness (Sarfati et al., 2009). Prevention and management of comorbid physical illness in people with mental illness is therefore a potentially amenable driver of cancer survival inequalities that deserves individual attention.

3.7.3 Cancer treatment

The treatment received for cancer is one of the most important prognostic indicators, and differential receipt of treatment has been found to be a contributing factor in cancer survival inequalities. For example, a study of lung cancer treatment in New Zealand found that Māori patients were significantly less likely to receive curative treatment, a difference not accounted for by differences in comorbidity, or by patient refusal of treatment (Stevens et al., 2008b). A review of ethnic disparities in cancer treatment receipt in the United States found that treatment disparities were widespread and not explained by clinically relevant factors, and were important explanatory factors for ethnic differences in cancer survival (Shavers and Brown, 2002).

Studies that have examined cancer treatment in the context of prior mental illness (Table 5) have consistently found that people with a history of mental illness are less likely to get cancer treatment compared to people without such a history, across a variety of countries, health care settings, cancer types and mental illness diagnoses. For example, a Western Australian study of 6586 people with a variety of cancers found that people with a history of contact with secondary mental health services were less likely to have surgical resection of breast, colorectal or cervical cancers compared to people without such a history (HR 0.81) (Kisely et al., 2013). A study of 2142 Medicaid enrolees with breast cancer found that women with a mental illness diagnosis recorded in the twelve months prior to cancer diagnosis were less likely to get guideline consistent breast cancer treatment, after adjustment for demographic factors, comorbidity, stage, and contact with health services (OR 0.79) (Mahabaleshwarkar et al., 2015). Other studies in the Medicare population have found that depression, schizophrenia and other mental disorders are associated with being less likely to receive treatment for cancer (Bergamo et al., 2014; Goodwin et al., 2004; Baillargeon et al., 2011).

In contrast, one recent study of breast cancer treatment in a US Medicaid population found that women with mental illness were no less likely to get definitive treatment for invasive breast cancer compared to other women (Koroukian et al., 2015).

However, it is notable that in this study the definition of mental illness used included more than 60% of the women with breast cancer in the study. It is unclear whether women with mental health service contacts after cancer diagnosis were included in the mental illness group. This may help explain the very high rates of mental illness in the population, as reactive mental disorders are common following cancer diagnosis, with up to one third of cancer patients estimated to meet diagnostic criteria for mental illness (Singer et al., 2010; Levy and Fann, 2008). This study design would be susceptible to immortality bias, as women who survived longer following cancer diagnosis would have more time to develop mental health problems. This may explain the findings of low rates of metastatic or unstaged cancer and high rates of definitive treatment among women with mental illness.

Other aspects of cancer care have also been examined, including investigations performed and treatment delays (see Table 6). These factors may also be important in survival differences. Most population-based studies do not have access to this level of detail about cancer management. However, understanding how the detailed steps of cancer management contribute to survival dipartites for people with mental illness will be important in finding ways to intervene to reduce these disparities.

The impact of cancer treatment differences on cancer survival disparities varies by the type of cancer. Where cancers are amenable to treatment, and have high rates of treatment success, treatment receipt is an important predictor of survival. On the other hand, where cancer prognosis is poor even with treatment, differences in treatment receipt are less important as drivers of unequal outcomes. Therefore, differences in treatment for cancers which are amenable to treatment such as breast and colorectal cancers are likely to be a more important area of focus for reducing cancer disparities associated with mental illness.

As noted in the previous chapter, there is a growing literature demonstrating inequalities in receipt of treatment for other physical health conditions in people with a history of mental illness. Multiple studies have found that a history of severe mental illness is associated with being less likely to receive indicated interventions after myocardial infarction (Druss et al., 2000; Kurdyak et al., 2012; Petersen et al., 2003; Kisely et al., 2009; Kisely et al., 2007). Studies of diabetes management have

also found treatment disparities associated with severe mental illness (Blanchard, 2014). It is therefore highly likely that treatment disparities are present in the cancer domain also.

The reasons for differential receipt of cancer treatment in people with a history of mental illness are likely to be multiple. Interactions between psychiatric and cancer medications can complicate cancer treatment (Yap et al., 2011). Parts of cancer treatment, such as radiotherapy, may also be difficult to tolerate for people already experiencing paranoia or anxiety (Howard et al., 2010). It has been suggested that ability to understand a cancer diagnosis, and to consent to and cooperate with complex cancer treatment regimens, may be impaired in people with severe mental illness (Inagaki et al., 2006) (Hwang et al., 2012). However, a recent cohort study from the United Kingdom demonstrated that breast cancer treatment, from consent to chemotherapy delivery, could be successfully delivered in a similar fashion to women with and without schizophrenia (Sharma et al., 2010). As was pointed out in a recent review of practical and ethical issues related to cancer care in severe mental illness, there is often a presumption that people with psychiatric disorders are difficult patients with impaired decision-making capacities, which can get in the way of offering cancer treatment (Howard et al., 2010).

3.7.4 Stigma and discrimination

Beyond the immediate determinants of cancer survival, broader societal factors are at work in determining poor cancer survival in the context of mental illness. The role of stigma and discrimination is difficult to measure in epidemiological studies based on routine data such as those reviewed here, it is none the less important to consider the social context and its role in generating disparities.

Discrimination has been shown to be an important predictor of unequal health outcomes (Harris et al., 2013; Williams et al., 2003; Pascoe and Smart Richman, 2009). Discrimination can impact on health through its impact on opportunities and access to resources, as well as through its association with harmful health behaviours (Pascoe and Smart Richman, 2009). As was noted in Chapter Two, there is considerable evidence that discrimination on the basis of mental health status occurs

commonly, including in the health sector (Sartorius, 2007b). It is likely that discrimination related to mental health is a factor in the health inequalities associated with mental health, including those seen in cancer survival.

Stigma and discrimination can therefore be thought of as factors likely to be underlying the other pathways examined. Addressing the fundamental right of people with experience of mental illness to be treated with respect and in a non-discriminatory way will therefore be important in addressing cancer inequalities related to mental illness.

3.7.5 Pathways conclusions

The important pathways by which mental illness is associated with cancer survival include access to primary care and timely cancer diagnosis, access to cancer treatment, and the burden of other physical illness at the time of cancer diagnosis. Underlying these pathways are fundamental social determinants including discrimination and the distribution of resources.

There is growing body of evidence exploring these pathways, although little is known about their contribution to survival disparities. Empirical research to investigate importance of different possible pathways is therefore required.

3.8 LITERATURE REVIEW CONCLUSIONS

There have been a great many studies examining cancer incidence in the context of mental illness, and the broad consensus seems to be that the risk of cancer in those with a history of mental illness, including those with schizophrenia, is similar to that in the general population, with some variation between cancers.

Methodological issues are however a major problem for cancer incidence studies. In particular, biases due to exclusion or inclusion of certain groups mean that study results are hard to interpret and frequently conflicting. By using a typology of study types, is it possible to demonstrate that these biases can account for a great deal of the variation found in study findings.

Findings regarding cancer mortality in individuals with mental illness are more consistent, with almost all recent studies finding that mental illness is associated with high cancer mortality. Cancer mortality also appears to be higher than expected given cancer incidence, suggesting survival disparities.

There have been few survival studies, although this is an increasing area of research. Those that have been done show consistently worse survival for those with a history of mental illness, including people with depression and schizophrenia, and people with prior mental health service use.

There has been little investigation of the possible mechanisms for worse cancer survival in those with mental illness. Understanding the mechanisms is important for focusing interventions. Mechanisms may differ between cancers as well as between health service settings and so studies of individual cancers in new settings are important for furthering our understanding.

Therefore, this study examines cancer burden in New Zealanders using mental health services, including cancer survival for individual major cancers and the determinants of any cancer survival disparities.

Table 4 Studies of the association between mental illness and cancer stage at diagnosis

Author year	Country	Cancer	Mental illness	N (MI)	Stage measure	Stage at diagnosis and MI	Comments, incl. prop missing
(Koroukian et al., 2015)	US (Medicaid)	Invasive breast cancer	Diagnosis of mental illness plus receipt of psychiatric medication or mental health service contact (not specified if only includes cancer diagnosis)	2177 (1310)	Metastases vs none, unstaged or unknown-stage vs stage recorded	Less likely to present with unstaged cancer: adj OR 0.61 (0.44-0.86) Less likely to present with distant cancer: adj OR 0.59 (0.4-0.85)	Adj for comorbidity, demographics, women with mental illness represented 60% of the study population
(Bergamo et al., 2014)	US (Medicare, national)	Lung	schizophrenia	96,702 (1,303)	SEER summary stage	More likely to be diagnosed with stage I-II disease 34.9% vs 30.6%, ($p<0.01$); less likely to diagnosed with late stage disease (OR 0.82) after adjusting for sociodemographics and comorbidity	1% missing stage
(Chang et al., 2014)	UK (South London)	All cancers combined	MHS use + specific diagnosis	28,477 (2,206; 507 with specific diagnoses)	Localised vs advanced	No significant difference in odds of advanced stage for any mental health diagnosis	
(Kisely et al., 2013)	Australia (WA)	All cancers	MHS use	13,442 (6,586)	Metastases	7.1% (6.5-7.8) vs 6.1% (6.0-7.2)	Not significant

Author year	Country	Cancer	Mental illness	N (MI)	Stage measure	Stage at diagnosis and MI	Comments, incl. prop missing
(O'Rourke et al., 2008)	US (VA)	Oesophageal	DSM diagnosis	160 (52)	Advanced stage	37% vs 18%	P<0.05
(Boyd et al., 2012)	US (Medicare, national)	Pancreatic	Depression	23,745 (1,868)	Loco regional vs distant stage (SEER)	Significantly less likely to have local and more likely to have distant or unstaged (71.1% vs 67.9%) disease	P<0.05
(Wadia et al., 2015)	US (Veterans Affairs, single hospital)	Solid tumours (colorectal, head and neck, urothelial)	DSMIV Axis 1 diagnosis >1 year prior to cancer diagnosis and MHS use or psychoactive medication	408 (151)	SEER summary stage 0-IV or unknown	No difference in stage distribution overall, borderline significant difference in people over 65 (earlier diagnosis)	
(Goodwin et al., 2004)	US (Medicare, national)	Breast	Depression	24,696 (1,841)	AJCC stage 0-4 or unknown	No difference in stage distribution, 40.5% stage 2 or greater vs 40.3%	
(Baillargeon et al., 2011)	US (Medicare)	Colon cancer	Any mental disorder diagnosis documented in 2 years prior	80,670 (20,699)	AJCC stage 0-4 or unknown or diagnosed at autopsy	People with prior MI significantly more likely to be diagnosed at autopsy or have unknown stage	Approx. 7% missing stage overall, 14.6% in people with prior MI, 23% missing for people with psychotic disorders

Table 5 Studies of cancer treatment receipt

Author year	Country	Cancer	Mental illness	N cancer (mi)	Treatment measure	Treatment receipt	Comments
(Koroukian et al., 2015)	US (Medicaid)	Invasive breast cancer	Diagnosis of MI plus receipt of psychiatric medication or mental health service contact (seems to include post-cancer diagnosis)	2177 (1310)	Definitive treatment for loco regional disease	Did not differ by presence of mental illness: adj OR 1.04 (0.84-1.29)	Adj for comorbidity, demographics, stage; women with mental illness represented 60% of the study population
(Mahabaleshwarkar et al., 2015)	US (Medicaid)	Breast	MI diagnosis on records in the 12 months prior to cancer diagnosis	2142 (806)	Guideline consistent breast cancer treatment	Adjusted OR 0.79 (0.65–0.97)	Aged 18-64, Medicaid Adj age, race, location, Charlson, stage, number of outpatient visits in previous 12 months
(Kisely et al., 2013)	Australia (WA)	All cancers	MHS use	6586	Surgery	HR 0.81 (0.76-0.86)	Significantly lower surgical resection for breast, cervical and crc (both sexes)
(O'Rourke et al., 2008)	US (Veterans' Affairs)	Oesophageal	DSM diagnosis	160 (52)	Surgery	38% vs 59%	P<0.05
(Boyd et al., 2012)	US (Medicare, national)	Pancreatic	depression	23,745 (1,868)	Surgery, chemotherapy (stage dependent definitive treatment)	Loco regional disease: Surgery OR 0.63 (0.52-0.76) Distant disease: Chemotherapy OR 0.79 (0.70-0.90)	Stratified by stage, adjusted for age, sex, ethnicity, marital status and comorbidities
(Bergamo et al., 2014)	US (Medicare, national)	Lung	schizophrenia	96,702 (1,303)	Stage appropriate treatment (surgery, chemotherapy, RT)	Significantly less likely to get appropriate treatment 38.4% vs 49.1%, p<0.01; adj OR 0.5 (0.43-0.58)	Elderly population, Medicare

Author year	Country	Cancer	Mental illness	N cancer (mi)	Treatment measure	Treatment receipt	Comments
(Chang et al., 2013)	Taiwan	Oral	MI diagnosis recorded at admission for cancer	16,687 (206)	Surgery with or without chemotherapy	OR 0.47 (0.34-0.65) adj for age, sex, region, sep, comorbidity, hosp characteristics	More likely to get chemotherapy or radiotherapy alone.
(Goodwin et al., 2004)	US (Medicare, national)	Breast	Depression	24,696 (1,841)	Definitive treatment	Less likely to get definitive treatment: 59.7% vs 66.2%, p<0.01; Odds of receiving non-definitive treatment 1.19 (1.06-1.33) adj age, ethnicity, marital status, comorbidity, region	
(Baillargeon et al., 2011)	US (Medicare)	Colon cancer	Any mental disorder diagnosis documented in 2 years prior	80,670 (20,699)	No treatment (all stages), no chemotherapy (stage 3)	Adj RR no treatment 2.06 (1.86-2.35), Adj RR no chemo 1.63 (1.49-1.79)	People with dementia, psychotic disorder and mood disorder all significantly more likely to get no treatment or no chemotherapy

Table 6 Studies of other aspects of cancer care

Author, year	Country	Cancer	Mental illness	N	Care measure	Results	Comments
(Wadia et al., 2015)	US (Veterans Affairs, single hospital)	Solid tumours (colorectal, head and neck, urothelial)	DSMIV Axis 1 diagnosis >1 year prior to cancer diagnosis and MHS use or psychoactive medication	408 (151)	Time symptoms to presentation, presentation to diagnosis, diagnosis to treatment	No significant difference in any timeliness measure	No difference when under and over 65s examined separately.
(Bergamo et al., 2014)	US (Medicare, national)	Lung	Schizophrenia	96,702 (1,303)	Use of diagnostic tests Cancer specialist visits	Significantly less likely to undergo most tests. Less likely to visit specialists	Elderly population, Medicare

Chapter Four: **STUDY ONE: THE BURDEN OF CANCER AMONGST MENTAL HEALTH SERVICE USERS**

4.1 INTRODUCTION

This chapter presents the methods and results for the first study of the thesis (Study One). This study aims to establish the extent to which cancer is being diagnosed and causing death amongst people in contact with mental health services in New Zealand.

4.1.1 Study aims

- To estimate the annual numbers and rates of cancer diagnosis in adults with recent contact (in five years prior) with mental health services in New Zealand, stratified by sex, for all cancers combined and for major cancers (breast, colorectal, lung, prostate).
- To estimate the relative annual incidence of cancer in people with recent contact with mental health services compared to the general population, stratified by sex and standardised by age, for all cancers combined for major cancers (breast, colorectal, lung, prostate).
- To estimate the annual numbers and rates of death attributed to cancer in adults with recent contact (in five years prior) with mental health services in New Zealand, stratified by sex, for all cancers combined and for major cancers (breast, colorectal, lung, prostate).
- To estimate the relative annual mortality from cancer in people with recent contact with mental health services compared to the general population, stratified by sex and standardised by age, for all cancers combined, and for major cancers (breast, colorectal, lung, prostate).

4.1.2 Summary of chapter

This chapter describes the methods used to explore the burden of cancer in people using mental health services, and the results of this investigation.

The introductory section discusses the important considerations in planning a study of cancer burden in this population. These considerations include the possible cancer outcomes of incidence, mortality and survival, and the choice of absolute and relative measures of difference. The implications of the methodological issues in cancer incidence studies highlighted in the previous chapter are then discussed, and the choice of method to avoid these issues is presented.

The second section describes the data sources used to identify a population with experience of mental illness, and identify cancer outcomes in this population.

The third section presents the methods used to identify the population with mental health service contact, describe this population, and establish the burden of cancer in this population in terms of absolute numbers and rates and standardised incidence and mortality ratios.

The fourth section gives the descriptive analysis results for the population using mental health services, describing the population by demographic and mental health factors.

The fifth and six sections present the results of cancer incidence and mortality analyses. Sensitivity analyses, exploring the implications of the choice of population and analysis methods are then presented in the seventh section.

This chapter builds on the existing literature on cancer in the context of mental illness, which has mainly focused on the relative burden compared to people without mental health service use or particular diagnosed mental health conditions, by considering different ways of assessing burden and different ways of defining the population affected. It also provides the first data on cancer in the context of mental illness in the New Zealand population.

The results lead on to the next chapter, which explores the reasons for higher cancer mortality in the context of similar cancer incidence by examining the determinants of cancer survival.

4.1.3 The relationship between mental health and cancer

The relationship between mental illness and cancer is complex. As set out in chapter two, mental illness can be associated with physical illness through factors at the individual, provider, system level, and through stigma and discrimination at all these levels. A causal diagram illustrating possible pathways connecting these factors to cancer outcomes is shown below (see Figure 5). Possible mediating factors were identified, including societal factors such as social deprivation, stigma and discrimination, health system factors such as access to primary and secondary care, and individual factors such as health behaviours, psychiatric medications and genetic factors. From this model it is clear that not only mental illness itself, but also its social and medical consequences, can influence cancer outcomes. The relationship between mental health and cancer can also go in either direction. This study focuses on the pathways leading from mental health problems to cancer outcomes, and the causal diagram is the theoretical model of connections used as the basis for analyses in this study, and in interpreting the results.

Figure 6 shows a more formal Directed Acyclic Graph of potential confounders and mediators of the relationship between mental illness and cancer diagnosis. Because routinely reported national data was used for the comparison population, only information on age, sex and ethnicity was available for adjustment. However other potential factors, particularly mediators, were also identified, which were used in the interpretation of the findings. A Directed Acyclic Graph was also used to inform the survival analysis, and this is shown in the next chapter.

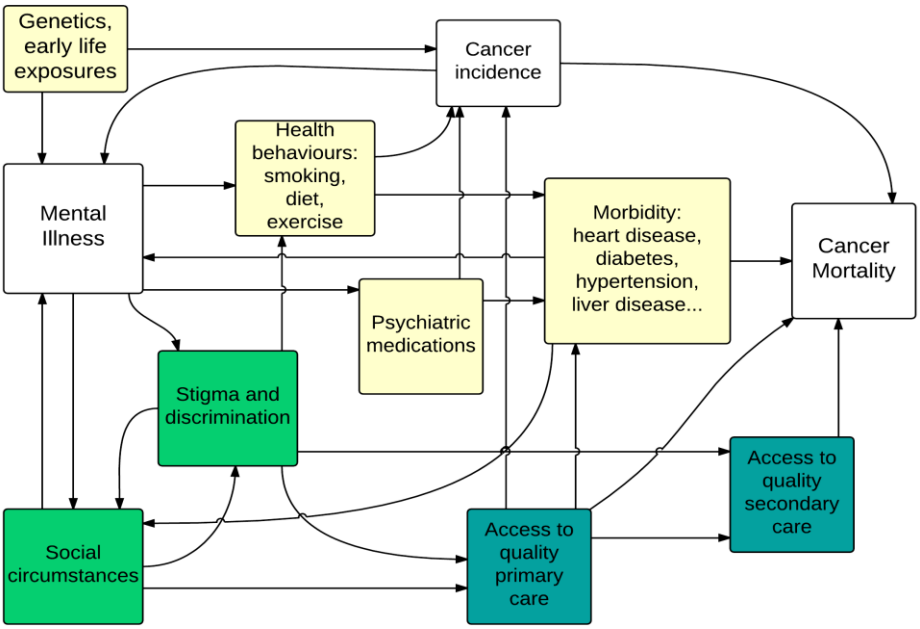

Figure 5 Causal diagram of relationships between mental illness and cancer outcomes

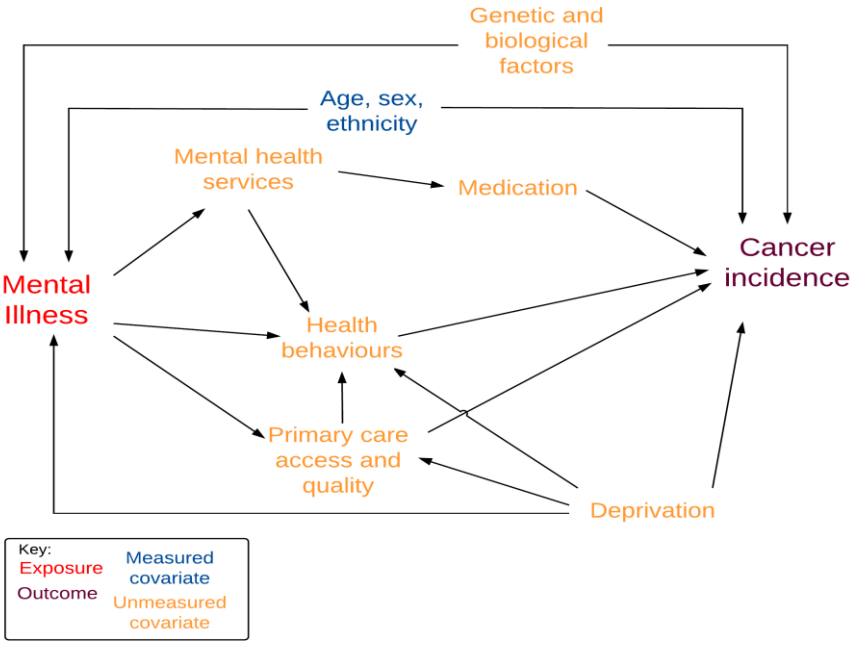

Figure 6 Directed Acyclic Graph of relationship between mental illness and cancer incidence

4.1.4 Cancer incidence, mortality and survival

Cancer burden can be measured through cancer incidence (the frequency of cancer diagnosis), cancer mortality (the frequency of deaths attributed to cancer), and cancer survival (the chances of surviving for a certain period after the cancer is diagnosed).

As described in the previous chapter, each approach identifies a different aspect of the impact of cancer on a population. Cancer incidence depends on the pattern of cancer risk and protective factors in the population. Cancer survival depends on the type and aggressiveness of the cancer, how early it is diagnosed, how well an individual is when cancer is diagnosed, and on all of the things that happen after cancer diagnosis. Cancer mortality depends on both cancer incidence and cancer survival, i.e. on both the factors which influence the occurrence of cancer and the factors which influence its prognosis. It also depends on mortality from competing causes of death. In the case of cancer mortality following mental illness diagnosis, distinguishing mental health problems prior to and following cancer diagnosis is not always possible, adding additional complexity to interpreting mortality rates.

Cancer incidence and survival are therefore the measures which are most easily interpreted. They also provide more useful information for identifying interventions to reduce the burden of cancer. However cancer mortality is also an important measure of cancer burden. It provides information about the numbers and rates of death from cancer, which helps to understand the impact of cancer on the population in question. Where a measure of cancer mortality is provided alongside a measure of cancer incidence in the same population, it also provides information about case fatality (the chances of dying from the cancer after cancer diagnosis), giving an indication of the likely importance of cancer survival differences in this population. This chapter examines cancer incidence and mortality, and looks at the relationship between the two. The following chapter examines cancer survival directly.

Cancer can also be examined as a combined disease entity (all cancers combined), and through separate examination of individual cancers. Many studies which examine the burden of cancer in the context of mental illness only give results for all

cancers combined, mostly due to small numbers of cases for any individual cancer. All cancers have different aetiologies, natural histories, treatment pathways and prognoses and so it is important also to examine individual cancers separately. This chapter examines major cancers separately where numbers allow.

4.1.5 Absolute measures – how important is cancer to this population?

Absolute cancer incidence and mortality rates show how often cancer is diagnosed in people under the care of mental health services, and how often cancer is a cause of death in this population. There are two reasons for starting with the absolute burden. Firstly, this is the degree to which cancer is likely to be important for the population experiencing mental illness. Even if the burden is relatively high compared to others, it is usually only if it is also absolutely high that it is a meaningful health issue for the population. Secondly, the relative burden depends on the burden in the comparison population. If the comparison population has unusually high rates of a disease then the relative burden will be reduced, whereas if the comparison population is relatively healthy, this can make the population being compared appear worse. Absolute cancer incidence and mortality numbers and rates are therefore an important starting point for assessing the burden of cancer in people with experience of mental illness.

4.1.6 Relative measures – how does the burden of cancer compare with the general population?

The incidence of, and mortality from, cancer among people with mental illness can also be compared to rates among people without a history of mental health service contact. Alternatively, the general population can be used as a comparison population, if it is not possible to specifically identify those without mental health problems, as the number in contact with mental health services is a very small proportion of the total population. This allows assessment of whether there is any inequality in the cancer burden for this population. The relative burden is measured through comparison of standardised rates (rates which are age and sex standardised

to make them directly comparable), to produce standardised incidence and mortality ratios.

4.1.7 Timing

The other important aspect of measuring cancer burden is to consider timing relative to experience of mental health problems. As the causal diagram demonstrates, cancer and mental illness can be related in many ways. The *overall* co-occurrence of mental illness and cancer in the population, regardless of which comes first, demonstrates how common it is to experience both of these conditions together. This study focuses on the group of people who experience mental distress requiring input from secondary services, and the way in which this experience, and its associated social and medical consequences, relate to cancer outcomes. And so, this section aims to assess the burden of cancer in people who have experience of mental illness and the consequences of such illness.

As discussed in Chapter Three, including cancers which preceded rather than followed mental illness can inflate the estimate of the burden of cancer in people with experience of mental illness. For example, a recent study of adults using mental health services in Western Australia found that cancer was one of the most common causes of excess deaths among people with adjustment and anxiety disorders (Lawrence et al., 2013). It is much more likely that terminal cancer diagnosis precipitated anxiety and adjustment disorders than that these disorders in some way increased susceptibility to death from cancer. Studies of cancer incidence may also be affected by this problem. For example, an American study of medically insured people with mental health claims (Carney et al., 2004) found an elevated incidence of central nervous system tumours in people with mental illness diagnoses, and this is likely to be due to these cancers presenting with psychiatric symptoms.

The usual method to deal with this problem of reverse causation, where cancers have caused mental distress rather than the other way around, is to exclude all cancer diagnosed prior to mental health service use, and include only mental health service use which began prior to cancer diagnosis (Grinshpoon et al., 2005; Lin et al., 2013a; Lawrence et al., 2000a; Whitley et al., 2012). However this method may

overcompensate for the reverse causation problem and result in biased underestimates of cancer incidence (Whitley et al., 2012), as discussed in detail in Chapter Three. If only those cancers diagnosed following contact with mental health services are included (and all mental health service contact that occurs after cancer diagnosis is excluded), then this introduces a time period where the "exposed" group are by definition invulnerable to the outcome (cancer diagnosis), because if they had this outcome prior to their mental health service contact then their mental health service contact would not "count" as an exposure. This is a variant of the bias known as immortality bias (Hanley and Foster, 2014) – where the exposed group have a period of "immortal time" where they cannot die because if they did they would not live long enough to be exposed. In this case, it is a period of invulnerable time, as illustrated in Figure 7 below.

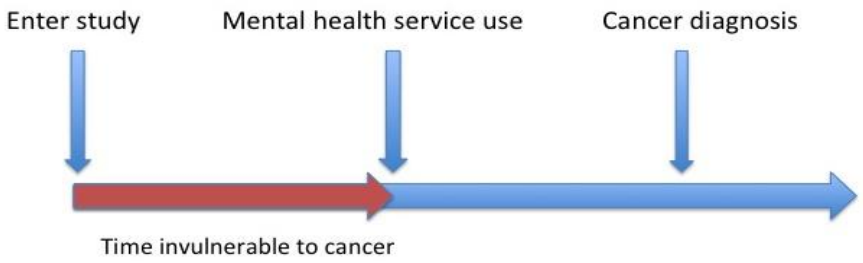

Figure 7 The problem of Invulnerable Time

This immortality bias can be dealt with in two ways, as detailed in Chapter Three: either to treat time prior to mental illness as unexposed, using a cohort study design (referred to as Design C in the previous chapter), or to exclude time prior to mental illness diagnosis from consideration of cancer incidence (Design D). Because routine annual data was used as a comparison population, it was not possible to treat time prior to mental illness as unexposed. Therefore, Design D was used. A series of annual cohorts were created, where each person is identified on the basis of their mental health service use in a period prior to the beginning of each index year, and then followed up for cancer diagnosis and cancer deaths over the following year. These cohorts could then be compared to the routinely reported annual data on the

whole population. The definition of the exposed group (mental health service use in the past five years) was therefore not influenced by prior cancer diagnosis.

For each index year in which cancer burden was examined, a cohort of individuals with contact with mental health services over the five years prior to the index year was created. These cohorts were then followed up for cancer diagnosis and death over the index year, and rates were compared with annual population rates.

4.2 DATA SOURCES

National level routinely collected administrative data sets (listed and described below) were obtained from the New Zealand Ministry of Health's Information Group and linked using the unique health service identifier the National Health Index (NHI). Once data linkage had been performed an anonymised data set, without NHI, was created for analysis.

Ethical approval to collect this information, along with all other aspects of the study, was granted by the New Zealand Multi-Region Ethics Committee in May 2012 (reference MEC/12/05/046).

4.2.1 Mental Health Service Use – PRIMHD

Mental health service use was identified using the Programme for Integration of Mental Health Data (PRIMHD), which records all service contacts for specialist mental health and addiction services nationally (i.e. not including primary mental health care). This includes child and young people's mental health services, and all public inpatient and community based services, as well as some non-governmental services. For some District Health Boards (DHBs) psychogeriatric care (for those over 65) is categorised as mental health care and reported to the PRIMHD database, while for other DHBs it is categorised as geriatric care and not reported to this database. For this reason it was not possible to include those over 65 in this study.

PRIMHD began collecting data in 1 July 2008. From 1 July 2000 data on community and inpatient mental health and addiction services was collected in the Mental Health Services Information Collection, and this data has been migrated across to the

PRIMHD system. Prior to 2000, only information on inpatient psychiatric service use was collected nationally via the National Minimum Data Set.

PRIMHD includes the date, location and provider for all mental health service contacts, and collects information on outcomes for service users, although over the time of this study not all services were submitting this data. It also includes information on the type of service provided, but assessment and treatment contacts are not clearly distinguished. Multiple psychiatric diagnoses can be recorded for each individual on PRIMHD records, including 'principal', 'other relevant', and 'provisional' diagnoses. A variety of classification systems are used, depending on clinician preference and DHB systems (ICD 9, ICD 10AM and DSMIV are all used). Nevertheless, many individuals either have no diagnostic information recorded, or an explicit coding with "no diagnosis" entered in the system. Diagnostic information is required only after a person has been in contact with mental health services for 3 months, with the result that many of those in short term contact with services have no diagnostic information recorded. Diagnoses are not attached to specific episodes of care.

At the time of embarking on this study, very little research had utilised the PRIMHD dataset. There were a number of reasons for this. Firstly, as a new data collection with new systems of reporting, it had taken time for all health services to begin submitting usable data. Secondly, large amounts of data were missing, some of it in new fields such as the Health of the Nation Outcomes Scale (HoNOS), but also in core areas such as psychiatric diagnosis. Thirdly, because PRIMHD includes a wide variety of community based services, as well as inpatient stays, the mental health data is not organised in the same way as routinely collected hospital services data, and so requires more manipulation to make it usable for population research.

4.2.2 Mortality collection

The National Mortality Database holds information on all deaths occurring in New Zealand. It is collected by the New Zealand Health Information Service from death registration information, medical cause of death certificates and coroners' reports.

Records include date and underlying cause of death, coded using ICD-10-AM and based on the World Health Organisation Rules and Guidelines for Mortality Coding.

4.2.3 New Zealand Cancer Registry

The New Zealand Cancer Registry (NZCR) is a population-based register of all malignant cancers diagnosed in New Zealand (except non-melanoma skin cancers), established in 1948 to monitor cancer incidence and mortality. Until 1994 information on cancer diagnosis came principally from public hospital records. The 1993 Cancer Registry Act made it mandatory for laboratories to copy pathology reports diagnosing cancers to the NZCR. The majority of cancer registrations are now identified from data supplied by pathology laboratories, with only a small proportion (<10%) coming from hospital records or death certificates. Trained coders input cancer registrations and perform cross-checks using all available information. ICD10 is used to code cancer site, and ICD-O is used to code cancer morphology. SEER summary staging (Young et al., 2001) is used to record cancer stage at diagnosis. The quality of NZCR data has been found to be comparable to other cancer registers internationally (Cunningham et al., 2008; Stevens et al., 2008a).

4.2.4 Comparison population

The 2006 New Zealand Census population (Statistics New Zealand, 2006) was used as the denominator for the comparison population for calculations of standardised cancer incidence and mortality ratios. The census population was limited to age 20-64 to enable comparability. Annual nationally-reported age and sex specific cancer registrations, and deaths attributed to cancer, were used to give numerator information for calculation of incidence and mortality rates.

4.2.5 Linking datasets

Data sets were linked using the National Health Index which assigns a unique identifier to each individual health service user in New Zealand. NHI numbers are recorded on the NHI database along with demographic information which is updated

at each contact with secondary health services. NHI numbers are also attached to all other health datasets and so provide a reliable method for linking an individual's information between datasets. Links were checked by date of birth and sex to check that there were no discrepancies in these fields when matching by NHI, and no discrepancies were found. A unique study ID was then created and NHI removed from the dataset to further preserve anonymity.

4.3 METHODS

4.3.1 The exposure – mental health service use

A cohort was created for each index year, including all people who had had contact with mental health services in the five years prior to the beginning of that year, and who were also still alive at the beginning of that year. The primary exposure was contact with mental health services, as recorded by a service contact on PRIMHD, in the five years prior to the beginning of each index year (2006 to 2010). For example, for 2006, the mental health service use (exposed) cohort consisted of all people who had had contact with mental health services between 1/1/01 and 1/1/06 and who were still alive on 1/1/06.

To maximise sensitivity (reduce the chances of excluding people who did in fact have mental illness), all those who had contact with services were included, even if they did not have a specific psychiatric diagnosis recorded. To improve the positive predictive value (increase the chances that contact with mental health service use did represent a significant mental illness), people who had had contact with mental health services only on a single day in the five year period were excluded, on the basis that this contact is likely to have been for assessment rather than treatment, and did not necessarily indicate that mental health problems were present.

Exclusions were also made on the basis of psychiatric diagnosis, in order to improve the internal validity of the study and reduce bias due to reverse causation. People with organic psychiatric conditions were excluded, because these conditions may represent manifestations of cancer. People with dementia were excluded, because the study is limited to those under age 65 and so those with dementia would not be

representative of the total population with dementia, and also because of differences in the natural history of dementia from other mental health conditions. People with a primary diagnosis of intellectual impairment (mental retardation), but without another mental health diagnosis, were excluded on the basis that intellectual impairment has a different aetiology and natural history from other mental health conditions, and is likely to have a different relationship with physical health outcomes, and should therefore be examined separately.

To maximise internal validity the study was restricted to those under 65, as complete information on mental health service contact was not available for those over 65. Those under 20 were also excluded because of the rarity of cancer before this age, and the different aetiology and prognosis of paediatric cancers.

Full inclusion and exclusion criteria are shown in Figure 8.

Inclusion criteria: Adults who had contact with public mental health services in New Zealand for more than one day in the five years prior to the index year (2006 to 2010), and were aged 20-64 on 1 January of the index year.

Exclusion: No more than one day of contact with services in the five years prior to the index year; service contacts 2001-2010 only recorded after death; a prioritised diagnosis of dementia or organic brain disease or mental retardation.

Figure 8 Inclusion and exclusion criteria

Prioritised diagnosis was used as a severity measure to distinguish within the population using mental health services. In order to identify a single primary psychiatric diagnosis for each individual, a prioritization process was used, based on that used in other similar studies (Lawrence et al., 2001), prioritising more specific diagnoses and more severe mental illness. The prioritized order of diagnoses is shown in Figure 9. Principal diagnosis was used if available. Where no principal diagnosis was recorded, provisional diagnosis information was used. A large number of people had no diagnosis information available (see Table 8).

1. Schizophrenia, schizoaffective disorder and other non-organic psychoses;
2. Bipolar affective disorder and other affective psychosis;
3. Organic disorders and dementia (excluded from the current study);
4. Depression and other mood disorders;
5. Anxiety and stress disorders;
6. Substance use disorders;
7. Mental retardation (excluded);
8. Other mental health diagnoses (includes personality disorders, eating disorders, etc.);
9. "No diagnosis" or "diagnosis deferred" recorded.

Figure 9 Diagnosis prioritisation order

In this study of cancer burden, diagnosis was used mainly for cohort descriptive purposes. Where diagnosis was used as an explanatory variable, the use of diagnosis information was restricted to identifying whether people had a diagnosis of schizophrenia, schizoaffective disorder or bipolar affective disorder (ICD10 codes: F20, F25, F30, F31). This group is referred to as Group A in analyses presented below. Group B is a residual group, consisting of all others in contact with mental health services (including those with no diagnosis). Further information on psychiatric diagnosis was not used, because of the large amount of missing diagnosis information (nearly 40% had no diagnostic information available).

Inpatient service use and treatment under the Mental Health (Compulsory Assessment and Treatment) Act 1992 were also examined. Service use was categorised as inpatient if there had been any inpatient admissions in the five years prior to the index year. Similarly individuals were categorised as having had Mental Health Act treatment if they had had any treatment under the Mental Health Act in the five years prior to the index year. For this study inpatient service use and Mental Health Act status were used in descriptive analyses only. In the survival study in the following chapter (Chapter 5), inpatient service use was used as an alternative to diagnosis as a measure of severity.

4.3.2 The outcome – cancer diagnosis and cancer mortality

Cancers registered with the New Zealand Cancer Registry between January 2006 and December 2010 were used to estimate cancer incidence in those using mental health services and the general population. All malignant neoplasms (ICD10 C00-C97) were included, limited to those diagnosed between the ages of 20 and 65 to enable comparison between mental health service users and the general population. Cancers were grouped by ICD10 code to allow estimation of the rates for different cancer types.

Cancer mortality was estimated based on the National Mortality Collection. Death registrations from 1/1/2006 to 31/12/2010 were included, where underlying cause of death was given as malignant neoplasm (ICD10 C00-C97), limited to those occurring between the ages of 20 and 65. Deaths from individual cancers were also examined separately for breast, colorectal, lung and prostate cancers.

4.3.3 Independent variables

Age and sex were drawn from the NHI master record, and used to produce age and sex specific incidence and mortality rates for comparison to population rates.

Age for the population in contact with mental health services was recorded as age at January 1st each index year (2006-2010). Age was grouped into five year age bands for standardised analysis. Age at cancer diagnosis or cancer death was calculated from date of birth and date of diagnosis or death (from the Cancer Registry and Mortality data sets respectively).

Sex was recorded as male or female on the NHI record. For all analyses presented by sex, people with sex recorded as "unknown" (n=3 for 2006 cohort) were excluded.

Other demographic and mental health service use variables were used to describe the sociodemographic and clinical characteristics of the population in contact with mental health services. This information was important for considering the generalisability of the results.

Prioritised ethnicity, as documented on the NHI record, was used. Multiple ethnic identities can be recorded on the NHI record, but for reporting, a single prioritised group is used, with the prioritisation order of Māori, then Pacific, then Asian, and then a residual group (Ministry of Health, 2004). In descriptive analyses, prioritised ethnicity has been reported. For analyses stratified by ethnicity, the indigenous Māori population was compared with all other (non-Māori) groups. Those with missing ethnicity data were included in the non-Māori group. The numbers of people in other ethnic groups (such as the Pacific group) were too small to undertake separate analysis.

The New Zealand Deprivation Index 2006 (NZDep2006) (Salmond et al., 2007) was used to assign a deprivation score to the area of residence (domicile) recorded on the NHI record. NZDep 2006 is a small area index of deprivation, based on census data. It summarises the age and sex standardised proportions of people living in the small area with certain characteristics of deprivation, including education, income, employment, housing tenure and crowding (Salmond and Crampton, 2012). The deprivation scores assigned to each census area are then grouped into deciles based on the variation of scores across the country to assign a relative deprivation score of one to ten to each area. For this study, NZDep was categorised into quintiles (1 to 5, 1 being the least deprived).

Place of mental health service use (first in the time period) was categorised by District Health Board (DHB) region to demonstrate the geographic distribution of the cohort across New Zealand. DHBs are the local level health service provider and funder, of which there are twenty in New Zealand). These were grouped into the four administrative regions for analysis: Northern (Northland, Auckland, Counties Manukau, Waitemata), Midland (Waikato, Bay of Plenty, Tairawhiti, Lakes and Taranaki), Central (Hawkes Bay, Whanganui, Midcentral, Capital and Coast, Hutt Valley and Wairarapa), and Southern (Nelson, Marlborough, West Coast, Canterbury, South Canterbury and Southern).

Table 7 Variables used in analysis: Mental Health Service (MHS) users cohort

Variable set	Variable	Values	Comments and definitions
Unique identifier	Study ID		
MHS use	Date first service use	1/1/2001-31/12/2010	First activity recorded over the study period
	Eligible MHS use	Y/N	MHS use > 1 day in the five years prior to the index year
Demographics	Age	20-64	Age at start of index year (1/1/06, 1/1/07 etc.) based on date of birth.
	Gender	F or M	
	Ethnicity	Māori, Pacific, Asian, European, other	Prioritised, dichotomised into Māori and non-Māori for analyses.
	Area level deprivation (NZDep cat)	1-5	Categorised as quintiles
Time and place	DHB region code	South Central Midland North	
MH diagnosis and severity	Prioritised diagnosis	1=schizophrenia 2=BPAD 3=depression 4=anxiety 6=other 7=substance 9=no diagnosis 99=no information	Derived from principal and provisional diagnosis information. No diagnosis – where 'no diagnosis' or 'diagnosis deferred' is recorded No information – where no diagnostic information is recorded
	Inpatient	Y, N	Inpatient at any time in the five years prior to the index year
	Mental Health Act	Y, N	Treated under the Mental Health (Compulsory Assessment and Treatment) Act 1992 at any time in the five years prior to the index year
	Grouped diagnosis	Group A Group B	Group A = Schizophrenia, schizoaffective disorder, bipolar affective disorder Group B = all other mental health service users
Cancer	Site	ICD10 C chapter codes	Malignant neoplasms recorded on NZCR
	Date of diagnosis	1/1/2006-31/12/2010	
Mortality	Mort_ICDA	ICD10 mortality codes C chapter	Cancer causes of death
	Date of death	1/1/2006-31/12/2010	

4.3.4 Missing data

Where data on a variable are missing, this can bias the results of analyses including this variable. There are three types of missing data: missing completely at random, where there are no systematic differences between missing and non-missing values; missing at random, where systemic patterns of missingness can be explained from other observed data (i.e. data is missing at random once other known information is taken into account); and missing not at random, where systematic patterns of missingness persist after other observed data is taken into account. (Sterne et al., 2009) Both missing at random and missing not at random data have the potential to result in biased or misleading results.

The options for dealing with missing data to reduce bias are 1) to exclude those individuals with any missing data in analyses using those variables (complete case analysis); 2) to create a "missing" category for the variable, where it is assumed that missingness in itself conveys some meaningful information (for example, missing cancer stage may mean that staging was not performed, which may be indicative of prognosis) rather than a failure in collecting information; 3) to assign an estimated value for missing variables (single imputation), for example the median value; or 4) to use multiple imputation methods to impute a range of values for the missing variable using non-missing information on other variables and use these values to perform the analyses multiple times and average the resulting parameter estimates across the samples. Sensitivity analyses can also be used to explore the potential for bias in analyses with missing data. Where data is missing completely at random, complete case analysis does not bias the results. Where data is missing at random, multiple imputation can be used to predict possible values for the missing data. Where data is missing not at random (which cannot be established with certainty), methods such as sensitivity analysis can be used to investigate the likely impact of missing data (Rothman et al., 2008).

Missing data was dealt with in a variety of ways for this study. Firstly, patterns of missingness were reviewed (these are shown in Appendix One, page 294). Because of the way variables were generated and inclusion criteria for the study there were no

missing values for the following variables: age, inpatient service use, care under the mental health act, simplified diagnosis, cancer site and date of diagnosis, cause of death and date of death. The main missing variable for the mental health service use cohort was mental health diagnosis (which was being used as a second level of exposure classification). Very small amounts of information were also missing on ethnicity, deprivation and gender variables.

Table 8 shows the methods used to deal with missing data.

Those missing psychiatric diagnosis were included as a separate category (no diagnosis), combining those missing any diagnostic information with those who had "no diagnosis" or "diagnosis deferred" recorded. Any principal or provisional diagnosis information available was used. When analyses were performed by diagnosis group, those with missing diagnosis were included in Group B, on the rationale that this group would be likely to have had a relatively short duration of contact with services and would be unlikely to have been given a diagnosis of Group A conditions (schizophrenia, bipolar disorder or schizoaffective disorder).

Ethnicity data was deemed to be missing if ethnicity was recorded as "Do not know" or "Refused to answer" or "Response unidentifiable" or "Not stated". People with missing ethnicity data were reported separately for descriptive analyses and included in the non-Māori group for Māori/non-Māori analyses. People with missing sex information were excluded from sex-specific analyses. People with missing deprivation score were excluded from the descriptive analyses by deprivation.

No imputation was performed for Study One. Imputation of missing deprivation was performed in the study of cancer survival reported in the next chapter.

Table 8 Methods used for dealing with missing data in Study One (all variables with any missing data shown): Recent mental health service use cohort 2006

Variable set	Variable	N missing (% missing) Total n = 131,077	Method for dealing with missing data
Demographics	Gender	3 (0.002%)	Complete case analysis (people with unknown gender treated as missing)
	Ethnicity	5316 (4.1%)	Include in non-Māori group
	NZDep cat	471 (0.36%)	Report missing, complete case analysis
Place	DHB region code	2094 (1.6%)	Report missing, complete case analysis
Mental Health diagnosis and severity	Prioritised diagnosis	24568 (18.7%)	Added to those with "no diagnosis" recorded to create a missing diagnosis value. Incorporated into Group B for main analyses.

4.3.5 Description of cohort

A descriptive analysis of people with contact with mental health services in the five years prior to assessment of cancer burden was performed, including demographic details, diagnosis and patterns of service use. The frequency of each characteristic and the proportion of the cohort with this characteristic were calculated and presented stratified by gender. This was done for each index year (2006 to 2010). The results for 2006 are presented here, with the other years included in Appendix One (see page 297).

4.3.6 Cancer incidence

Numbers of cancers registered per year and crude rates per 100,000 people per year were calculated for major cancer sites for each index year (2006 to 2010). The first cancer of each type diagnosed in an individual was included. It was therefore possible for an individual to contribute more than one cancer to total cancer counts.

The New Zealand Cancer Registry (NZCR) similarly includes all registered cancers in a given year and is not limited to a single cancer per individual, and so multiple cancers per individual were included for comparison purposes. Each individual alive at the beginning of each index year contributed one full year of person time at risk (i.e. the small numbers who died during the year were not removed from the population at risk). This was done in order to be comparable to the comparison group (the general population) where each individual contributes a full year of person time at risk for calculation of cancer incidence from cancer registrations. The calculated incidence may therefore arguably be better referred to as a risk rather than a rate.

Standardised incidence ratios (SIR) were calculated using indirect standardisation. That is, the observed cancer incidence in those using psychiatric services was divided by the cancer incidence that would have been expected if those using psychiatric services had the same patterns of cancer incidence by age and sex as the total New Zealand population. NZCR cancer registrations for 2006 to 2010, by cancer type and five-year age groups, were used for the comparison. Only cancers diagnosed prior to age 65 were included in the calculations, for the purposes of comparison to the New Zealand population. Estimates were calculated for men and women separately and then combined. This was done for each year for all cancers combined, and then annual estimates were combined to give an SIR for the entire period 2006 to 2010. Annual counts were pooled by combining cancer numbers (numerator) and population time at risk (denominator) for each year to calculate average age-specific annual rates for the period 2006 to 2010, for both the mental health service use and general populations.

SIRs were calculated for cancers which are the major contributors to both cancer incidence and cancer mortality in the general population, namely female breast (C50), colorectal (C18-C20), and lung (C34) cancers. The five years were combined for these calculations because of small numbers. Prostate cancer (C61) was also examined separately, because of international evidence of inequalities in prostate cancer incidence for people with mental illness. SIRs were not calculated for all cancers because of concern that small numbers would result in spurious findings, but

it is recognised that there may have been sufficient power to examine some other common cancers such as melanoma.

For breast cancer, the rates for post-menopausal women were also examined separately, because of the differences in risk factors for pre- and post-menopausal breast cancers. Post-menopausal was defined as age 50 or greater (an older age cut off was not used because of limited numbers). Because of small numbers, it was not possible to separately examine the rates for younger women.

SIRs for all cancers combined were calculated for those in Group A (people with diagnoses of schizophrenia or bipolar affective disorder), to allow comparisons to other studies, and as a sensitivity analysis to assess the effect of misclassification of exposure on the results. SIRs for other specific diagnoses were not calculated because of the large amount of missing diagnostic information.

Standardised incidence rates were calculated for Māori and non-Māori separately (i.e. stratified by ethnicity) to test for effect modification by ethnicity.

4.3.7 Mortality analysis

Numbers of deaths from cancer per year and crude rates per 100,000 people per year were calculated for each index year (2006 to 2010) by cancer site.

Standardised cancer mortality ratios (SMRs) were calculated using indirect standardisation, taking the observed cancer mortality in those using psychiatric services and dividing this by the mortality that would be expected if those using psychiatric services had the same patterns of cancer mortality as the total New Zealand population. The national mortality data for 2006 to 2010, by cause and five-year age groups, were used for the comparison. Deaths in those under 25 were excluded from the SMR calculations as their small numbers could lead to unstable results. Only deaths prior to age 65 were included in the calculations, for the purposes of comparison to the New Zealand population. SMR for all cancers combined were calculated for each year 2006 to 2010, and then a combined SMR was calculated. As with incidence, annual counts were combined to give average

annual rates by combining numbers of cancer deaths (numerator) and population at risk for each year (denominator). SMRs were calculated for those in Group A, and for major cancers (breast, colorectal, prostate and lung).

4.3.8 Sensitivity analyses

Sensitivity analyses were performed to explore the impact of exclusions to the mental health service users' cohort.

Firstly the impact of restricting to those who had had contact with mental health services for greater than one day was explored, by examining the standardised incidence and mortality ratios produced for the population with recent mental health service use including those with service contact only on a single day.

Secondly, the issue of reverse causation and its impact on cancer mortality results was further explored. Although all cancer deaths occurred following mental health service use, it is possible (even likely) that some of the contact with mental health services which occurred immediately before death from cancer was precipitated by the diagnosis and experience of terminal cancer. Therefore further mortality analyses were performed where all those who had had contact with mental health services only in the twelve months before their death from cancer were excluded. The resulting SMRs for all cancers combined and for breast, colorectal and lung cancers are presented.

As a final sensitivity analysis, the results were compared to the usual method of assessing cancer burden, where all those with cancer diagnosed prior to mental illness are excluded from the study (Design A in the typology presented in Chapter 3). To do this, an overlapping cohort is required. That is, the period over which mental health service use and cancer diagnosis are examined needs to overlap, so that information is known about cancer diagnoses both before and after mental health service use. Therefore, the population identified with mental health service use at any time in a ten year period (2001-2010) was treated as the annual denominator population, and all the cancers diagnosed in this population over the same period were identified and used to calculated age and sex specific cancer rates. Experience

of mental illness was treated as a time invariant exposure rather than something which ‘starts’ at the point of mental health service use (i.e. these individuals are treated as having been exposed for the entire follow-up period, regardless of when they were first identified). This approach assumes that service use in the time period is an indicator of mental health problems which extended at least over the time period of the study. Cancer incidence and mortality were assessed over the whole period for which information was available, and all people who had cancers diagnosed prior to first contact with mental health services in the study period were excluded on the basis that their mental health service contact may have been due to cancer.

4.4 RESULTS: THE COHORT OF MENTAL HEALTH SERVICE USERS

4.4.1 Cohort numbers

Table 9 shows the cohort numbers for each year using recent service use as a proxy for recent/current experience of mental illness. The population at risk was identified for each year 2006-2010. The numbers are shown at each step in defining the cohort.

Table 9 Recent mental health service (MHS) use cohorts for each year – numbers at each step in cohort creation

Year	**2006**	**2007**	**2008**	**2009**	**2010**
Description	People with records of MHS activity in five years prior to 2006	People with records of MHS activity in five years prior to 2007	People with records of MHS activity in five years prior to 2008	People with records of MHS activity in five years prior to 2009	People with records of MHS activity in five years prior to 2010
Recent service use, alive 1 Jan index year	218311	221713	228289	239728	253990
Recent service use, aged 20-64, 1 Jan of index year	154132	156854	161589	169325	178826
Recent service use, aged 20-64, without excluded diagnoses	151399	153937	158536	166169	175707
Recent service use, aged 20-64, without excluded diagnoses, >1 day over five years	131077	136065	141378	148465	156506

4.4.2 Description of mental health service user cohort

Table 10 describes the 2006 cohort of recent mental health service users (as an example), after exclusions on the basis of diagnosis and age and service use length. Men and women are equally represented and more than 2/3rds were under the age of 45. The majority were of European ethnicity, with about 20% Māori and small numbers in other ethnic groups. Male service users were more likely to be of Māori or Pacific ethnicity than female service users, who were more likely to be European. The majority of both men and women lived in deprived areas. There was fairly even

geographical spread, with slightly higher numbers from the northern region. Depression was the most common diagnosis for women and substance use for men. Almost 40% of men and women had no diagnostic information. Approximately one quarter had a history of recent inpatient service use, and 4-6% had been treated under the Mental Health Compulsory Assessment and Treatment) Act 1992 (i.e. had compulsory treatment) in the previous 5 years.

The cohorts for each year between 2007 and 2010 are shown in Appendix One (page 294).

Table 11 shows the cohort characteristic averaged over the five cohorts (i.e. the mean numbers and proportions of people with each characteristic).

The distribution of characteristics in the population with recent mental health service use did not change markedly over time. Later cohorts had slightly more men than women (in 2010 52% were men compared to 50% in 2006). The age distribution did not change markedly over time. A slightly higher proportion of Pacific and Asian people had contact with services in the later cohorts (9% of service users in the 2010 cohort vs 7% in the 2006 cohort), but otherwise the ethnic distribution was similar over time. Levels of deprivation did not change over time. The numbers of people in contact with services increased over time particularly for DHBs in the Northern region, with 39% of those in contact with services over the five years prior to 2010 contacting services in the Northern region, compared to 32% in 2006.

The main change over time was in the diagnosis field. In 2006, 19% of those in contact with services for greater than one day over the previous five years had no diagnosis recorded, whereas in 2010 this had reduced to 6%. However, there was not a corresponding increase in the proportion with other diagnoses documented, but rather an increase in those who had “no diagnosis” or “diagnosis deferred” recorded.

Table 10 People with mental health service contact >1 day in the five years prior to 2006: Cohort characteristics

Characteristic		Women	%	Men	%
Total with MHS use in five years prior to 2006*		65464		65610	
Age (at 1/1/06)	20-29	17311	24.6	18881	26.8
	30-44	29392	41.8	28933	41.1
	45-64	18722	26.6	17764	25.3
Ethnicity	European	46048	70.4	42829	65.3
	Māori	12757	19.5	14106	21.5
	Pacific	2082	3.2	2939	4.5
	Asian	2241	3.4	1457	2.2
	Other	689	1.1	596	0.9
	Unknown	1647	2.5	3683	5.6
NZDep Score (quintile)^	1 (least deprived)	8549	13.1	6819	10.4
	2	10549	16.1	9457	14.4
	3	13870	21.2	13003	19.8
	4	18646	28.5	19187	29.2
	5 (most deprived)	18544	28.3	21597	32.9
DHB region	North	20383	31.2	21610	32.9
	Midland	13345	20.4	12080	18.4
	Central	15522	23.7	16117	24.6
	South	15512	23.7	14411	22.0
Prioritised diagnosis	Schizophrenia, other psychoses	6947	10.6	10866	16.6
	Bipolar affective disorder	4201	6.4	2814	4.3
	Depression and other mood	15620	23.9	8961	13.7
	Anxiety and stress disorders	6367	9.7	4455	6.8
	Substance use	5670	8.7	11892	18.1
	Other mental health diagnoses	1865	2.9	1297	2.0
	"no diagnosis" or "diagnosis deferred"	12024	18.4	13528	20.6
	No diagnostic information	12770	19.5	11797	18.0
Service type	Any inpatient service use	17582	26.9	18592	28.3
	any Mental Health Act	3475	5.3	4748	7.2

* 3 people were of unknown sex and are not included in this table; ^ 614 (0.4%) had missing NZDep information;

Table 11 People with mental health service contact >1 day in the five years prior to index year:

Average cohort characteristics

Characteristic		**Women**	**%**	**Men**	**%**
Total with MHS use in five years prior to index year (mean 2006-2010)		69928		72760	
Age (at 1 Jan index year)	20-29	19275	27.6	21537	29.6
	30-44	29851	42.7	30671	42.2
	45-64	20802	29.7	20545	28.2
Ethnicity	European	48355	69.1	46124	63.4
	Māori	14002	20.0	16275	22.4
	Pacific	2563	3.7	4146	5.7
	Asian	2624	3.8	1884	2.6
	other	813	1.2	735	1.0
	unknown	1579	2.3	3597	4.9
NZDep Score (quintile)	1 (least deprived)	8720	12.5	7199	9.9
	2	10607	15.2	9765	13.4
	3	13931	19.9	13557	18.6
	4	18599	26.6	19890	27.3
	5 (most deprived)	18844	26.9	23006	31.6
DHB region	North	23955	34.3	26662	36.6
	Midland	13856	19.8	12798	17.6
	Central	15767	22.5	17079	23.5
	South	15602	22.3	14896	20.5
Prioritised diagnosis	Schizophrenia, other psychoses	7166	10.2	11427	15.7
	Bipolar affective disorder	4449	6.4	3004	4.1
	Depression and other mood	17488	25.0	10002	13.7
	Anxiety and stress disorders	7326	10.5	5088	7.0
	Substance use	6411	9.2	13618	18.7
	Other mental health diagnoses	2301	3.3	1723	2.4
	“no diagnosis” or “diagnosis deferred”	17396	24.9	20898	28.7
	No diagnostic information	7399	10.6	7001	9.6
Service type	Any inpatient service use	18513	26.5	19825	27.2
	Any Mental Health Act use	3942	5.6	5420	7.4

4.5 RESULTS: CANCER INCIDENCE

4.5.1 Absolute numbers and rates, by cancer and diagnosis

An average (mean) of 375 cancers were diagnosed each year among people aged 20-64 with mental health service use in the previous five years (as shown in Table 12). The most common cancer sites were lung cancer, female breast cancer and melanoma. The frequencies of other cancers varied by year, and colorectal cancers, haematological malignancies, prostate cancer, oral/upper GI and liver cancers were also among the more common cancers in some years.

It should be noted that these small numbers reflect the fact that only the population under 65 is included in this study, and cancer is predominantly a disease of later life.

Table 12 Numbers and crude rates of specific cancers for each recent service use cohort 2006 to 2010

		2006		2007		2008		2009		2010	
Primary site	**ICD10 code**	**n**	**crude rate per 100,000**	**n**	**crude rate per 100,000**	**n**	**crude rate per 100,000**	**n**	**crude rate per 100,000**	**n**	**crude rate per 100,000**
Breast*	C50	72	110.0	61	90.3	85	122.2	78	108.2	95	126.5
Lung	C33-34	35	26.7	50	36.7	31	20.9	43	29.0	55	35.1
Melanoma	C43	35	26.7	29	21.3	40	26.9	40	26.9	40	25.6
Colorectal	C18-20	25	19.1	26	19.1	32	21.6	23	15.5	23	14.7
Lymph/haem	C81-96	22	16.8	28	20.6	36	24.2	38	25.6	46	29.4
Head/neck/ Upper GI	C00-16	22	16.8	27	19.8	22	14.8	20	13.5	29	18.5
Prostate#	C61	13	19.8	21	30.6	22	30.6	26	34.0	24	29.5
Cervix/uterus*	C53-55	13	19.9	9	13.3	16	23.0	13	18.0	16	21.3
Liver/pancreas	C22,C25	11	8.4	15	11.0	25	16.8	24	16.2	22	14.1
Kidney/bladder	C64-68	9	6.9	5	3.7	10	6.7	20	13.5	13	8.3
Brain/CNS	C70-72	9	6.9	2	1.5	4	2.7	9	6.1	7	4.5
Endocrine	C73-75	7	5.3	12	8.8	12	8.1	7	4.7	8	5.1
Total cancers	C00-97	320		326		387		403		440	

*rate per 100,000 women, # rate per 100,000 men

4.5.2 Cancer incidence compared to the general population

Standardised incidence ratios (SIR) comparing cancer incidence in people with recent mental health service use with cancer incidence in the general population are shown in Table 13.

All estimated incidence ratios were close to 1.0 (the null), and all confidence intervals include the null, indicating that there is unlikely to be a difference in cancer incidence between people with recent mental health service use and the rest of the population. Similar patterns were seen for men and women using mental health services compared to men and women in the general population.

Table 13 Relative cancer incidence (standardised incidence ratios) for people with recent contact with mental health services compared to the general population, excluding people with mental health service use on a single day

Year	Female (n)	SIR	95% CI	Male (n)	SIR	95% CI	Combined SIR	95% CI
2006	184	1.04	0.90-1.20	136	1.00	0.85-1.19	1.02	0.92-1.14
2007	185	0.99	0.85-1.14	141	1.00	0.85-1.18	0.99	0.89-1.10
2008	228	1.09	0.95-1.24	159	1.00	0.86-1.17	1.05	0.95-1.16
2009	204	0.98	0.85-1.12	199	1.09	0.95-1.25	1.03	0.93-1.14
2010	240	1.04	0.91-1.18	200	1.01	0.88-1.16	1.02	0.93-1.12
All yrs^	1041	1.03	0.97-1.09	835	1.03	0.96-1.10	1.03	0.98-1.08

^includes up to one cancer per year per person

Table 14 shows the standardised incidence ratios for breast, colorectal, prostate and lung cancers, as four of the most common cancers. Colorectal and breast cancer incidence rates in people in recent contact with mental health services were similar to those for the general population. The risk of breast cancer in post-menopausal women (over 50) appeared to be slightly raised, with a central estimate of 13% excess risk and confidence intervals ranging from 1% reduced rate to 29% excess.

Lung cancer incidence was found to be nearly doubled in people in recent contact with mental health services compared to the general population. Prostate cancer incidence on the other hand was 34% lower in this group than the general population. There were no marked differences in relative cancer burden between men and women using mental health services for lung or colorectal cancers.

Table 14 Standardised incidence ratios for specific cancers, recent mental health service users compared to the general population, 2006-2010 combined

Group	Female (n)	SIR	95% CI	Male (n)	SIR	95% CI	Combined SIR	95% CI
Colorectal	80	1.06	0.85-1.32	77	0.92	0.74-1.15	0.99	0.84-1.15
Lung	109	1.92	1.59-2.32	105	2.05	1.69-2.48	1.98	1.73-2.26
Breast	390	1.01	0.91-1.11					
Breast>50 yrs.	208	1.13	0.99-1.29					
Prostate				106	0.66	0.54-0.80		

Table 15 shows the results of stratification by ethnicity, to test for effect modification (i.e. a different effect of mental health service use on cancer incidence in Māori compared to non-Māori). The patterns for Māori and non-Māori women are not markedly different (SIR Māori women 1.00, SIR non-Māori women 1.03). However, for Māori men, using mental health services was associated with an increased risk of cancer (SIR 1.21), whereas for non-Māori men this was not the case (SIR 0.99).

Table 15 Standardised cancer incidence ratios for mental health service users compared to the general population stratified by ethnicity, all years combined

Group	Female (n)	SIR	95% CI	Male (n)	SIR	95% CI	Combined SIR	95% CI
Māori	214	1.00	0.87-1.14	172	1.21	1.04-1.41	1.08	0.98-1.20
Non-Māori	839	1.03	0.96-1.10	668	0.99	0.92-1.07	1.01	0.96-1.06

Table 16 shows the standardised incidence of cancer in mental health service users in Group A (with recorded diagnoses of Schizophrenia or Bipolar affective disorder or schizoaffective disorder). Cancer incidence was slightly higher in women and men in this group compared to those with no history of mental health service use (an estimated 15% increase among cancer incidence in women with these diagnoses and a 12% increase among men).

Table 16 Standardised cancer incidence ratios for people diagnosed with schizophrenia or bipolar disorder compared to the general population, all years combined

Group	Female (n)	SIR	95% CI	Male (n)	SIR	95% CI	Combined SIR	95% CI

Group A[1]	250	1.15	1.01-1.30	168	1.12	0.96-1.30	1.13	1.03-1.25

4.6 RESULTS: CANCER MORTALITY

4.6.1 Absolute cancer mortality

The absolute numbers of deaths from cancer, by cancer type, are shown for each annual cohort in Table 17. In total, between 129 and 200 deaths occurred annually. The total number of cancer deaths per year was approximately 40% of the number of cancers diagnosed in the same year. However, because of the lag time between cancer diagnosis and death, these will not represent the same cancers. The most common cause of cancer death in each year was lung cancer, followed by colorectal and breast cancers.

The total number of deaths in each cohort, and the number and proportion of deaths from each cause, is shown in Table 18. As a proportion of all deaths occurring in this group of people using mental health services, cancer was the cause of approximately 20% of deaths.

Table 17 Absolute numbers and crude rates of death from specific cancers by year, excluding one day service use

		2006		2007		2008		2009		2010	
Primary site	**ICD 10 code**	**n**	**crude rate per 100,000**	**n**	**crude rate per 100,000**	**n**	**crude rate per 100,000**	**n**	**crude rate per 100,000**	**n**	**crude rate per 100,000**
Lung	C50	27	20.6	33	24.3	36	25.5	49	33.0	40	25.6
Breast*	C33-34	18	27.5	24	35.5	25	36.0	21	29.1	25	33.3
Colorectal	C43	14	10.7	25	18.4	30	21.2	22	14.8	31	19.8
Lymph/ haem	C18-20	13	9.9	15	11.0	14	9.9	22	14.8	16	23.3
Head/Neck/ Upper GI	C81-96	13	9.9	15	11.0	15	10.6	17	11.5	17	10.9
Liver/ pancreas	C00-16	9	6.9	10	7.3	16	11.3	14	9.4	12	7.7
Melanoma	C61	7	5.3	6	4.4	5	3.5	5	3.4	7	4.5
Brain/ CNS	C53-55	5	3.8	6	4.4	7	5.0	8	5.4	9	5.8
Cervix/ uterus*	C22,C25	3	4.6	5	7.4	4	5.8	3	4.2	8	10.7
Kidney/	C64-68	3	2.3	3	2.2	3	2.1	7	4.7	5	3.2

[1] Standardised incidence ratios are not presented for the residual group of mental health service users

bladder											
Prostate#	C70-72	0	0.0	5	7.3	2	2.8	4	5.2	4	4.9
Endocrine	C73-75	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0
Total cancer deaths	C00-97	129	98.4	170	124.9	165	116.7	182	122.6	182	116.3

*rate per 100,000 women, # rate per 100,000 men

Table 18 Absolute numbers and proportions of total deaths by cause of death in adults with recent mental health service use >1day, 2006 to 2010

	2006		2007		2008		2009		2010	
Cause of death	**no.**	**Proportion of all deaths**	**no.**	**Proportion of all deaths**	**no.**	**Proportion of all deaths**	**no.**	**Proportion of all deaths**	**no.**	**Proportion of all deaths**
Cancer	129	17.4	170	21.5	165	21.3	182	22.4	182	23.6
Cardiovascular	125	16.6	154	19.2	149	19.0	146	17.6	121	15.3
Accidental	117	15.6	120	15.0	132	16.8	120	14.5	120	15.1
Suicide	153	20.4	158	19.7	123	15.7	150	18.1	149	18.8
Assault	8	1.1	13	1.6	9	1.2	17	2.1	9	1.1
Other natural causes	217	28.9	184	23.0	205	26.1	210	25.4	207	26.1
Total	543		627		585		624		601	

4.6.2 Cancer mortality compared to the general population

Rates of cancer mortality for people with a history of recent mental health service use were then compared to the general population rates, taking into account age and sex difference between populations through the indirect standardisation procedure.

Table 19 shows that the rate of cancer mortality in people using mental health services is more than double the general population rate. The relative cancer mortality for this group also appears to be increasing over time.

Table 19 Relative cancer mortality in mental health service users compared to the general population

Year	Female (n)	SMR	95% CI	Male (n)	SMR	95% CI	Combined SMR	
2006	72	1.64	1.30-2.07	57	1.59	1.23-2.06	1.62	1.36-1.92
2007	87	1.99	1.61-2.45	83	2.25	1.81-2.79	2.11	1.81-2.45

2008	95	2.41	1.97-2.94	70	2.19	1.73-2.77	2.31	1.98-2.69
2009	93	2.39	1.95-2.92	89	2.83	2.30-3.48	2.58	2.23-2.99
2010	82	2.38	1.92-2.95	100	3.29	2.70-4.00	2.80	2.42-3.24
all years	428	2.10	1.91-2.31	398	2.34	2.12-2.58	2.21	2.07-2.37

Table 20 shows standardised mortality ratios for breast, colorectal, prostate and lung cancers in adults with recent contact with mental health services compared to the general population. All are more than double the general population rates. For lung cancer, both incidence and mortality were increased in adults using mental health services compared to the general population (SIR 1.98, SMR 2.90). However, for breast and colorectal cancers there was a marked discrepancy between the similar incidence rates (SIR 1.01 and 0.99 respectively) and the increased mortality rates (SMR 2.06 and 2.08 respectively). This discrepancy suggests survival disparities. For prostate cancer the discrepancy was even more marked, with lower incidence (SIR 0.66) but higher mortality (SMR 2.10) compared to the general population (although death from prostate cancer is very uncommon in those under 65 and so the SMR estimate is imprecise).

Table 21 shows cancer mortality in mental health service users compared to the general population stratified by ethnicity for all years combined. The increase in cancer mortality associated with mental health service use was more marked for non-Māori than Māori (combined SMR 1.99 for non-Māori and 1.57 for Māori).

Table 22 shows cancer mortality amongst those in Group A (with diagnoses of schizophrenia or bipolar disorder) compared to the general population. Cancer mortality was significantly increased for this group, with a combined SMR of 1.95. However, the increase in cancer mortality compared to the general population was less than that seen for all those using mental health services combined (combined SMR 2.21).

Table 20 Relative cancer mortality in mental health service users compared to the general population for specific cancer types

Cause of death	Female (n)	SMR	95% CI	Male (n)	SMR	95% CI	Combined SMR	95% CI
Colorectal cancer	44	2.51	1.87-3.37	35	1.70	1.22-2.37	2.08	1.66-2.59
Lung cancer	89	2.66	2.16-3.28	91	3.17	2.58-3.89	2.90	2.50-3.35
Breast cancer	113	2.06	1.72-2.48					
Prostate				16	2.10	1.29-3.43		

Table 21 Relative cancer mortality for mental health service users compared the general population, stratified by ethnicity

Group	Female (n)	SMR	95% CI	Male (n)	SMR	95% CI	Combined SMR	95% CI
Māori	88	1.43	1.16-1.76	90	1.72	1.40-2.12	1.57	1.35-1.81
Non-Māori	339	1.96	1.76-2.18	308	2.02	1.80-2.25	1.99	1.84-2.15

Table 22 Relative cancer mortality for mental health service users diagnosed with schizophrenia or bipolar disorder compared to the general population

Group	Female (n)	SMR	95% CI	Male (n)	SMR	95% CI	Combined SMR	95% CI
Group A[2]	102	1.88	1.55-2.29	90	2.03	1.65-2.50	1.95	1.69-2.25

[2] Standardised mortality ratios are not presented for the residual group of mental health service users

4.7 SENSITIVITY ANALYSES

4.7.1 Including people with mental health service use on a single day

Standardised incidence and mortality rates were calculated with the inclusion of people who had only had contact with mental health services on a single day in the five years prior to the index year, in order to examine the effect of the decision to exclude those people from the examination of cancer burden.

Table 23 shows the standardised cancer incidence ratios for people with a history of recent mental health service use compared to the general population, including people with only a single day of contact with services. As with the main analyses, the estimates are close to the null (combine SIR for all years 1.03 for women and 1.04 for men), indicating that there is unlikely to be a difference in cancer incidence between people with recent mental health service use and the general population, and no effect of including people with a single day of service use.

Table 23 Relative cancer incidence comparing people with recent mental health service to the general population, including people with mental health service use on a single day

Year	Female (n)	SIR	95% CI	Male (n)	SIR	95% CI	Combined SIR	95% CI
2006	205	1.01	0.88-1.16	164	1.05	0.90-1.22	1.03	0.93-1.14
2007	207	0.99	0.87-1.14	161	1.04	0.89-1.21	1.01	0.91-1.12
2008	257	1.12	0.99-1.26	170	0.98	0.84-1.14	1.06	0.96-1.16
2009	224	0.98	0.86-1.11	213	1.06	0.93-1.22	1.02	0.93-1.12
2010	260	1.01	0.89-1.14	220	0.99	0.87-1.13	1.00	0.92-1.09
All years	1153	1.03	0.97-1.09	928	1.04	0.98-1.11	1.04	0.99-1.08

Table 24 shows standardised cancer mortality ratios for people with a history of recent mental health service use compared to the general population, including people with only a single day of contact with services. A greater number of deaths from cancer were included in the analyses (107 extra deaths from cancer, or a 13% increase in the number of cancer deaths in people in contact with mental health services included in the analyses). Estimates of mortality ratios are similar to the estimates for the more restricted population of mental health service users, with a

combined SMR of 2.29 when people with a single day of service use are included, compared to a combined SMR estimate of 2.21 when this group are excluded.

Table 24 Relative cancer mortality comparing people with recent mental health service to the general population, including people with mental health service use on a single day

Year	Female (n)	SMR	95% CI	Male (n)	SMR	95% CI	Combined SMR	95% CI
2006	84	1.67	1.35-2.07	69	1.67	1.32-2.11	1.67	1.42-1.96
2007	103	2.17	1.79-2.64	98	2.35	1.93-2.86	2.26	1.96-2.59
2008	110	2.49	2.07-3.00	82	2.29	1.85-2.85	2.40	2.09-2.77
2009	101	2.33	1.92-2.83	99	2.81	2.31-3.43	2.55	2.22-2.93
2010	93	2.42	1.98-2.97	106	3.11	2.57-3.77	2.75	2.39-3.16
All yrs	490	2.19	2.00-2.39	453	2.41	2.19-2.64	2.29	2.14-2.44

4.7.2 Removing recent mental health service contact from mortality analyses

Cancer mortality estimates may be inflated by the inclusion of people who have had contact with mental health services secondary to terminal cancer. In order to investigate the degree to which this may be occurring, a further analysis was performed excluding those who had only had mental health service contact in the year prior to the year in which cancer mortality is assessed. In other words, these analyses only include people who had contact with mental health services at least one year prior to their death from cancer. The results using this method (Table 25) show that it does not affect the estimate of cancer mortality, with the risk of cancer mortality being approximately twice that of the general population using either method (SMR 2.23 using this method versus 2.21 when those with recent contact are included).

Table 25 Relative cancer mortality for mental health service users compared the general population, mental health service use >12 months prior to death

Year	Female (n)	SMR	95% CI	Male (n)	SMR	95% CI	Combined SMR	95% CI
2006	59	1.52	1.17-1.96	50	1.58	1.20-2.09	1.55	1.28-1.86
2007	76	2.01	1.61-2.52	74	2.26	1.80-2.84	2.13	1.81-2.50
2008	84	2.38	1.92-2.94	62	2.19	1.71-2.81	2.29	1.95-2.70
2009	90	2.56	2.09-3.15	77	2.75	2.20-3.44	2.65	2.27-3.08
2010	73	2.33	1.86-2.94	87	3.19	2.58-3.93	2.73	2.34-3.19
All yrs	381	2.13	1.93-2.35	349	2.36	2.12-2.62	2.23	2.08-2.40

4.7.3 Using Design A for calculating cancer incidence and mortality

Cancer incidence and mortality were assessed over the period 2001 to 2010, excluding all people who had cancers diagnosed prior to first contact with mental health services in the study period.

As previously explained, it is expected that the exclusion of people with prior cancer from the mental health service use group but not the comparison group will lead to estimates of cancer incidence and mortality which are biased downwards. Table 26 and Table 27 show the results for cancer incidence and mortality using this method. Overall, cancer incidence was estimated to be reduced by 24% in those in contact with mental health services compared to the general population when this method was used (combined SIR 0.76 (95% CI 0.73-0.78)). Breast cancer incidence, and colorectal cancer incidence in men but not women, was more than 30% lower in those in contact with mental health services compared to the general population. Lung cancer incidence was found to be increased in this service user group (SIR 1.44), although to a lesser degree than estimated using the main methods above.

Cancer mortality was found to be increased, both overall and for each individual cancer assessed, but again this disparity was smaller than estimated in the main analyses (SMR all cancers 1.35 compared to SMR 2.21 using main methods). A different pattern was seen between cancer types for this method compared to the main method, with the highest mortality ratio found for breast cancer using this method, and for lung cancer using the main method.

Table 26 Relative cancer incidence for mental health service users compared the general population, Design A

Group	Female (n)	SIR	95% CI	Male (n)	SIR	95% CI	Combined SIR	95% CI
All cancers	2005	0.77	0.74-0.80	1555	0.74	0.71-0.78	0.76	0.73-0.78
Breast	690	0.68	0.63-0.74					
Lung	192	1.33	1.15-1.53	204	1.57	1.37-1.80	1.44	1.31-1.59
Colorectal	166	0.90	0.77-1.05	140	0.64	0.54-0.75	0.76	0.68-0.85

Table 27 Relative cancer mortality for mental health service users compared the general population, overlapping cohort method

Group	Female (n)	SMR	95% CI	Male (n)	SMR	95% CI	Combined SMR	95% CI
All cancers	897	1.35	1.26-1.44	793	1.35	1.26-1.44	1.35	1.28-1.41
Breast	348	1.95	1.76-2.17					
Lung	165	1.45	1.25-1.69	176	1.70	1.47-1.97	1.57	1.41-1.75
Colorectal	93	1.57	1.28-1.92	80	1.10	0.89-1.37	1.31	1.13-1.52

4.8 SUMMARY AND CONCLUSIONS

This chapter has investigated the cancer incidence and mortality in people with severe mental illness in New Zealand. Recent contact (in the past five years) with mental health services was used a proxy for experience of severe mental illness. Cancer was found to be common, with approximately 400 cancers diagnosed each year in people under 65 in recent contact with mental health services. Cancer was also found to be an important cause of premature death for this population, with approximately 150 deaths from cancer each year among people with a history of recent mental health service use under the age of 65.

Overall, cancer incidence was similar in people with severe mental illness and the rest of the population (SIR 1.03). Cancer incidence varied by cancer, with higher rates of lung cancer [SIR 1.98 (95% CI 1.73-2.26)] and lower rates of prostate cancer [SIR 0.66 (0.54-0.80)] in people with mental illness compared to the general population. Rates of colorectal and breast cancer diagnosis were no different among those with mental illness and among the general population. There may also be varying patterns in less common cancers, which were not assessed here.

Estimates of cancer incidence were affected by the method chosen to identify the population at risk. Where people with cancer diagnosis prior to mental health service use were excluded from the population at risk, overall cancer incidence was estimated to be significantly lower among those with a history of mental illness compared to the general population [SIR 0.76 (0.73-0.78)].

Cancer mortality was found to be much higher among those with severe mental illness compared to the general population (SMR 2.21). Standardised cancer mortality rates were significantly higher among those with mental illness for all cancers examined.

Studying cancer survival is important for understanding the reasons for the higher mortality in the context of similar cancer incidence. This should be done for individual cancers, as the patterns of incidence and mortality vary by cancer. Studying the factors that explain differences in cancer survival are important for identifying ways to improve care and to reduce the disparities. This forms the basis for Study Two, detailed in the next chapter of this thesis.

Chapter Five: **STUDY TWO: CANCER SURVIVAL IN PEOPLE IN CONTACT MENTAL HEALTH SERVICES**

5.1 INTRODUCTION

This chapter presents the methods and results for the second study of the thesis (Study Two). This study aims to establish the impact of mental illness on cancer survival in the New Zealand context. The previous chapter demonstrated that while cancer incidence rates in people using mental health services in New Zealand are largely comparable to rates in the general population (with the exception of lung and prostate cancers), cancer mortality is higher. This chapter builds on these results to investigate survival after diagnosis with a common cancer (breast and colorectal cancers were chosen), comparing people with a history of contact with mental health services in the five years prior to cancer diagnosis to people without such a history.

This chapter also investigates the contribution of specific factors to cancer survival disparities. Understanding the pathways that lead from experience of mental illness to worse outcomes from physical health conditions is crucial in enabling health services to improve outcomes for this group. The literature on possible pathways to apparently worse cancer survival was explored in Chapter Three. Comorbid physical illness, late stage at diagnosis, and treatment differences were identified as possible factors. This chapter examines the relative importance of potential drivers in explaining differences in survival after diagnosis for those with mental illness. It also investigates how the impacts of these drivers differ by psychiatric diagnosis and cancer type.

The work presented in this chapter has been published as *Cancer survival in the context of mental illness: A national cohort study*, in the journal General Hospital Psychiatry (see Appendix Four, page 318).

5.1.1 Study aims

- To estimate the relative survival after diagnosis with breast and colorectal cancers among people with a prior history of contact with mental health services compared to people without such a history;
- To examine the way in which survival varies by psychiatric diagnosis (schizophrenia or bipolar disorder compared to others using mental health services) and cancer type (breast compared to colorectal cancer);
- To estimate the relative importance of the different drivers of cancer survival (particularly stage and comorbid illness) in explaining differences in survival after cancer diagnosis for those with a history of mental illness; and
- To examine the way in which the role of these drivers differs by psychiatric diagnosis and cancer type.

5.1.2 Summary of chapter

This chapter describes the methods used to examine cancer survival in people using mental health services, and the results of this investigation.

This introductory section sets out the aims and summarises the chapter.

The second section describes the methods used for this study. The study population, data sources, and variables used are similar to those in the first study. These are briefly described again and any differences noted. The methods for descriptive and survival analyses are presented. Options for survival analysis, including the use of competing cause methods, are discussed.

The third section presents the results of the methods used to select study cohorts, including the numbers after each exclusion.

The fourth section gives the descriptive analysis results for the comparison of those with a history of mental health service contact in the five years prior to cancer diagnosis to those without such a history, for both the breast and colorectal cancer cohorts.

The fifth and six sections present the results of survival analysis for breast and colorectal cancer cohorts respectively. Sensitivity analyses, exploring the implications of the choice of population and analysis methods are then presented in the seventh section.

This chapter builds on the results of the previous chapter, demonstrating high mortality associated with cancer in people using mental health services. It also builds on the existing literature on cancer survival inequalities. Breast and colorectal cancers were chosen as the two most commonly registered cancers in New Zealand (aside from prostate cancer). The Cancer Registry and mental health services database are used to identify a complete national cohort up to the age of 65.

5.2 METHODS FOR CANCER SURVIVAL ANALYSIS

5.2.1 Study population

The most common incident cancers registered in New Zealand are colorectal cancer, lung cancer, and melanoma, as well as breast cancer in women, and prostate cancer in men (Ministry of Health, 2014a). As was demonstrated in the previous chapter, the same five cancers are also the most commonly diagnosed cancers in people using mental health services in New Zealand.

Breast and colorectal cancers were chosen for investigation of survival disparities. These are two of the most commonly diagnosed cancers. They are also cancers for which prognosis is highly dependent on health service intervention, and for which inequalities in outcomes by ethnicity or socioeconomic status are known to occur (Hill et al., 2010; Sarfati et al., 2006). In New Zealand they also represent one cancer for which there was population screening (breast) and one for which there was no such screening programme (colorectal cancer), at the time of the study.

All adults diagnosed with Breast cancer (ICD10 code C50) or Colorectal cancer (ICD code C18 or C19 or C20) in New Zealand between 1/1/2006 and 31/12/2010 were identified from the New Zealand Cancer Registry, limited to those diagnosed between ages 18 and 64 to allow linking with mental health service data.

5.2.2 Data sources

The New Zealand Cancer Registry (NZCR), the New Zealand Mortality data collection, and the Programme of Integration of Mental Health Data (PRIMHD) are described in the previous chapter, and were also used for this part of the study. NZCR data and mortality data for the period 1/1/2006 to 31/12/2010 were used. PRIMHD data for the period 1/1/2001 to 31/12/2009 were used to define exposure status.

Health services receipt data collections were also used – the National Minimum Data Set (NMDS) and the National Non-Admitted Patients Collection (NNPAC). NMDS includes records of all inpatient and day stay contacts with public hospital services in New Zealand. This data includes admission and discharge dates, and diagnostic and procedure codes recording all diagnoses made and interventions received in a given admission. Some (but not all) private health service providers also submit data about admitted patients to NMDS. NNPAC records all non-admitted face to face public secondary care events, such as outpatient and emergency department visits.

NMDS data from 1/1/2001 to 31/12/2010 were used to identify comorbid conditions recorded in the five years prior to cancer diagnosis. Cancer treatment data were also extracted from NMDS for the period 1/1/2006 to 31/12/2010, including information on private facility cancer treatment supplied to the Ministry of Health. These data were supplemented by information on public outpatient cancer treatment from the NNPAC data set (1/1/2006 to 31/12/2010). However, there is no requirement on private providers to supply data, and so hospital and outpatient events at private facilities are not fully captured in the available data, resulting in an unknown amount of missing treatment data.

5.2.3 Cancer survival analysis

Five-year survival was examined for the cohort of adults diagnosed with breast or colorectal cancers between 1/1/2006 and 31/12/2010, comparing those in contact with public psychiatric services in the five years prior to cancer diagnosis to those without such a history.

Survival analysis was chosen to investigate any differences in cancer survival between those who have recently used mental health services and those who have not. Survival analysis can be used to compare the time to an event (such as death) between two groups, and to investigate the determinants of any differences in the time to the event between groups.

5.2.4 Variables used in analyses

Table 28 summarises the variables used in the analyses and how they were derived.

Exposure

Recent mental illness was defined as mental illness that has been disruptive enough to lead to contact with adult secondary mental health services (including assessment and/or treatment contacts) for greater than one day in the five years prior to cancer diagnosis. Those with mental health service use on only a single day were treated as not having had a history of disruptive mental illness for the purposes of this study, on the basis that contact on a single day is likely to have been for assessment rather than treatment, and did not necessarily indicate that mental health problems were present.

Within the broad group of mental health service users, measures of severity were used to identify the most disadvantaged group. The principal measure used was *prioritised psychiatric diagnosis*. Multiple psychiatric diagnoses were prioritised as discussed in the preceding chapter (see Figure 9) in order to identify a single primary diagnosis for each individual. Diagnosis was then simplified into two levels: Group A (people with diagnoses of schizophrenia or bipolar affective disorder or schizoaffective disorder: ICD10 codes: F20, F25, F30, F31); and Group B (all others in contact with mental health services). The remainder of the cohort (with no recorded contact, or only contact for one day) was treated as the reference group for calculation of hazard ratios.

Treatment as an inpatient, and treatment under the Mental Health Act, were also considered as severity measures. Those with any inpatient service use recorded in the five years prior to cancer diagnosis were categorised as having received inpatient

care, and likewise those with any treatment received under the Mental Health Act (MHA) during the five years prior were categorised as having been treated under the MHA. Inpatient service use was used as an alternative severity measure for sensitivity analysis. Because of small numbers, MHA treatment was used for cohort description purposes only.

Outcomes

Cancer specific survival (where cancer, either at the same site as the registered cancer or a secondary malignancy, was identified as the underlying cause of death on the death certificate) was used as the primary outcome. Those dying of non-cancer causes were censored at time of death. All cause survival was also estimated, with mortality from any cause being treated as the event of interest. Participants who were still alive at the end of the follow-up period (31/12/2010) were treated as censored at that time in both analyses.

Cancer specific survival taking into account the presence of competing risks, where deaths from cancer and deaths from other causes are treated as separate categories of event, was also estimated. This method is further explained below. Results from competing risk analyses are presented as sensitivity analyses.

Independent variables

Age at cancer diagnosis was calculated from date of diagnosis and date of birth, and was complete for the cohort. Age was modelled in the survival analyses using a restricted cubic spline function with three knots (knots at 10th, 50th, and 90th percentiles).(Desquilbet and Mariotti, 2010) A spline function was used to give a more flexible model fit than treating the age-cancer survival relationship as a linear function, while avoiding issues with using a multi-categorised split on age-group.

Sex, as recorded on the Cancer Registry (male or female), was used. This information was complete for both cancer cohorts (no one was recorded as having ‘unknown’ sex).

Prioritised ethnicity as recorded on the Cancer Registry was used. For descriptive purposes, the following categories were used: Māori, Pacific, Asian, European, other (Ministry of Health, 2004). For analyses by ethnicity, the indigenous Māori population was compared with all other (non-Māori) groups. Those with missing ethnicity data were included in the non-Māori group. Further analysis using more detailed ethnicity information was not feasible because of the small numbers of people in contact with mental health services in non-European, non-Māori ethnic groups.

Level of deprivation was measured using the NZDep (2006) index, which is a small area measure of deprivation based on data from the 2006 Census used to assign a deprivation score to the area of residence (domicile) recorded on the NHI record for each patient at the time of cancer diagnosis (Salmond et al., 2007). Deprivation quintiles were used in survival analysis.

The C3 comorbidity index (Sarfati et al., 2014b) was used to estimate the level of comorbid illness present at the time of cancer diagnosis. This index, specifically developed to measure comorbidity in the context of cancer using administrative hospitalisation data, includes up to 42 conditions. For the C3 index, conditions are identified from ICD-10 coded diagnoses recorded for any hospitalisation event for a given patient in the 5 years prior to cancer diagnosis. Each condition is weighted according to its impact on 1-year non-cancer mortality (as a mark of severity), as calculated and validated previously (Sarfati et al., 2014b). The weights are summed to give an overall index score for each patient, with a higher score indicating a higher level of comorbidity. The index was adapted for the current study to exclude psychiatric diagnoses. Comorbidity was modelled using a restricted cubic spline function using three knots for the survival analysis (for breast cancer knots at 0, 0.5 and 1.3; for colorectal cancer knots at 0, 0.5 and 2.0) (Desquilbet and Mariotti, 2010). As with age, a spline function allowed for a non-linear relationship between comorbidity and cancer survival, and provided a better model fit than treating the comorbidity-survival relationship as a linear function or a categorical function. For the descriptive analysis C3 scores were divided into three categories: 0 (all values less than or equal to zero), 1-2 (including all values between zero and 3, non-

inclusive), and 3+ (all values 3 or greater). As a sensitivity analysis, the Charlson comorbidity index (Charlson et al., 1987) was used as an alternative measure of comorbidity status. The Charlson index uses 22 conditions, weighted depending on their relationship with one year mortality, and is not specific to cancer populations. Conditions for the Charlson index were identified on the basis of ICD10 codes recorded on NMDS in the five years prior to cancer diagnosis. Charlson was treated as a four-category variable for analysis (0, 1, 2 and 3+), and this was summarised into three categories for descriptive purposes (0, 1-2, 3+).

Stage at diagnosis is recorded on the Cancer Registry based on all available information on staging within three months of diagnosis. The SEER summary staging system (Young et al., 2001) was used, and this was converted into local (stage 1), regional (stage 2 and 3) and distant (stage 4) disease for analyses. Cancers with no recorded stage information were categorised as "Unstaged".

Data on receipt of cancer surgery, chemotherapy and radiotherapy were drawn from the NMDS and NNPAC held by the Ministry of Health. Other work suggests that substantial amounts of private cancer treatment data are missing from NMDS, and that missingness is differential by ethnicity (non-Māori are more likely to have missing cancer treatment data than Māori) (Gurney et al., 2013). It is therefore likely that treatment data are also differentially missing by mental health status, with the most advantaged group (those without mental health problems) being more likely to access private treatment and therefore being less likely to have complete treatment data available. Therefore, treatment data were not used beyond the exploratory stage.

Table 28 Variables used in cancer cohort description and survival analysis

Variable set	Variable	Values	Comments and definitions
Unique identifier	Study ID		
MHS use (exposure)	MHS use	Yes, No	Mental health service use in the five years prior to cancer diagnosis
	Diagnosis	Group A, Group B	Prioritised diagnosis of mental health service users, grouped in to Group A (schizophrenia and bipolar disorder) and Group B (all other diagnoses and those with no diagnosis defined)
	Inpatient	Yes, No	Inpatient at any time in the five years prior to cancer diagnosis
Cancer	Site	C50; C18-C20	
	Extent (Stage)	Local, Regional, Distant, Unstaged	
	Age at cancer diagnosis	18-64	
Demographics	Gender	F or M	
	Ethnicity	Māori, Pacific, Asian, European, other	Prioritised
		Māori, non-Māori	
	NZ Deprivation Index category	1-5	Deciles grouped as quintiles for regression analyses
Time and place	DHB region	North Midland Central Southern	
	Year of cancer diagnosis	2006-2010	
Comorbidity	Charlson score	0,1-2,3+	
	C3 Index continuous	-0.1-12	
	C3 index categorical	0, 1-2, 3+	
Treatment	Surgery	Y, N	Private treatment missing
	Chemotherapy	Y, N	Private treatment missing
	Radiotherapy	Y, N	Private treatment missing
Mortality	Cause of death	Cancer, non-cancer causes	Cancer death = death from breast or colorectal cancers (respectively) or death from metastatic cancer (C77-C80)

5.2.5 Missing data

Age and comorbidity had no missing data because of the way they were generated. Age was generated from date of birth and date of cancer diagnosis, both of which were required for inclusion in the study. For comorbidity, all available information on other diagnoses recorded on NMDS in the five years prior to cancer diagnosis was used to generate the score, and if no comorbid diagnoses were found in the five year period the C3 score was zero by definition.

Deprivation level was missing where information on area of residence at the time of cancer diagnosis was not available, or where no deprivation level had been mapped to the area of residence (for areas with very small populations and new residential areas the deprivation index is incomplete). Missing data were imputed using values from multiple other variables (age, sex (for colorectal cancer), ethnicity, cancer stage, comorbidity score and whether the person died) to impute a deprivation score. This multiple imputation was performed using the "Proc MI" procedure in the statistical software SAS, and five output datasets were created.

Those with missing stage data were treated as having unstaged disease and this was used as a stage category. Complete case analysis was also performed as a sensitivity analysis, excluding all those with missing stage.

Within each cancer cohort, missing data patterns were examined by mental health service use status (See Appendix Two, page 301). Stage was the most common missing variable and was more frequently missing in those who had used mental health services. On the other hand, deprivation and ethnicity were more commonly missing in those without a history of using mental health services.

Table 29 summarises the methods used to deal with missing data in Study Two.

Table 29 Methods used for dealing with missing data: Cancer survival cohort

Variable set	Variable	% missing (breast)	% missing (colorectal)	Method for dealing with missing data
MHS use (exposure)	MHS use	0	0	
	Diagnosis	8.7%	11.5%	Included in "no diagnosis" category together to those who had "no diagnosis" recorded, included in Group B where simplified diagnostic categories used
	Inpatient	0	0	
Cancer	Date of diagnosis	0	0	
	Site	0	0	
	Extent (Stage)	8.5%	10.9%	Unstaged category, complete case analysis (as a sensitivity analysis)
Demographics	Age at diagnosis	0	0	
	Gender	0	0	0
	Ethnicity	2.9%	3.3%	Include in non-Māori group
	NZ Deprivation Index category	3.2%	2.8%	Multiple imputation used to create values for missing data
Time and place	DHB region	0.1%	0.3%	Not used as a predictor
	Year of cancer diagnosis	0	0	
Comorbidity	Charlson score	0	0	
	C3 Index	0	0	
Treatment	Surgery	Unknown, likely to be differential	Unknown, likely to be differential	Not included in models
	Chemotherapy	Unknown, likely to be differential	Unknown, likely to be differential	Not included in models
	Radiotherapy	unknown	unknown	Not included in models
Mortality	Date of death	0	0	
Cause of death	Cause of death	0	0	

For the people with cancer and a history of mental health service use there was a lot of missing data for psychiatric diagnosis (as with the mental health service users cohort defined in the previous chapter). Table 30 shows the patterns of diagnosis for breast and colorectal cancer patients with a history of recent mental health service use. As described previously, mental health service users were categorised by diagnosis into Group A and Group B, and those with no diagnostic information were included in Group B.

Table 30 Mental health diagnoses by cancer type, mental health service users only

Mental health diagnosis	**Breast cancer**		**Colorectal cancer**	
	n	%	n	%
MHS total	401		174	
Group A				
Schizophrenia	68	17.0	21	12.1
BPAD[a]	44	11.0	12	6.9
Group B				
Depression	95	23.7	44	25.3
Anxiety	37	9.2	13	7.5
Other	5	1.2	6	3.4
Substance	33	8.2	27	15.5
No diagnosis[b]	84	20.9	31	17.8
No information[c]	35	8.7	20	11.5

a. Bipolar Affective Disorder; b. "no diagnosis" or "diagnosis deferred" recorded; c. no diagnostic information on clinical record

5.2.6 Descriptive analysis – comparing cohorts

Breast and colorectal cancer cohorts with a history of recent mental health service use (in the five years prior to cancer diagnosis) were compared to those without such a history in terms of demographics, cancer characteristics, and comorbidity.

Initial comparisons were made for each cancer cohort between those who had recently used mental health services and those who had not. Comparisons were then made separately for Group A and Group B mental health service users compared to those without a history of mental health service use.

Comparisons were made by personal factors such as age, sex and ethnicity, by level of community deprivation, by indicators of time and place (year of diagnosis and DHB region), by cancer stage at diagnosis, and by level of comorbidity. Proportions

were compared for each characteristic. Comparisons were also made on the basis of treatment receipt, however because of emerging information on the degree of bias in routine treatment data these results are presented in an Appendix only (see page 302).

The relationship between these possible predictors and the main outcome (cancer specific survival) was explored using Kaplan Meier failure plots.

5.2.7 Pathways exploration

A directed acyclic graph (DAG) was used to plot the assumed causal relationships to be investigated. A DAG is a causal diagram in which the direction of the arrows indicates the causal relationships assumed, and which does not include bidirectional relationships or loops.

Figure 10 (below) shows the DAG developed to guide the analysis. It includes demographic confounders, and more explicitly lays out important factors for cancer survival, for example by including cancer stage at diagnosis. Ideally, an analytical model would include all these factors, however routine data did not allow measurement of all these factors. The DAG was used to identify possible confounding and mediating factors.

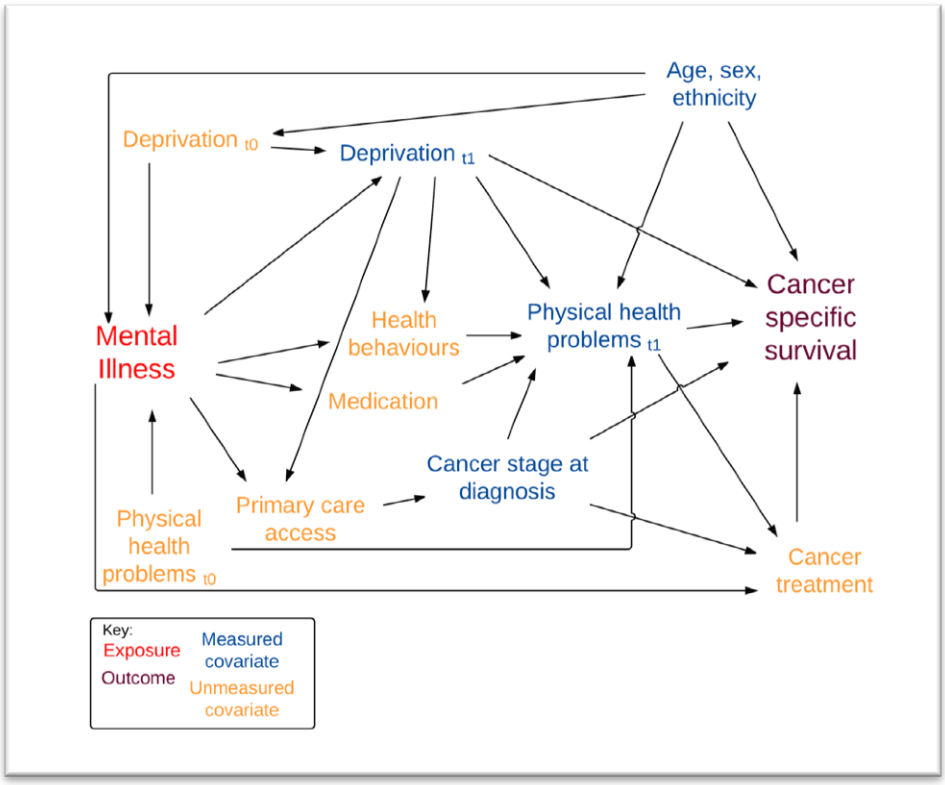

Figure 10 Directed Acyclic Graph (DAG) used for planning analysis

Age, sex and ethnicity are confounders of the relationship between mental illness and cancer survival, as they are prior causes of both.

Deprivation at t_0 (before cancer diagnosis) is also a prior cause for both mental illness and cancer survival. However, it was not possible to directly measure deprivation prior to cancer diagnosis and mental illness. Deprivation at t_1 (at cancer diagnosis) was measured, and will be strongly related to deprivation at t_0 (before cancer diagnosis), and so could be used as a proxy for deprivation at t_0. Deprivation at t_1 is also a mediator of the relationship between mental illness and cancer survival (as experience of mental illness can lead to living in more deprived circumstances). These two relationships are known as social causation (social deprivation leading to mental illness) and social selection (mental illness leading to social deprivation). There is evidence to suggest that both occur, and that social selection is stronger for more severe mental illness such as schizophrenia, while social causation is the stronger pathway for common mental illness such as depression (Dohrenwend et al., 1992). Deprivation at t_1 could therefore be included in the model as a mediator or a

confounder. In this case, I have chosen to treat deprivation as a mediator for my main model, on the basis that social selection is likely to be occurring for people with experience of mental illness disruptive enough to lead to contact with mental health services. However it should be noted that inclusion of deprivation at t_1 in the model will include the effects of both social causation and social selection, because of the strong correlation with prior deprivation (at t_0).

Mediating pathways through comorbid physical health problems, cancer stage at diagnosis, and cancer treatment were also identified. It was not possible to reliably assess the role of cancer treatment because of the high likelihood of differentially missing private treatment data. However the roles of cancer stage at diagnosis and comorbid physical health problems were assessed through sequential adjustment and model comparison.

5.2.8 Options for survival analysis

Survival in a population with cancer can be measured as time to death from any cause, or time to death from cancer (with deaths from other causes treated as censored or as competing outcomes). For a population with high rates of chronic disease, such as those using mental health services, all-cause mortality will be substantially higher compared to the general population (see Appendix Three, page 307). Cancer specific survival was therefore chosen as the main outcome to be used in the survival models. Cancer specific survival allows for investigation of factors influencing cancer survival independent of the overall higher mortality rates of those using mental health services (Sarfati et al., 2010a). In this method, bias can occur through misclassification of cause of death (deaths from cancer being misclassified as due to other causes and vice versa), particularly where misclassification occurs differentially (for example is more likely to occur in people using mental health services than others). Therefore, as a sensitivity analysis, time to death from any cause (all-cause mortality) was also used as the outcome of interest. This analysis will not have the problem of misclassification, as all deaths are treated as outcomes of interest. Comparison of the results for all cause and cancer specific survival models will indicate the magnitude of possible bias caused by misclassification.

In traditional (e.g. Kaplan-Meier) survival methods, deaths from causes other than cancer are treated as non-informative and are censored. This can cause selection bias where the risk of death from other causes is not independent of the risk of death from cancer (i.e. the people who die of other causes would have had a different risk of dying from cancer compared to those who did not die from other causes), because the censoring assumes that they would have had the same survival experience as others if they had not died from the other cause. In fact, death from (for example) cardiovascular disease or diabetic complications is not independent of the risk of death from cancer in a population with cancer – those who have the underlying chronic conditions that predispose to these causes of death also have an increased risk of dying from their cancer. Competing risk methods have therefore been developed to deal with this potential bias by treating deaths from other causes as competing events. However the bias caused by censoring competing deaths will depend on the proportion of all deaths that are caused by non-cancer causes. Where the population is relatively young, as in this study, deaths from other causes will be relatively rare and so the magnitude of bias will be small. Moreover, adjustment for comorbidity, which is a prior cause of both causes of death, will further reduce the effect of censoring competing deaths.

Most research examining cancer survival in the context of mental illness has used all-cause mortality as the outcome (for example (Chang et al., 2014) (Kisely et al., 2013) (Bergamo et al., 2014)), although cancer specific mortality (Batty et al., 2012b) or both cancer specific and all-cause mortality (Baillargeon et al., 2011) have also been reported. Competing risk methods are not common, but have been occasionally used (Dalton et al., 2007).

In this case, cancer-specific survival was used as the main outcome measure, and competing causes of death were censored in the main analyses, because the young population made other causes of death uncommon. However, the results from both traditional and competing risk methods were compared, to check that bias was not introduced through the method chosen.

5.2.9 Crude survival differences

The proportion of deaths due to cancer and due to other causes in each cohort was documented.

Kaplan Meier five-year survival curves for cancer-specific and all-cause mortality were estimated for those with and without a history of mental health service use, and visually compared to assess proportionality of hazards. Mental health service use was treated both as a binary variable (mental health service use vs not), and as a three level variable, with two levels of mental health service use (service use with psychosis diagnoses – Group A, and service use without these diagnoses – Group B), and well as the no service use group.

Failure curves (inverse survival curves) were also plotted using both Kaplan Meier (i.e. 1 – S(t) [the survival function]) and cumulative incidence (Fine Gray) methods (which take into account deaths from competing causes) (Haller et al., 2013). This allowed assessment of the possibility of bias arising from traditional methods, and consideration of the potential utility of competing risk regression methods in full regression analyses.

The crude relationships between each putative confounding or mediating factor and cancer-specific survival were also plotted using Kaplan Meier methods, in order to examine whether each of these factors was in fact associated with the outcome as hypothesised, and to assess the proportionality of hazards for each variable.

5.2.10 Cox regression models

Cox proportional hazards modelling was used to compare cancer-specific survival between those with recent mental health service use and those without, and to investigate the contribution of demographic confounders (age, sex, and ethnicity) and factors likely to be on the causal pathway (deprivation, comorbidity, and stage at diagnosis). The maximum post-diagnosis follow-up time for the survival analysis was five years.

Five models were fitted sequentially to assess the relationship between history of recent mental health service use and cancer survival, and the contribution of confounding and mediating variables. Model 0 provided the crude hazard ratios of cancer mortality comparing those with a history of recent mental health service use to those without. Both Group A and Group B were compared to those with no history of recent mental health service contact. Model 1 provided the HR estimate adjusted for demographic confounding factors (age, sex, and ethnicity). Model 2 was further adjusted for cancer stage at diagnosis. Model 3 adjusted for the additional impact of deprivation, and model 4 further adjusted for comorbidity. Stage at diagnosis was adjusted for prior to other potential mediators so that pre-diagnosis factors (which impact on stage at diagnosis) could be distinguished from post-diagnosis factors (impacting on prognosis after diagnosis).

The results of the full models (when treating other causes of death as censored) were compared with full models using the same exposure and confounder/mediator variables but treating deaths from other causes as competing outcomes.

All analysis was performed using SAS version 9.3, except for comparisons with cumulative incidence function plots and competing risk regression which used STATA version 13.

5.2.11 Sensitivity analyses

Sensitivity analyses were performed to investigate the impact of analysis decisions on the results, and to assess the potential for and magnitude of possible biases.

In order to assess the potential for misclassification bias by including those with missing stage at diagnosis as a separate ‘unstaged’ category, a complete data analysis was performed including only those with recorded stage at diagnosis. People with incomplete data on deprivation were also excluded from the complete data analysis.

In order to assess the likely impact of possible misclassification bias due to large amount of missing data on mental health diagnosis, an alternate method of distinguishing more from less severe mental illness was also used. This method

conceptualised severity on the basis of the use of inpatient services at any time in the five years prior to cancer diagnosis. The second exposure group were people who only used outpatient services over the five years prior to cancer diagnosis, and the comparison group were people with no history of mental health service use over this time.

Comorbidity was measured using a new index specifically developed for using New Zealand routine data to assess comorbidity in cancer patients. However, any measure of comorbidity will necessarily be subject to measurement error. The more commonly used Charlson Index (Charlson et al., 1987) was also used to estimate the proportion of cancer survival differences attributable to comorbidity. It should be noted that both of these indices use the same information sources to identify comorbidity, and so both will be subject to mismeasurement in a similar way. However, in order to compare to the results of other studies which have used Charlson to assess the burden of comorbid disease it was important to demonstrate the impact of choosing an alternative tool.

In order to assess the impact of excluding people with service use on a single day from the mental health service users group, main analyses were rerun including this group as mental health service users.

5.3 RESULTS: SELECTION OF STUDY COHORTS

A total of 8762 women with malignant (not in situ) breast cancers diagnosed between the ages of 18 and 64 and registered over the period 1/1/2006 to 31/12/2010 were identified from the New Zealand Cancer Registry. Of these women, 401 had had contact with mental health services for greater than one day in the five years prior to cancer diagnosis, and were treated as the exposed cohort, while all others formed the unexposed comparison group. Of those with recent mental health service use, 112 had a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder recorded (Group A), while 289 had no such diagnosis recorded (Group B).

A total of 4022 people diagnosed with malignant colorectal cancer between the ages of 18 and 64 over the period 1/1/2006 to 31/12/2010 were identified, of whom 174

had had contact with psychiatric services for greater than a single day in the five years prior. Of this group, 33 people had a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder recorded (Group A).

5.4 Results: Comparison of cohorts by mental health service use

Descriptive analysis was performed to examine the distribution of the cohort over time and place and the distribution of possible confounding and mediating factors by exposure status. The group with a history of mental health service use is presented divided into Group A (those with a history of diagnosis with schizophrenia, bipolar disorder or schizoaffective disorder), and Group B (a residual group of all other mental health service users).

Table 31 shows the characteristics of the cohort of women with breast cancer, by mental health service use status and mental health diagnosis. Women with a history of mental health service use were more likely to be of indigenous (Māori) ethnicity, live in deprived areas, and have a higher level of physical comorbidity than women without a history of mental health service use in the five years prior to cancer diagnosis, and these patterns were most marked for women in Group A. Women in Group B were more likely to be under 45, but the mean age was similar across all groups. Women in Group A had a less favourable distribution of cancer stage at diagnosis, with a higher proportion of cancers having spread to distant sites at diagnosis (9.8% vs. 4.8% for women in Group B and 3.3% for women without a history of recent mental health service contact).

The spread of cancer cases over time and place was similar between those with a history of mental health service use and those without. A similar proportion of the breast cancers included were diagnosed in each year and in each region.

Table 31 Breast cancer cohort demographic characteristics by mental health service use history and mental health diagnosis

	MHS use* Group A		MHS use Group B		No MHS use	
	n	%	n	%	n	%
Total number	112		289		8361	
Age at diagnosis (years)						
18-44	21	18.8	88	30.4	1757	21.0
45-64	91	81.3	201	69.6	6604	79.0
mean age	52.3		49.6		51.7	
Sex						
Female	112	100.0	289	100.0	8361	100.0
Ethnicity						
NZ Māori	31	27.7	56	19.4	1205	14.4
Non-Māori	81	72.3	233	80.6	7156	85.6
NZDep Quintile						
1	10	8.9	44	15.2	1681	20.1
2	11	9.8	43	14.9	1515	18.1
3	17	15.2	55	19.0	1604	19.2
4	34	30.4	69	23.9	1708	20.4
5	37	33.0	74	25.6	1633	19.5
NMDS comorbidity score						
0	62	55.4	197	68.2	7291	87.2
1-2	41	36.6	73	25.3	944	11.3
3+	9	8.0	19	6.6	126	1.5
Stage						
Local	53	47.3	148	51.2	4481	53.6
Regional	38	33.9	103	35.6	3041	36.4
Distant	11	9.8	14	4.8	279	3.3
Unstaged	10	8.9	24	8.3	560	6.7
Year diagnosed						
2006	22	19.6	52	18.0	1614	19.3
2007	19	17.0	46	15.9	1588	19.0
2008	25	22.3	58	20.1	1705	20.4
2009	24	21.4	61	21.1	1733	20.7
2010	22	19.6	72	24.9	1721	20.6
DHB region						
Northern	37	33.3	111	38.4	3187	38.1
Midland	16	14.3	44	15.2	1387	16.6
Central	33	29.5	65	22.5	1869	22.4
Southern	26	23.2	69	23.9	1905	22.8
Inpatient care						
Any	84	75.0	45	15.6	0	
None	28	25.0	244	84.4		

*MHS use = Mental health service contact >1day in 5 years prior to cancer diagnosis

One third of the women with a history of mental health service use prior to cancer diagnosis (129 women) had had inpatient mental health treatment in the five years prior to cancer diagnosis, of whom two thirds (84) also had a Group A diagnosis.

Table 32 shows the characteristics of the men and women with colorectal cancer, by mental health service use status and mental health diagnosis. A similar pattern to breast cancer is seen, with men and women with a history of recent mental health service contact more likely to be Māori, live in deprived areas, and have a higher burden of comorbidity. Both Group A and Group B were more likely to be female than those without a history of mental health service use, and people in Group B were more likely to be under 45. People in Group A were more likely to have their cancers diagnosed late than people in group B or people without a history of mental health service use.

The pattern seen for inpatient mental health care was different from that seen in the breast cancer cohort. Only one quarter of those with mental health service contact prior to cancer diagnosis had been treated as an inpatient. Of these people, 30% (14) had a Group A diagnosis.

Receipt of treatment including surgery, chemotherapy and radiotherapy was also examined for colorectal and breast cancers, comparing people with a history of recent mental health service contact with those without such a history. However cancer treatment data is known to be missing in a non-random way in routine data collections in New Zealand(Gurney et al., 2013) Cancer treatment comparisons are therefore likely to be misleading, and so are provided as an appendix only (see Appendix Two, page 302).

Table 32 Colorectal cancer cohort demographic characteristics by mental health service use history and mental health diagnosis

	MHS use* Group A		MHS use* Group B		No MHS use	
	N	%	N	%	N	%
Total number	33		141		3848	
Age at diagnosis						
18-44	4	12.1	34	24.1	458	11.9
45-64	29	87.9	107	75.9	3390	88.1
Mean age	54.4		52.7		55.3	
Sex						
Female	17	51.5	73	51.8	1765	45.9
Male	16	48.5	68	48.2	2083	54.1
Ethnicity						
NZ Māori	3	9.1	22	15.6	332	8.6
Non-Māori	30	90.9	119	84.4	3516	91.4
NZDep Quintile						
1	3	9.1	17	12.1	754	19.6
2	5	15.2	26	18.4	660	17.2
3	1	3.0	25	17.7	793	20.6
4	9	27.3	43	30.5	831	21.6
5	15	45.5	29	20.6	700	18.2
NMDS comorbidity score						
0	22	66.7	92	65.2	3332	86.6
1-2	8	24.2	33	23.4	390	10.1
3+	3	9.1	16	11.3	126	3.3
Stage						
Local	4	12.1	37	26.2	891	23.2
Regional	13	39.4	47	33.3	1502	39.0
Distant	13	39.4	33	23.4	841	21.9
Unstaged	3	9.1	24	17.0	614	16.0
Year diagnosed						
2006	2	6.1	26	18.4	779	20.2
2007	9	27.3	20	14.2	721	18.7
2008	11	33.3	27	19.1	755	19.6
2009	5	15.2	33	23.4	793	20.6
2010	6	18.2	35	24.8	800	20.8
DHB region						
Northern	12	36.4	42	29.8	1224	31.8
Midland	6	18.2	22	15.6	659	17.1
Central	6	18.2	33	23.4	834	21.7
Southern	9	27.3	44	31.2	1118	29.1
Inpatient care						
Any	14	42.4	34	24.1		
None	19	57.6	107	75.9		

*MHS use = Mental health service contact >1day in 5 years prior to cancer diagnosis

5.5 RESULTS: BREAST CANCER SURVIVAL

This section presents the results of breast cancer survival analysis. Results for the colorectal cancer cohort are presented in the following section.

Firstly, crude comparisons were made between survival in mental health services users and others. Secondly, Cox proportional hazards regression analysis was used to adjust for confounding and estimate the importance of mediators.

5.5.1 Mortality and crude survival differences

Table 33 shows numbers of deaths that occurred during follow up time in each exposure group. A total of 529 deaths occurred in the follow up period. The majority of deaths (474) were from breast cancer or metastatic cancer, and very few deaths were from other causes. Approximately 10% of deaths (55 deaths) were due to other causes, with a higher proportion of deaths for people in Group A (3/17, or 18%) but small absolute numbers in this group. Within other causes, other cancer sites were the most common causes of death (n= 18). Cardiovascular causes (11) and external causes (4) were the most common non-cancer causes of death, with the remaining deaths from a wide variety of causes including diabetes and congenital conditions.

The low proportion of deaths from other causes means that standard cancer-specific survival analysis methods are likely to give similar results to methods that take into account the impact of deaths from competing causes.

Table 33 Mortality in breast cancer cohort by cause of death

	MHS use Group A		MHS use Group B		No MHS use	
	n	% of total cohort	n	% of total cohort	n	%
Total cohort	112		289		8361	
Total deaths	17	15.2	27	9.3	485	5.8
Deaths from breast cancer	14	12.5	24	8.3	436	5.2
Deaths from other causes	3	2.7	3	1.0	49	0.6

Kaplan Meier plots were used to examine crude breast cancer-specific survival differences by mental health service use and by mental health diagnosis. Figure 11 shows breast-cancer specific survival plotted against analysis time in years, comparing women with a history of contact with mental health services for greater than one day in the five years prior to cancer diagnosis (red line) to women without such a history of contact with mental health services (blue line). 95% confidence limits are shown. The log-rank test gave a significant result ($X^2 = 17.9$, $p < 0.0001$), supporting the finding of a difference in survival between the two groups. Figure 12 also shows breast-cancer specific survival, but with the two groups of women with a history of mental health service use shown separately – Group A (women with recorded diagnoses of schizophrenia, bipolar affective disorder or schizoaffective disorder) – shown in red, and Group B (all other women with a history of mental health service use for greater than one day in the five years prior to cancer diagnosis) – shown in green. Confidence intervals are not shown on this plot because the main result lines would be obscured. The log-rank test gave a significant result ($X^2 = 19.9$, $p < 0.0001$), supporting the finding of a difference in survival between the three groups.

All-cause survival was also plotted using Kaplan Meier methods. Figure 13 shows all cause survival plotted against time for Group A and Group B and women with no history of recent mental health service contact. A very similar pattern is shown to that found for breast cancer-specific survival. Again the log-rank test gave a significant result ($X^2 = 26.96$, $p < 0.0001$), supporting the finding of a difference in survival between the three groups.

Standard methods for assessing survival differences were then compared to methods that take into account the competing risk of mortality from non-cancer causes. Figure 14 is a comparison of failure plots, comparing Kaplan Meier methods to estimate cancer-specific survival with competing risk methods. The same pattern is evident using the two methods, with Group A having a higher failure rate than Group B, who in turn have a higher failure rate than the group with no recent mental health service contact. Because of the low rate of non-cancer deaths, Kaplan Meier methods which

censor other causes of death do not create a spurious relationship between mental health service contact and cancer survival.

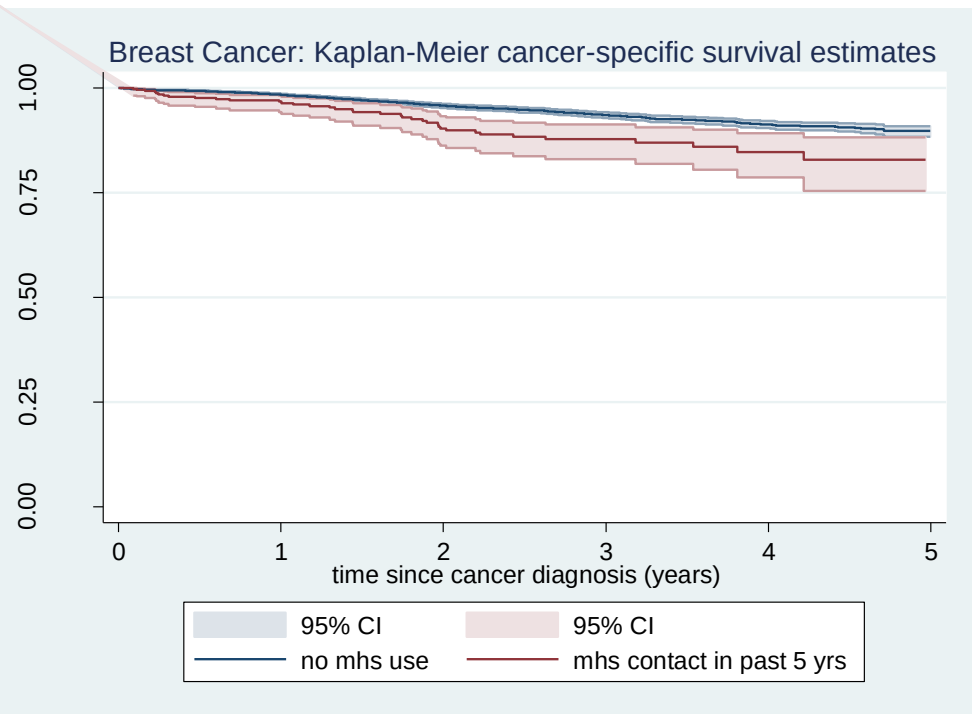

Figure 11 Breast cancer-specific survival KM plot, contact with mental health services in the five years prior to cancer diagnosis vs no contact

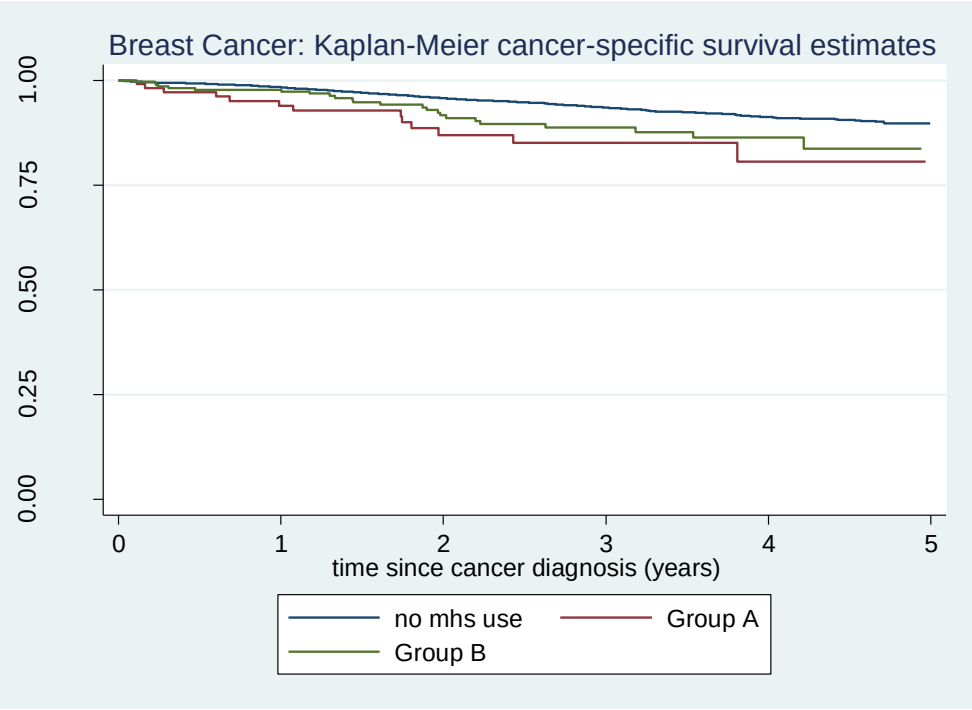

Figure 12 Breast cancer-specific survival KM plot, Group A and Group B vs no contact with mental health services

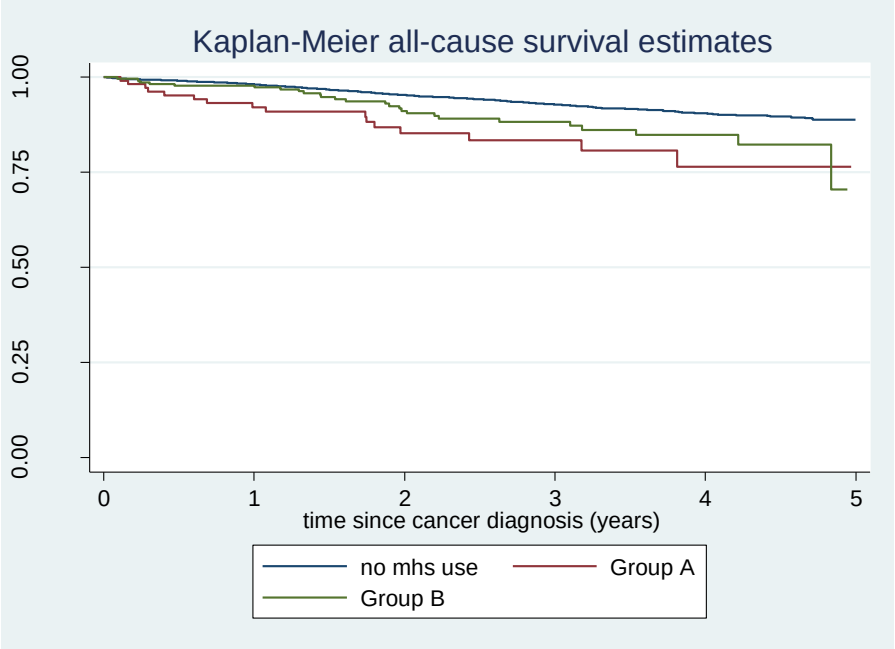

Figure 13 All-cause survival after breast cancer diagnosis: KM plot, Group A and Group B vs no contact with mental health services

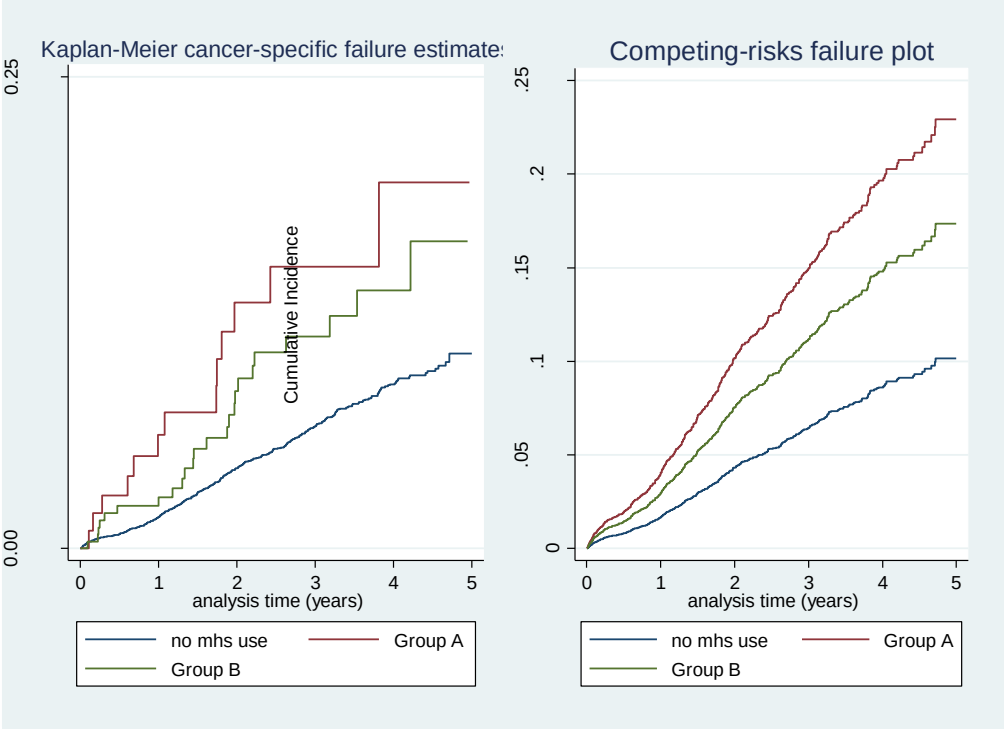

Figure 14 Comparison of cumulative incidence curves for Breast Cancer-specific survival, Kaplan Meier vs competing risk methods

5.5.2 Relationships between predictors and outcomes

The following Kaplan Meier plots demonstrate the crude relationships between the potential explanatory variables and cancer-specific survival.

When demographic variables were examined, age, ethnicity and deprivation all had clear relationships with cancer survival. Younger women were shown to have worse survival than those aged 45 and older. Māori women had worse survival than non-Māori. Women living in more deprived areas had worse survival than those living in affluent areas.

Measures of time and place had less influence on cancer survival. The year of diagnosis did not appear to make an appreciable difference to survival, although follow up time was limited for those diagnosed in later years. DHB region, which is a crude measure of health service geographical area, did not significantly predict survival.

Both stage at diagnosis and comorbidity as measured by the C3 index were strongly related to survival.

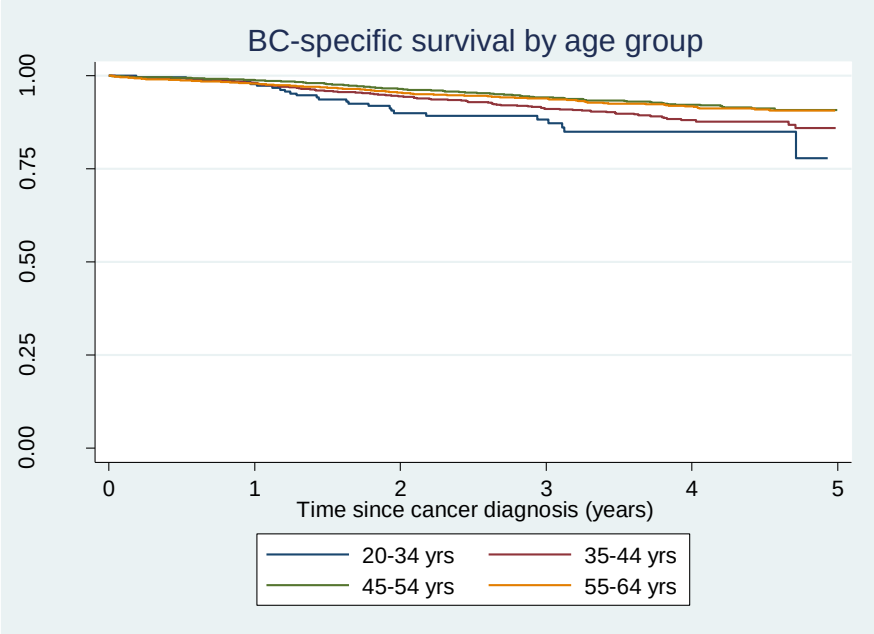

Figure 15 Kaplan Meier plot of breast cancer specific survival by age group

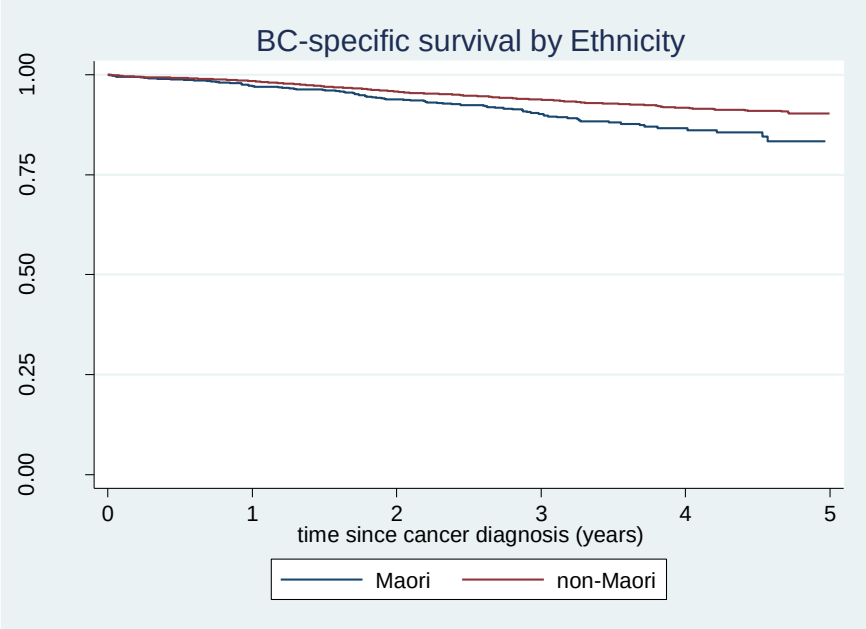

Figure 16 Kaplan Meier plot of breast cancer specific survival by ethnic group

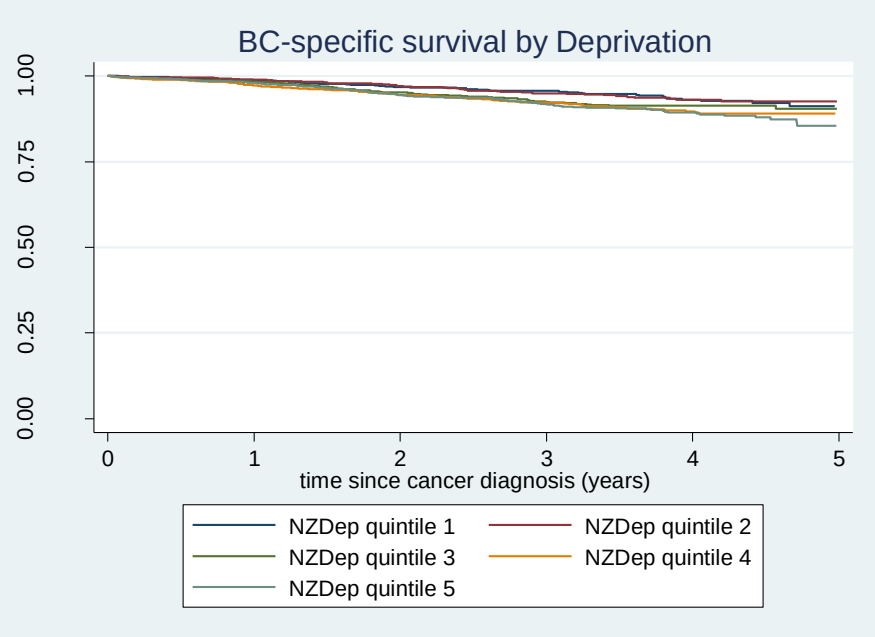

Figure 17 Kaplan Meier plot of breast cancer specific survival by deprivation

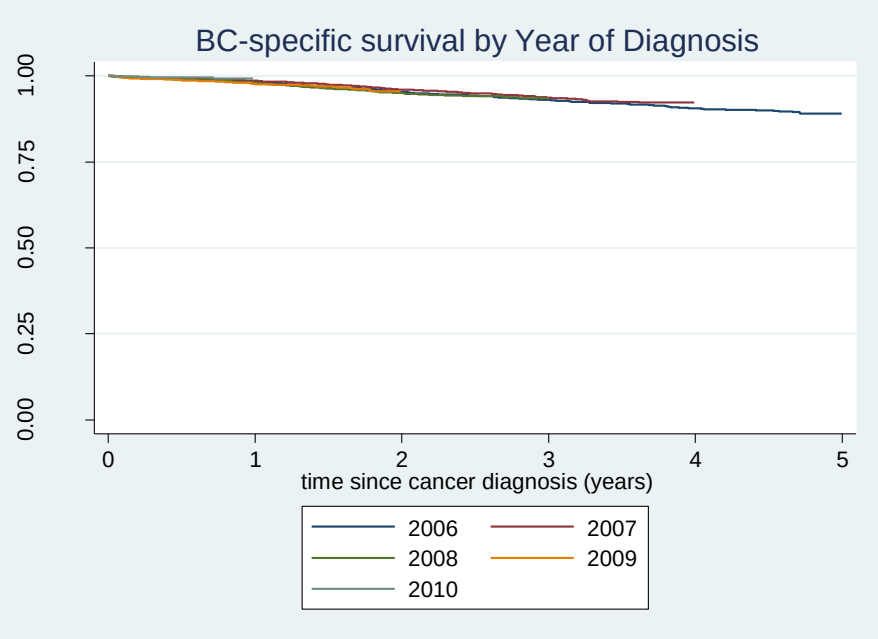

Figure 18 Kaplan Meier plot of breast cancer specific survival by year of diagnosis

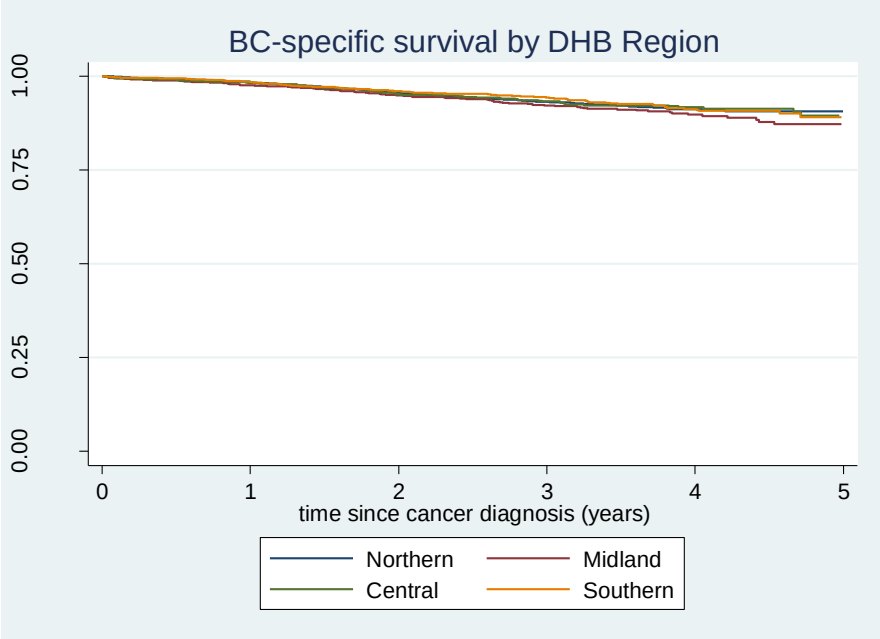

Figure 19 Kaplan Meier plot of breast cancer specific survival by DHB

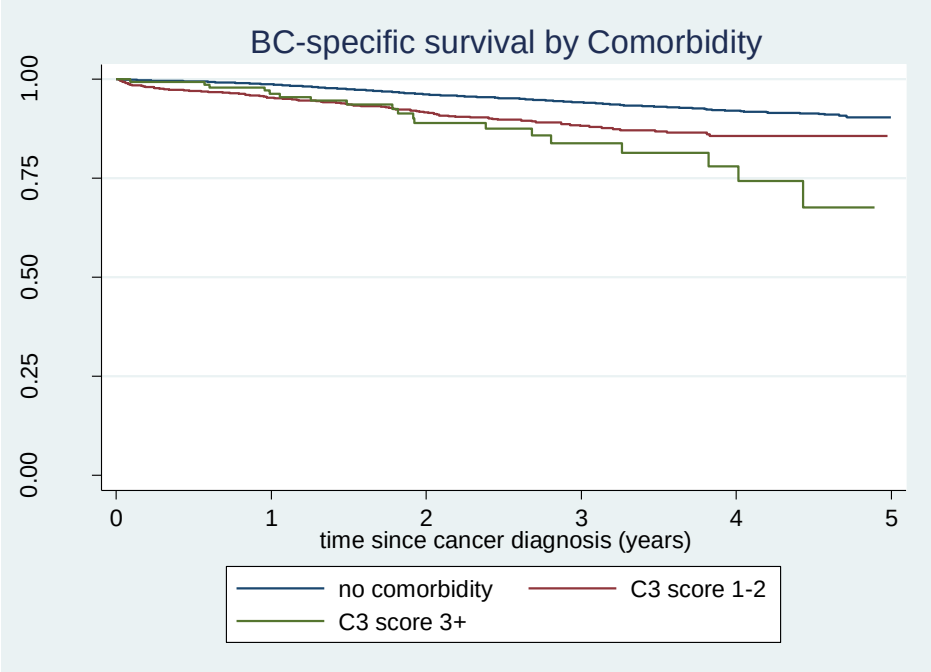

Figure 20 Kaplan Meier plot of breast cancer specific survival by comorbidity

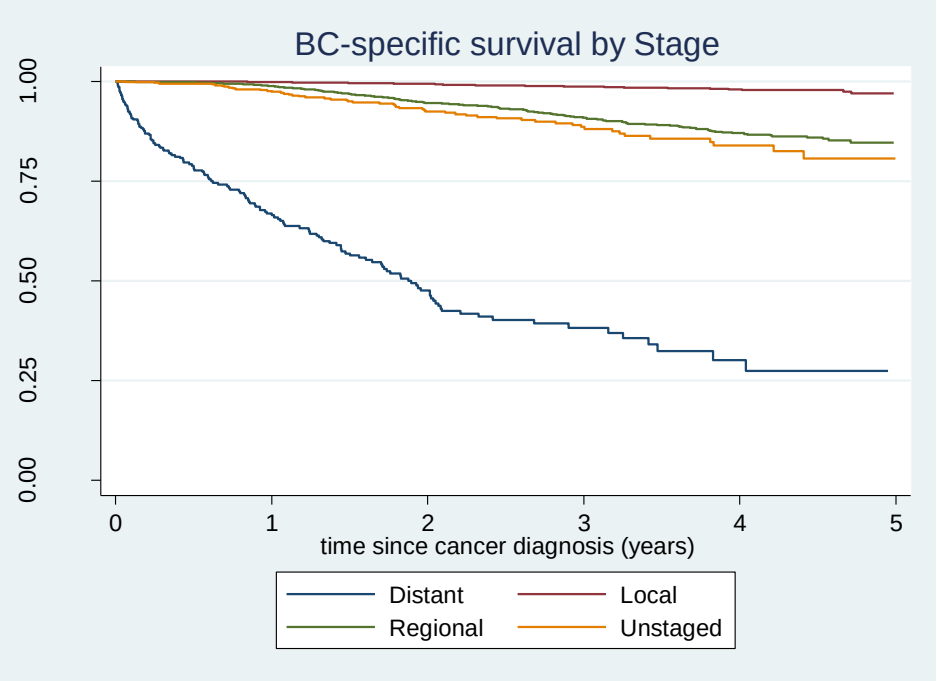

Figure 21 Kaplan Meier plot of breast cancer specific survival by stage at diagnosis

5.5.3 Cox regression models

Cox proportional hazards regression models were used to examine the role of confounders and mediators in producing the crude survival differences by mental health service history demonstrated above. The proportional hazards assumption was assessed as being met based on visual inspection of the Kaplan Meier curves above. Competing causes of death were treated as censored, because the outcome being examined was cancer mortality in the absence of death from other causes. Competing cause models were also run as a sensitivity analysis (see below).

Model 0 is the unadjusted model, and corresponds to the crude relationships already graphically demonstrated. This model gives the hazard ratio for survival for mental health service users compared to non-users of mental health services. Four models were then used to explore the magnitude of confounding and mediation.

Model 1 provides the estimate of the main association adjusted for confounding by age and ethnicity. DHB region and year of diagnosis were

also considered as possible confounders, but because of their small effect on survival (as shown above) and the limited numbers in the mental health service use groups, a decision was taken to limit the model to core factors and not include these potential confounders.

Model 2 further adjusts for stage of diagnosis, to assess the proportion of the remaining relationship between mental illness and cancer survival explained by stage at diagnosis.

Model 3 additionally adjusts for the impact of deprivation on cancer survival.

Model 4 further adjusts for a measure of physical comorbidity at the time of cancer diagnosis (the C3 index), in order to estimate the proportion of the survival difference explained by comorbidity not already accounted for by confounding, or the mediating effects of stage or deprivation.

Table 34 shows the results of Cox modelling for breast cancer specific mortality, comparing women with a history of contact with mental health services for greater than one day with women without such a history. Crude mortality was estimated to be nearly double for women with a history of mental health service use compared to other women (HR 1.99). Confounding (model 1), and stage at diagnosis (model 2) each accounted for approximately one sixth of the survival difference. Deprivation was not a significant contributor over and above the effects of confounders and stage at diagnosis. Comorbid illness (model 4) accounted for a further one sixth of the survival difference. After adjustment for all available factors, approximately half of the crude survival difference remained unexplained, with cancer mortality in the five years after cancer diagnosis being 48% higher in women with a history of mental health service use, and this difference in survival remained statistically significant (HR 1.48; 95% CI 1.05-2.08).

Table 34 Hazard ratio estimates (from Cox regression models) for breast cancer mortality according to mental health service use history, unadjusted and adjusted for confounders/mediators.

	MHS use[#]	
Model*	HR	95% CI
0	1.99	1.43 - 2.77

1	1.86	1.33 - 2.59
2	1.69	1.21 - 2.36
3	1.66	1.19 - 2.32
4	1.48	1.05 - 2.08

* 0 = crude survival; 1 = adj for age + ethnicity; 2 = 1 + SEER stage at diagnosis; 3 = 2 + NZ Deprivation Index score; 4=3 + C3 comorbidity index score
#401 women with a history of mental health service use, 8361 women with no history of mental health service use

Table 35 shows a similar sequential adjustment for confounders and mediators of breast cancer survival, separately examining factors for women diagnosed with schizophrenia or bipolar disorder (Group A) and women in contact with mental health services for other reasons (Group B). Women with Group A diagnoses had a much greater crude risk of dying from their breast cancer than women without a history of mental health service use (160% greater, HR 2.61). Women who had been in contact with mental health services for other conditions also had increased breast cancer mortality compared to women without a history of mental health service use (crude HR 1.74).

Adjustment for confounding by age and ethnicity (Model 1) slightly reduced the hazard of cancer mortality, but this remained significantly increased for both groups. Additional adjustment for differences in stage at diagnosis (Model 2) accounted for nearly half of the remaining survival difference for Group A, but did not account for any of the survival difference for Group B. Adjustment for deprivation (Model 3) did not reduce the estimates of the survival difference, after accounting for differences in stage and demographics. Comorbidity (Model 4) accounted for 20-30% of the remaining difference after adjusting for stage and deprivation for both Group A and Group B. After adjustment for all available factors, a substantial survival difference remained, and was similar in magnitude for Group A (fully adj. HR 1.64(0.95-2.83) and Group B (fully adj. HR 1.40 (0.93-2.13).

Table 35 Hazard ratio estimates (from Cox regression models) for breast cancer mortality according to mental health service use history and psychiatric diagnosis, unadjusted and adjusted for confounders/mediators.

	MHS use Group A#		**MHS use Group B#**	
Model*	HR	95% CI	HR	95% CI
0	2.61	1.53 - 4.45	1.74	1.16 - 2.63
1	2.54	1.49 - 4.34	1.61	1.06 - 2.43

2	1.84	1.07 - 3.16	1.62	1.07 - 2.44
3	1.81	1.05 - 3.11	1.59	1.05 - 2.40
4	1.64	0.95 - 2.83	1.40	0.93 - 2.13

*0 = crude survival; 1 = adj for age + ethnicity; 2 = 1 + SEER stage at diagnosis; 3 = 2 + NZ Deprivation Index score; 4=3 + C3 comorbidity index score
#112 women in Group A, 289 women in group B, 8361 women with no history of mental health service use

Table 36 shows the HR estimates for each factor in the fully adjusted model (model 4). Stage at diagnosis (regional, distant or unstaged disease vs local disease) was the strongest independent predictor of mortality. Age less than 50 and a comorbidity score of greater than zero were also associated with worse survival.

Table 37 shows the results of Chi squared tests for significance of the relationship of each factor with cancer survival in the final model. Age, stage at diagnosis and comorbidity score had p values less than 0.05 across all five imputed datasets, indicating that these factors were independent predictors of the outcome in the final model.

Table 36 Hazard ratio estimates (from Cox regression models) for breast cancer mortality according to mental health service use history and psychiatric diagnosis from fully adjusted model

Parameter	HR	95 CI	
No MHS use		Ref	
MHS Group A		1.64	0.95-2.83
MHS Group B		1.40	0.93-2.13
non-Māori		Ref	
Māori		1.15	0.90-1.46
Age 35*		2.04	1.59-2.62
Age 50		Ref	
Age 60*		1.13	0.96-1.34
Local stage		Ref	
Regional Stage		6.84	5.02-9.34
Distant Stage		86.40	62.26-119.91
Unstaged		9.26	6.29-13.63
NZDep 1		Ref	
NZDep 2		1.07	0.76-1.51
NZDep 3		1.29	0.93-1.78

NZDep 4	1.44	1.04-2.00
NZDep 5	1.24	0.90-1.70
C3 score 0	Ref	
1*	1.51	1.18-1.94
4*	2.21	1.62-3.02
6*	2.77	1.75-4.39

*Values taken from splined distributions (see Figures below)

Table 37 Chi-sq. tests and p values for each parameter in final model (range from imputed data sets)

Parameter	Degrees of freedom	Wald Chi squared (range)*	P value (range)*
MHS use	2	5.36 - 5.45	0.066 - 0.068
Ethnicity	1	1.09 - 1.41	0.235 - 0.269
Age	2	17.45 - 17.81	0.0001 - 0.0002
Stage	3	896.9 - 899.1	<0.0001
NZDep	4	4.84 - 10.64	0.031 - 0.305
C3 score	2	24.92 - 25.79	<0.0001

* range from 5 imputed datasets: < 0.0001 means all imputed datasets returned values lower than this limit

Figure 22 and Figure 23 show the association between age and comorbidity (respectively) and the risk of dying of breast cancer from the splined terms used in the fully adjusted main model. Age younger than 50 was associated with an increased hazard of breast cancer mortality. The non-linear association of age with death from breast cancer in this data set is apparent. For comorbidity, a non-linear increase in hazard of death with increasing C3 score is apparent.

Note that the majority of data points are within the two outermost dots (knots) on the red lines. Values beyond these points should therefore be interpreted with caution.

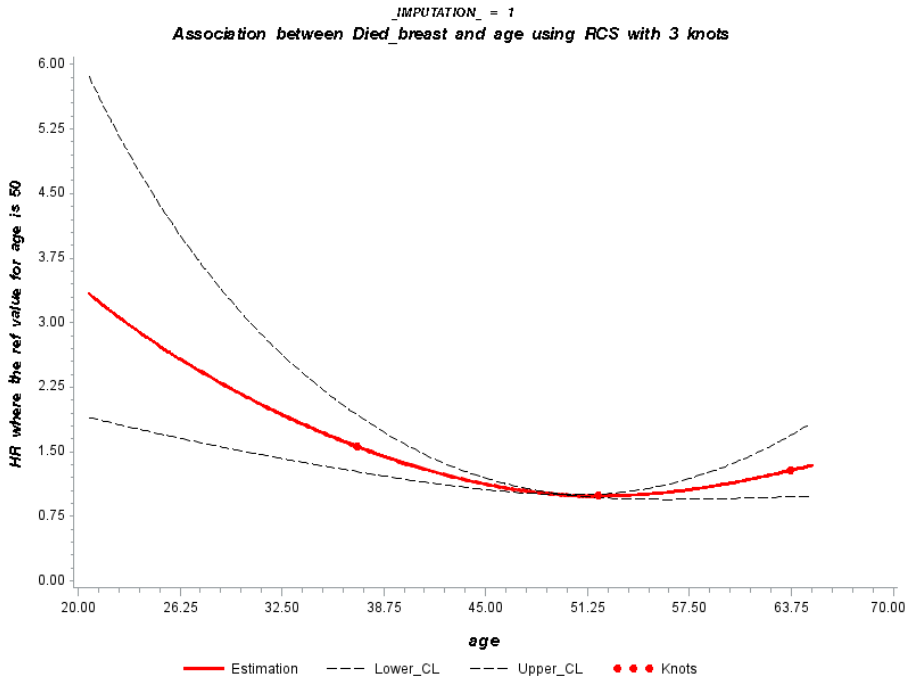

Figure 22 Association between splined variable age and breast cancer specific survival

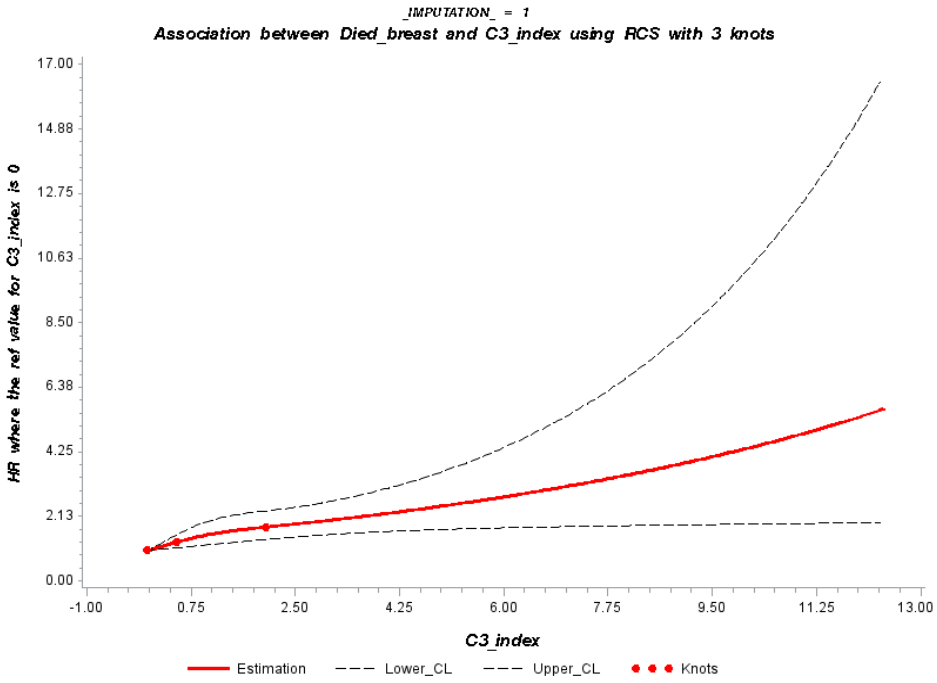

Figure 23 Association between splined variable C3 index score and breast cancer specific survival

Table 38 shows the same series of models of the association of mental health service use and breast cancer survival, but using all-cause rather than cancer-specific mortality as the outcome. A similar pattern is evident to that seen with cancer-specific survival, with significantly worse survival in Group A and Group B compared to those with no mental health service use history. Estimates of worse survival associated with mental health service use at each point in sequential regression are, however, greater than for cancer-specific survival. Stage at diagnosis (Model 2) (for group A) and comorbid physical illness (Model 4) (for both groups), were important factors in survival disparities.

Table 38 Hazard ratio estimates (from Cox regression models) for all-cause mortality in breast cancer patients according to mental health service use history and diagnosis, unadjusted and adjusted for confounders/mediators.

	MHS use Group A[#]		**MHS use Group B[#]**	
Model*	HR	95% CI	HR	95% CI
0	2.85	1.75 - 4.62	1.76	1.19 - 2.59
1	2.72	1.67 - 4.42	1.66	1.12 - 2.44
2	2.01	1.23 - 3.28	1.64	1.11 - 2.42
3	1.96	1.20 - 3.22	1.61	1.09 - 2.38
4	1.74	1.06 - 2.86	1.34	0.91 - 1.99

*0 = crude survival; 1 = adj for age + ethnicity; 2 = 1 + SEER stage at diagnosis; 3 = 2 + NZ Deprivation Index score; 4 = 3 + C3 comorbidity index score
#112 women in Group A, 289 women in group B, 8361 women with no history of mental health service use

5.5.4 Competing risk regression

Table 39 shows the Hazard Ratio estimates for Group A and Group B compared to those with no history of mental health service use, for both Cox regression models using breast-cancer specific survival as the outcome, and for competing risk models, where deaths from competing causes are treated as competing outcomes and not censored. Results are shown for crude (unadjusted) models and fully adjusted models (adjusted for age, ethnicity, stage, deprivation and comorbidity). The results produced by competing cause models do not differ in any substantial way from the results from cancer-specific survival models.

Note that the results for cancer specific survival in this table are slightly different from those presented in Table 35 because it was necessary to use STATA for competing risk regression and a simpler complete case analysis (without imputation or utilising splines to model variables) was performed using both methods to ensure comparability.

Table 39 Breast cancer: results of regression analyses modelling breast-cancer specific survival compared to competing risk regression

		MHS use Group A		MHS use Group B	
		HR	95% CI	HR	95% CI
Crude	Competing risk	2.43	1.39 - 4.26	1.78	1.18 - 2.68
	Cox ca-specific	2.47	1.42 - 4.30	1.78	1.18 - 2.68
Fully adj*	Competing risk	2.00	1.12 - 3.60	1.68	1.10 - 2.56
	Cox ca-specific	1.99	1.14 - 3.48	1.53	1.01 - 2.33

*adj for age + ethnicity + SEER stage at diagnosis + NZ Deprivation Index score + C3 comorbidity index score

5.6 RESULTS: COLORECTAL CANCER SURVIVAL

This section presents the results of colorectal cancer survival analysis. Firstly crude (unadjusted) comparisons were made between cancer survival in mental health service users and others, and secondly Cox proportional hazards regression analysis was used to adjust for confounding and estimate the importance of mediators.

5.6.1 Mortality and crude survival differences

Table 40 shows the crude data on deaths that occurred during follow up time in each exposure group. It can be seen that the majority of deaths were from the cancers and very few deaths were from other causes. Approximately 10% of deaths were due to other causes, with a slightly higher proportion in people with a history of mental health service use. Within other causes, other cancer sites were the most common causes of death (n=31). Cardiovascular causes (13) and external causes (i.e. accidental or intentional injuries) (9) were the most common non-cancer causes of death for both sites, with the remaining deaths from a wide variety of causes including diabetes, gastric ulcers and congenital conditions.

As with breast cancer, the low proportion of deaths from other causes means that standard cancer-specific survival analysis methods are likely to give similar results to methods that take into account the impact of deaths from competing causes. Using all-cause mortality as the outcome will also give similar results.

Table 40 Mortality in colorectal cancer cohort by cause of death

	MHS use Group A		MHS use Group B		No MHS use	
	n	% of total cohort	n	% of total cohort	n	%
Total cohort	33		141		3848	
Total deaths	15	45.5	41	29.0	952	24.7
Deaths from colorectal cancer	15	45.5	36	25.5	866	22.5
Deaths from other causes	0		5	3.5	86	2.2

Kaplan Meier plots were used to examine crude survival differences by mental health service use and by mental health diagnosis. Cancer specific and all-cause survival were examined.

Figure 24 shows that mental health service contact in the five years prior to colorectal cancer diagnosis is associated with worse cancer-specific survival particularly in the two years immediately following diagnosis. Figure 25 shows that within this overall worse survival, Group A have much worse survival than Group B.

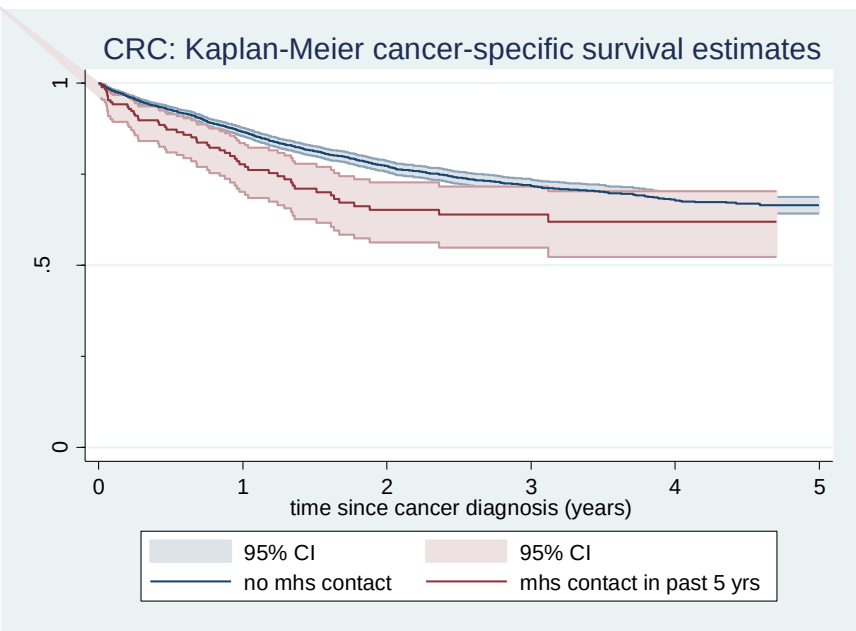

Figure 24 Colorectal cancer-specific survival KM plot, contact with mental health services in the five years prior to cancer diagnosis vs no contact

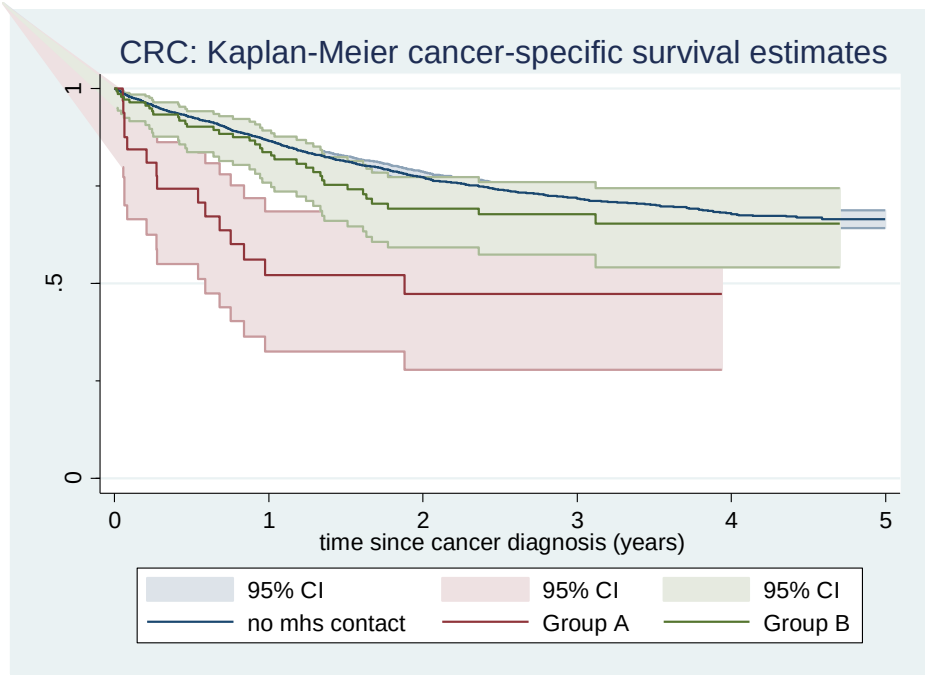

Figure 25 Colorectal cancer-specific survival KM plot, Group A and Group B vs no contact with mental health services

Figure 26 shows the KM plot of survival after colorectal cancer diagnosis for Group A and B and those with no mental health service use, using all-causes mortality as the outcome. A very similar pattern is seen to colorectal cancer specific survival, with worse survival in both groups of mental health service users compared to those with no history of mental health service use.

Standard methods for assessing survival differences were then compared to methods that take into account the competing risk of mortality from non-cancer causes. Figure 27 shows failure plots, comparing Kaplan Meier methods to estimate cancer-specific survival with competing risks methods. These show that the same pattern is evident using the two methods, with group A having a higher failure rate than Group B, who in turn have a higher failure rate than the group with no recent mental health service contact. Because of the low rate of non-cancer deaths, Kaplan Meier methods which censor other causes of death do not create a spurious relationship between mental health service contact and cancer survival.

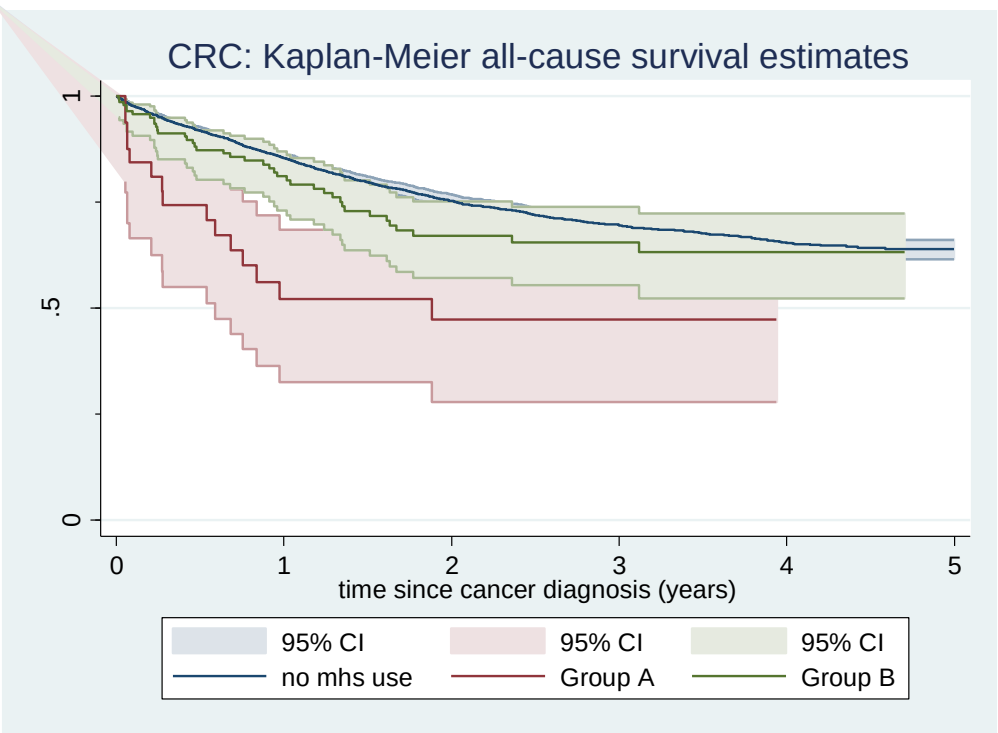

Figure 26 All-cause survival after colorectal cancer diagnosis: KM plot, Group A, Group B and no MHS use

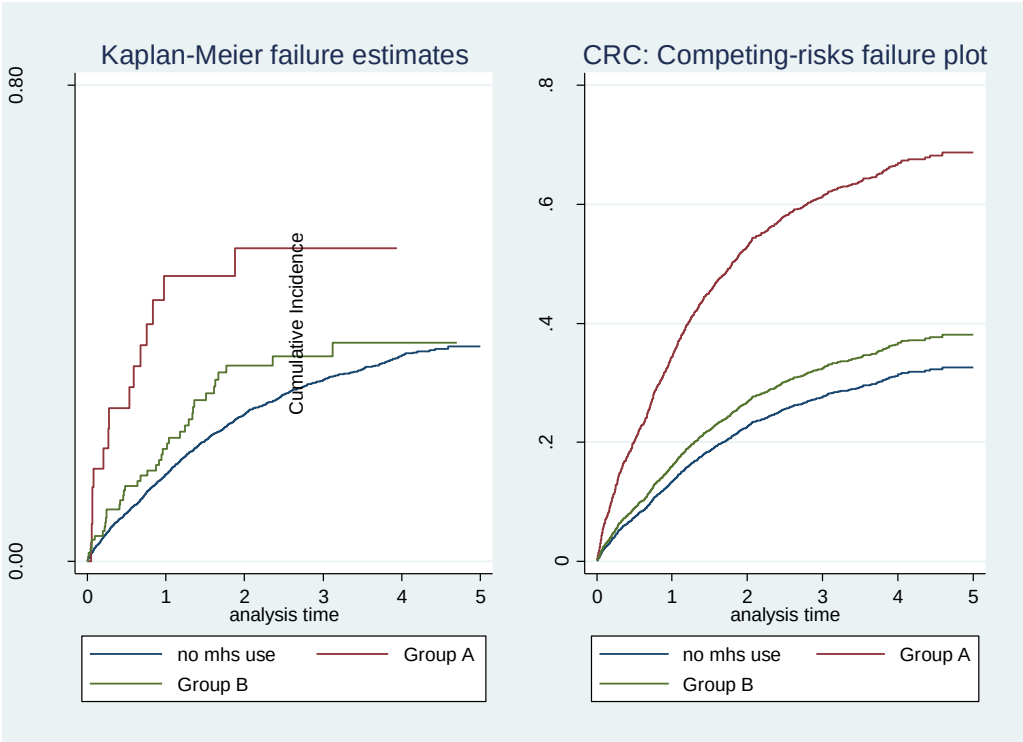

Figure 27 Comparison of cumulative incidence curves for Colorectal Cancer-specific survival, Kaplan Meier vs Competing risk methods

5.6.2 Relationships between predictors and cancer-specific survival

The relationships between each potential predictor and the main outcome (colorectal cancer-specific survival) were then examined. The figures below show the relationship between each predictor and colorectal cancer specific survival, plotted as Kaplan Meier curves.

Figure 28 demonstrates the relationship between colorectal cancer survival and age. Those under 35 appear to have the worst survival, particularly after the first year, while in the other age groups there is little difference in survival by age.

Figure 29 shows little variation in survival by sex, but a slight survival advantage for women.

Figure 30 shows worse cancer–specific survival for Māori compared to non-Māori at every time point.

Figure 31 shows worse cancer survival for those living in the most deprived areas (quintile 5).

Figure 32 and Figure 33 show little variation in survival by year of diagnosis or region of residence.

Figure 34 and Figure 35 show clear relationships between stage at diagnosis and comorbidity score and cancer-specific survival.

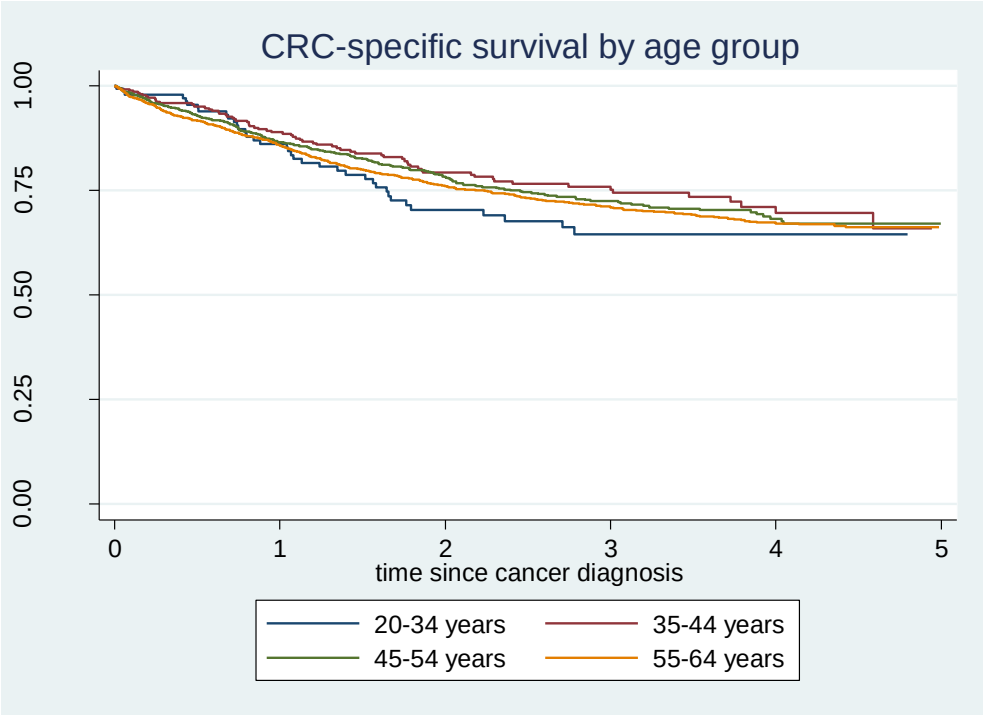

Figure 28 Kaplan Meier plot of colorectal cancer-specific survival by age group

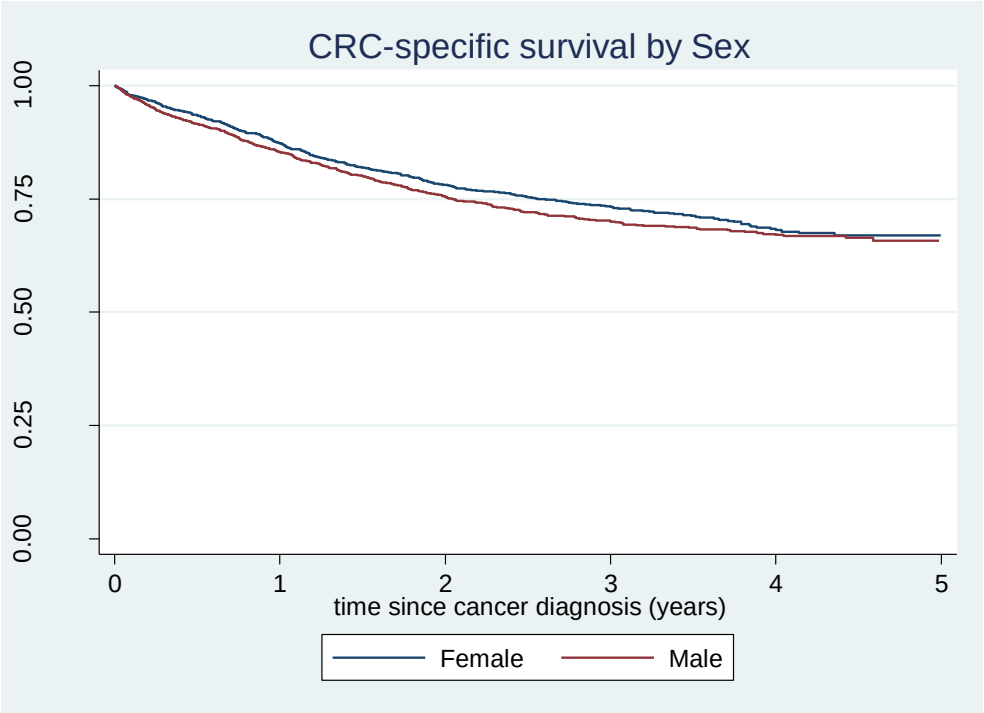

Figure 29 Kaplan Meier plot of colorectal cancer-specific survival by sex

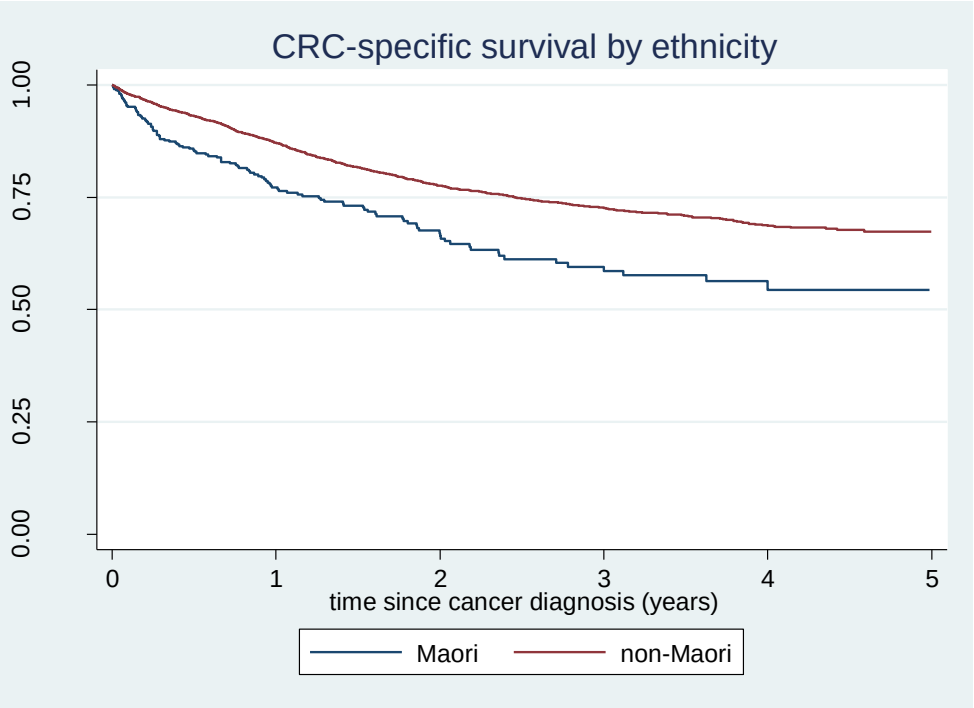

Figure 30 Kaplan Meier plot of colorectal cancer-specific survival by ethnicity

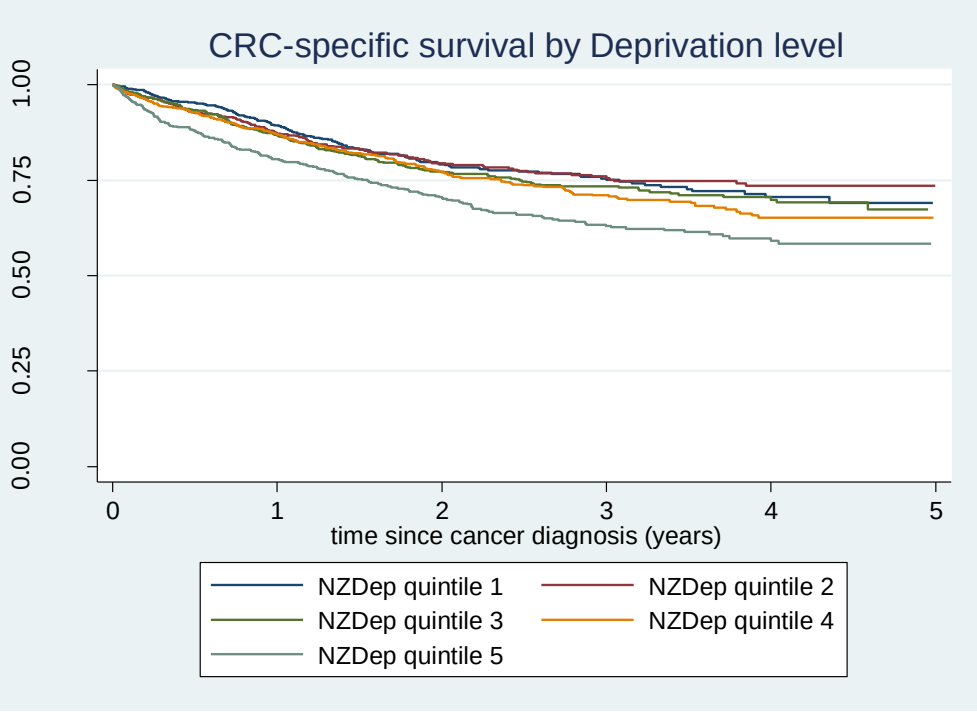

Figure 31 Kaplan Meier plot of colorectal cancer-specific survival by deprivation

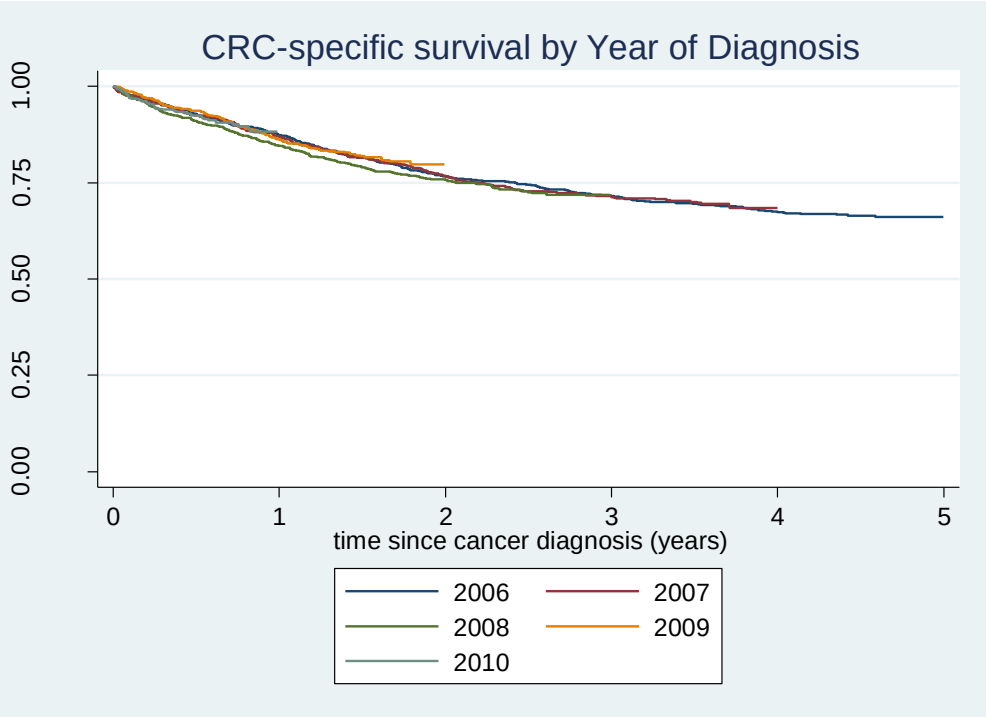

Figure 32 Kaplan Meier plot of colorectal cancer-specific survival by year diagnosis

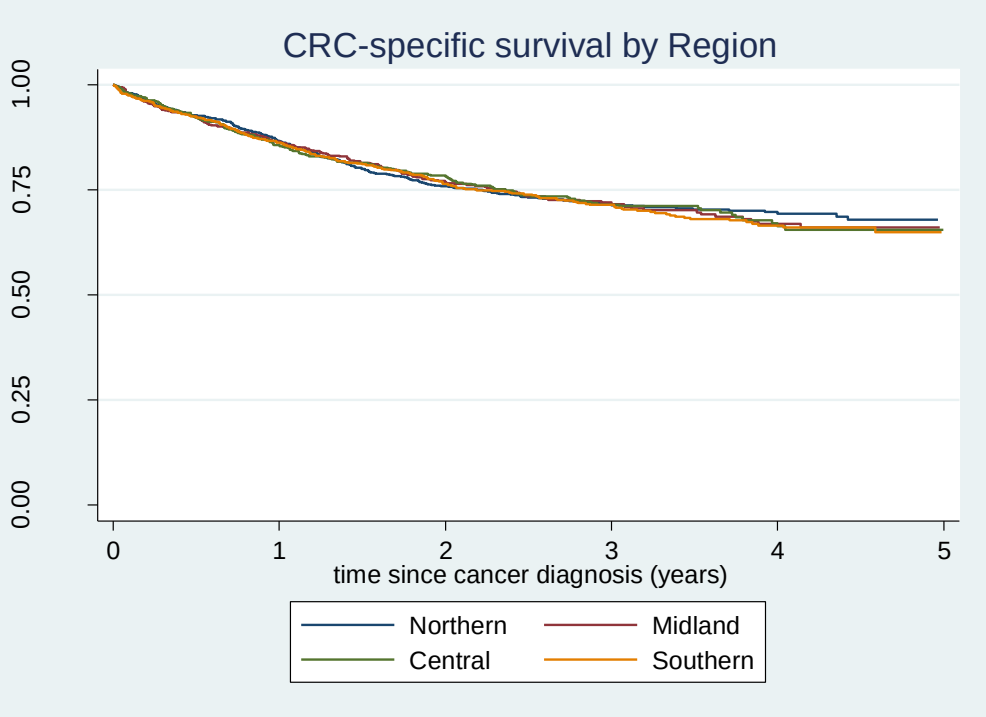

Figure 33 Kaplan Meier plot of colorectal cancer-specific survival by region

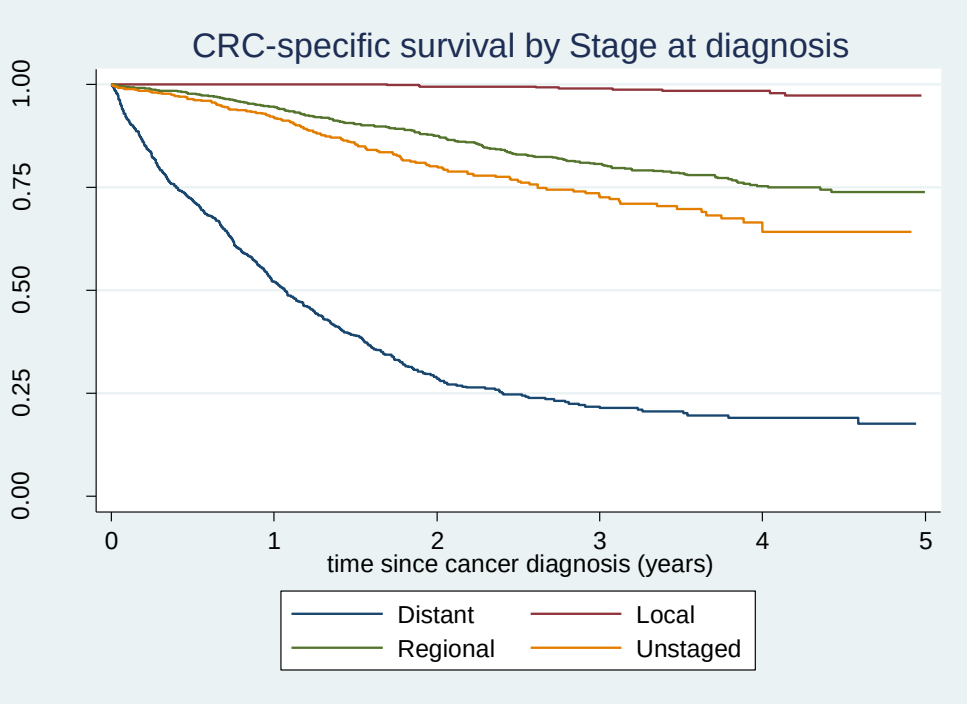

Figure 34 Kaplan Meier plot of colorectal cancer-specific survival by stage at diagnosis

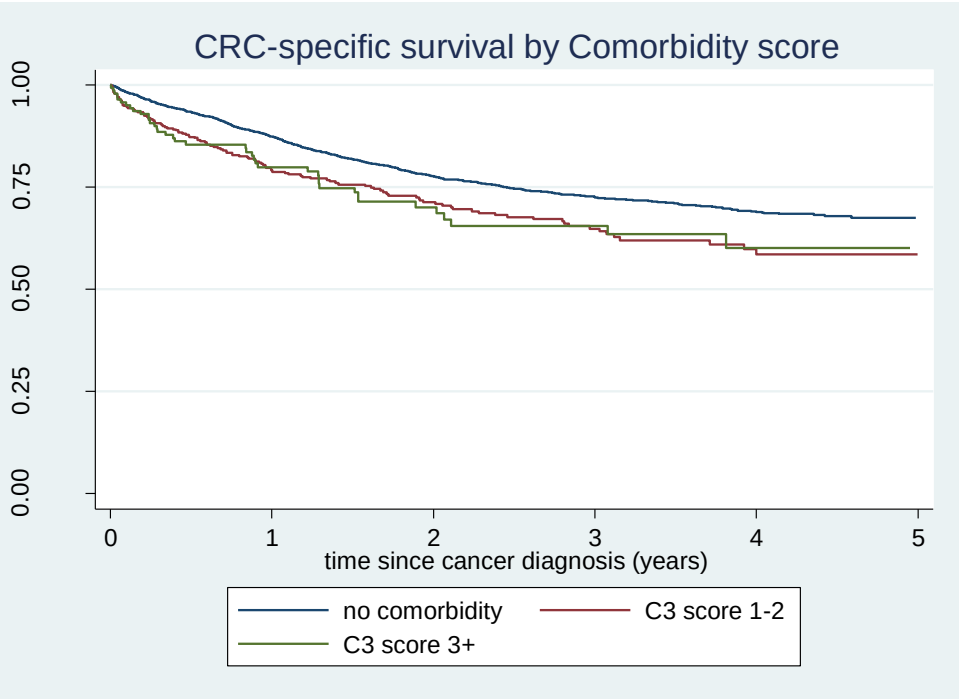

Figure 35 Kaplan Meier plot of colorectal cancer-specific survival by comorbidity score

5.6.3 Cox regression models

Cox proportional hazards regression models were used to examine the role of confounders and mediators in the crude survival differences demonstrated above. Four models were used.

Model 0 is the unadjusted model.

Model 1 is the estimate adjusted for confounding by age, sex, and ethnicity.

Model 2 further adjusts for stage of diagnosis, to assess the proportion of the remaining relationship between mental illness and cancer survival explained by stage at diagnosis.

Model 3 further adjusts for the level of small area residential deprivation as measured by the NZ Deprivation Index, to assess the proportion of the remaining difference explained by social deprivation amongst those using mental health services.

Model 4 further adjusts for the C3 measure of physical comorbidity at the time of cancer diagnosis, in order to estimate the proportion of the survival difference explained by comorbidity not already accounted for by confounding or stage differences.

Table 41 shows the risk of dying from colorectal cancer in those with a history of recent mental health service contact compared to those without such a history. In the crude (unadjusted) model, the hazard of dying is 50% increased for this group, and adjustment for confounding (Model 1) does not change the estimate appreciably. Further adjustment for stage of cancer at diagnosis (Model 2) increases the difference in survival for those with mental health service use compared to those without, suggesting that those using mental health services are overall having their cancers diagnosed earlier and if this were not the case then the observed difference in survival would be greater than suggested by analysis that does not consider stage. Further adjustment for socioeconomic deprivation did not change the estimate (Model 3). Adjustment for comorbidity (Model 4) reduced the estimate of the

increased risk of dying from colorectal cancer associated with mental illness, and after adjustment for all these factors the risk of dying from colorectal cancer was 45% higher in those with a prior history of mental health service use than in those who did not have such a history.

Table 41 Hazard ratio estimates (from Cox regression models) for colorectal cancer mortality according to mental health service use history, unadjusted and adjusted for confounders/mediators

	MHS use[#]	
Model*	HR	95% CI
0	1.50	1.13 - 1.99
1	1.46	1.10 - 1.93
2	1.66	1.25 - 2.21
3	1.63	1.22 - 2.17
4	1.45	1.08 - 1.94

*0 = crude survival; 1 = adj for age + sex + ethnicity; 2 = 1 + SEER stage at diagnosis; 3 = 2 + NZ Deprivation Index score; 4 = 3 + C3 comorbidity index score
174 people with a history of mental health service use, 3848 people without a history of mental health service use

Table 42 shows the results using the same models, but separately examining those with a history of recent mental health services use with diagnoses of schizophrenia or bipolar affective disorder (Group A) and those who had had contact with mental health services for other reasons (Group B), each compared to those without a history of mental health service use. People in Group A had markedly worse survival than those in Group B, for both crude survival and at each subsequent stage of adjustment. Adjustment for stage at diagnosis (Model 2) reduces the estimate of the survival difference markedly for Group A, while it increases the difference for Group B, suggesting that delayed diagnosis is a factor in survival disparities for Group A but not Group B. In contrast adjustment for stage results in an increased hazard ratio estimate for Group B, indicating that this group have worse survival than expected given their earlier cancer staging profile. Deprivation (Model 3) explains some of the survival difference for Group A, and comorbidity (Model 4) is a factor in poor survival for both groups.

Table 42 Hazard ratio estimates (from Cox regression models) for colorectal cancer mortality according to mental health service use history and psychiatric diagnosis, unadjusted and adjusted for confounders/mediators

	MHS use Group A[#]		MHS use Group B[#]	
Model*	HR	95% CI	HR	95% CI
0	2.84	1.70 - 4.73	1.25	0.90 - 1.75
1	2.92	1.75 - 4.87	1.20	0.86 - 1.68
2	2.17	1.30 - 3.63	1.51	1.08 - 2.12
3	2.00	1.20 - 3.36	1.51	1.08 - 2.11
4	1.89	1.13 - 3.17	1.32	0.93 - 1.86

*0 = crude survival; 1 = adj for age + sex + ethnicity; 2 = 1 + SEER stage at diagnosis; 3 = 2 + NZ Deprivation Index score; 4 = 3 + C3 comorbidity index score
33 people in Group A, 141 people in Group B, 3848 people without a history of mental health service use

Table 43 shows the HR estimates for each factor in the fully adjusted model (Model 4). Stage at diagnosis was the strongest independent predictor of mortality (HR 14.3 for regional disease and 115.18 for distant disease compared to local disease). Having a Group A diagnosis, Māori ethnicity, living in the most deprived areas, and having a comorbidity score of greater than zero, were all also associated with worse survival independent of other factors.

Table 44 shows the results of Chi squared tests for significance of the relationship of each factor with cancer survival in the final model. Mental health service use, ethnicity, deprivation, stage at diagnosis and comorbidity score had p values less than 0.05 across all five imputed datasets, indicating that these factors were independent predictors of the outcome in the final model.

Table 43 Hazard ratio estimates (from Cox regression models) for colorectal cancer mortality according to mental health service use history and psychiatric diagnosis for each parameter in fully adjusted model

Parameter	HR	95% CI
No MHS use	ref	
Group A vs no MHS use	1.89	1.13 - 3.17
Group B vs no MHS use	1.32	0.93 - 1.86
non-Māori	ref	
Māori	1.28	1.04 - 1.57
Female	ref	
Male	1.13	0.99 - 1.29
Age 35*	1.04	0.85 - 1.28
Age 50	ref	
Age 60*	1.04	0.94 - 1.15
Local stage	ref	
Regional Stage	14.13	7.72 - 25.88
Distant Stage	115.18	63.30 - 209.56
Unstaged	21.16	11.42 - 39.20
NZDep 1	ref	
NZDep 2	1.02	0.79 - 1.30
NZDep 3	1.04	0.82 - 1.31
NZDep 4	1.20	0.96 - 1.49
NZDep 5	1.26	1.01 - 1.57
C3 score 0	ref	
C3 score 1*	1.23	1.05 - 1.45
C3 score 4*	1.65	1.34 - 2.03
C3 score 6*	1.99	1.45- 2.72

*Values taken from splined distributions

Table 44 Chi-sq. tests and p values for each parameter in final model (range from imputed data sets)

Parameter	Degrees of freedom	Wald Chi squared (range)*	P value (range)*
MHS use	2	7.95 - 8.09	0.017 - 0.019
Ethnicity	1	5.28 - 5.81	0.016 - 0.022
Age	2	2.25 - 2.34	0.310 - 0.324
Sex	1	3.01 - 3.23	0.072 - 0.083
Stage	3	951.0 - 953.2	<0.0001
NZDep	4	22.7 - 23.1	<0.0001
C3 score	2	22.4 - 23.1	<0.0001

* range from 5 imputed datasets: < 0.0001 means all imputed datasets returned values lower than this limit

Figure 36 and Figure 37 show the association between age and comorbidity (respectively) and the risk of dying of colorectal cancer from the splined terms used in the fully adjusted main model. The hazard of death from colorectal cancer increases with age (reference = 50 years) and comorbidity score (reference = 0), and for age this trend appears to be linear.

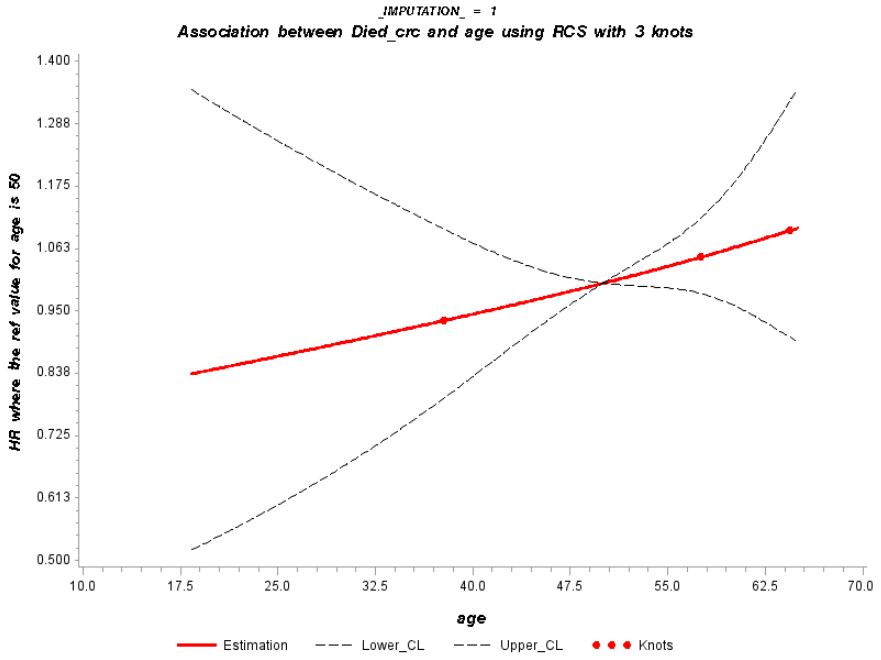

Figure 36 Association between splined variable age and colorectal cancer specific survival

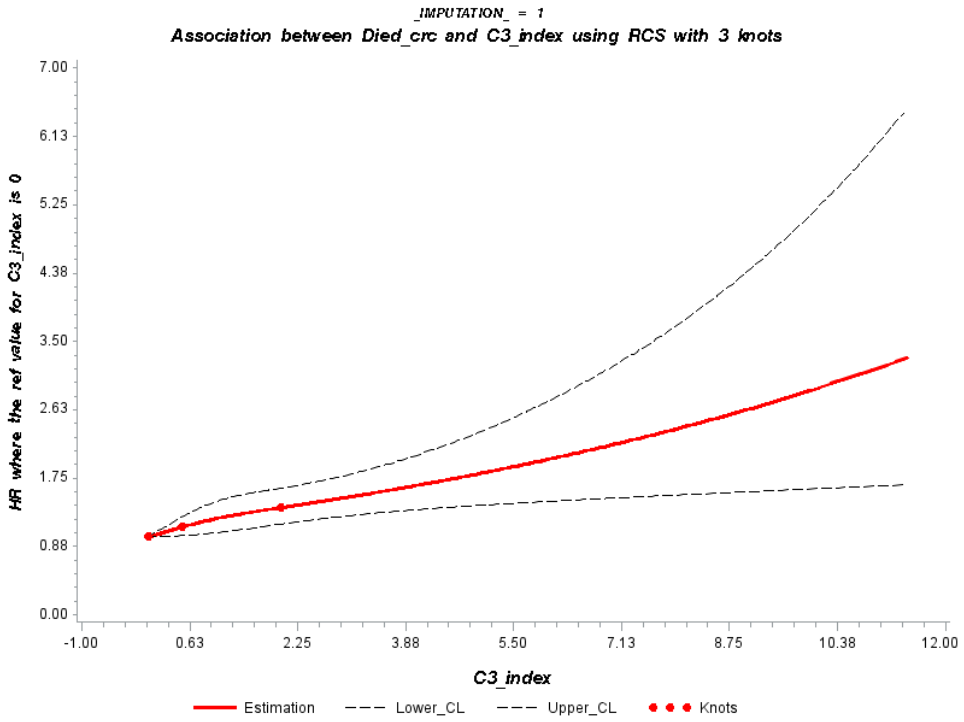

Figure 37 Association between splined variable C3 index score and colorectal cancer specific survival

Table 45 shows the same series of models of the association of mental health service use and colorectal cancer survival, but using all-cause rather than cancer-specific mortality as the outcome. A similar pattern is evident to that seen with cancer-specific survival, with significantly worse survival in Group A but not Group B compared to those with no mental health service use history. Stage at diagnosis (for group A) and comorbid physical illness (for both groups) were important factors in survival disparities. As with cancer-specific survival, earlier stage at diagnosis in Group B had a masking effect on the impact of mental health service use history on cancer survival.

Table 45 Hazard ratio estimates (from Cox regression models) for all-cause mortality in colorectal cancer patients according to mental health service use history and diagnosis, unadjusted and adjusted for confounders/mediators

	MHS use Group A		MHS use Group B	
Model*	HR	95% CI	HR	95% CI
0	2.58	1.55 - 4.30	1.30	0.95 - 1.77
1	2.68	1.61 - 4.47	1.25	0.91 - 1.71
2	2.00	1.20 - 3.33	1.54	1.13 - 2.12
3	1.83	1.10 - 3.07	1.54	1.12 - 2.11
4	1.72	1.03 - 2.89	1.26	0.91 - 1.74

*0 = crude survival; 1 = adj for age + sex + ethnicity; 2 = 1 + SEER stage at diagnosis; 3 = 2 + + NZ Deprivation Index score; 4 = 3 + C3 comorbidity index score

5.6.4 Competing risk regression

Table 46 shows the risk estimates for Group A and Group B compared to those with no history of mental health service use, for both Cox regression models using colorectal-cancer specific survival as the outcome, and for competing risk models, where deaths from competing causes are treated as competing outcomes and not censored. Results are shown for crude (unadjusted) models and fully adjusted models (adjusted for age, sex, ethnicity, stage, deprivation and comorbidity). As with breast cancer, the results produced by competing cause models do not differ in any substantial way from the results from cancer-specific survival models.

Table 46 Colorectal cancer: Results of regression analyses modelling colorectal-cancer specific survival compared to competing risk regression

		MHS use Group A		MHS use Group B	
		HR	95% CI	HR	95% CI
Crude	Competing cause	2.94	1.63 - 5.28	1.21	0.86 - 1.71
	Cox ca-specific	2.90	1.74 - 4.83	1.24	0.88 - 1.73
Fully adj*	Competing cause	2.08	1.10 - 3.94	1.30	0.91 - 1.85
	Cox ca-specific	1.96	1.17 - 3.29	1.31	0.92 - 1.86

* adjusted for age, sex, ethnicity, stage, deprivation and comorbidity

5.7 SENSITIVITY ANALYSES

Sensitivity analyses were performed to investigate the impact of analysis decisions on the results, and to assess the likelihood and magnitude of possible biases.

5.7.1 Complete case analysis

In order to assess the potential for misclassification bias due to the methods used to deal with missing data on stage and deprivation, a complete case analysis was performed, including only those with complete information on stage at diagnosis and deprivation.

For the breast cancer cohort, 571 people (6.5%) were missing stage at diagnosis information. Missing information on stage at cancer diagnosis was more common in women with a history of mental health service use (8.9% of women in Group A and 8.3% of women in Group B were missing stage). Missing stage was slightly more common in younger women (8.6% of 20-44 year olds); Māori women (8.1%); women living in the most deprived areas (8.2%); and women with more comorbid disease (9.7% of women with a C3 index score of 3 or more). For 227 women information was missing on the deprivation level of the place they lived (2.6% of the total cohort), of whom only 7 had a history of mental health service use. Missing deprivation information was more common in women with local or regional disease (7.3% and 4.7% respectively) but was not otherwise clearly patterned by other characteristics.

For the colorectal cancer cohort, stage was missing for 641 people (15.9% of the cohort), of whom 27 people had a history of mental health service use. Missing stage was more common for men (18%); Māori (19.3%); and people living in the most deprived areas (18.3%). Deprivation was missing for 111 people (2.8%), of whom only one person had a history of mental health service use. Missing deprivation information was not clearly patterned by other characteristics.

Table 47 (compare to Table 35) and Table 48 (compare to Table 42) show the results of running the same models on the data set restricted to people with complete stage

and deprivation information. For breast cancer 776 people were removed from the dataset for these analyses, and for colorectal cancer 731 people were removed.

The results were similar to the main analysis results (see Table 35 and Table 42). For breast cancer, the crude estimates of survival difference between mental health service users and others were similar between this restricted data analysis (Group A HR 2.77, Group B HR 1.65) and the analysis which included those with incomplete data (Group A HR 2.61, Group B HR 1.74). However fully adjusted models accounted for less of the difference in survival for Group A and the final estimate excluded the null (fully adjusted estimate 1.99 in this model compared to 1.64 in main model). The most notable difference from the main model is the extent to which stage explains the relationship between mental illness and cancer survival for Group A, with a lower proportion explained by stage in these restricted data models (seen as the difference between model 1 and model 2).

For colorectal cancer, the results found with restricted data were more similar to the main analyses than for breast cancer. However, full adjustment using complete data accounted for less of the difference in survival for Group A compared to the main analysis (fully adjusted estimate 1.92 in this model compared to 1.72 in the main model).

Table 47 Hazard ratio estimates (from Cox regression models) for cancer mortality in breast cancer patients according to mental health service use history and diagnosis, unadjusted and adjusted for confounders/mediators, including only those with complete stage and NZDep data (n=7964)

	MHS use Group A		MHS use Group B	
Model*	HR	95% CI	HR	95% CI
0	2.77	1.56 - 4.92	1.65	1.04 - 2.62
1	2.68	1.50 - 4.76	1.56	0.98 - 2.48
2	2.38	1.33 - 4.26	1.62	1.02 - 2.57
3	2.34	1.31 - 4.20	1.60	1.01 - 2.54
4	1.99	1.11 - 3.59	1.40	0.88 - 2.24

*0 = crude survival; 1 = adj for age + sex + ethnicity; 2 = 1 + SEER stage at diagnosis; 3 = 2 + NZ Deprivation Index score; 4 = 3 + C3 comorbidity index score

Table 48 Hazard ratio estimates (from Cox regression models) for cancer mortality in colorectal cancer patients according to mental health service use history and diagnosis, unadjusted and adjusted for confounders/mediators, including only those with complete stage and NZDep data (n=3291)

	MHS use Group A		MHS use Group B	
Model*	HR	95% CI	HR	95% CI
0	2.83	1.67 - 4.80	1.16	0.80 - 1.70
1	2.94	1.73 - 4.99	1.15	0.79 - 1.68
2	2.20	1.29 - 3.75	1.48	1.01 - 2.17
3	2.04	1.19 - 3.49	1.47	1.00 - 2.15
4	1.92	1.12 - 3.29	1.24	0.84 - 1.84

*0 = crude survival; 1 = adj for age + sex + ethnicity; 2 = 1 + SEER stage at diagnosis (complete); 3 = 2 + NZ Deprivation Index score (complete); 4 = 3 + C3 comorbidity index score

5.7.2 Using inpatient status as an alternate measure of severity

The use of inpatient services at any time in the five years prior to cancer diagnosis was used as an alternative to diagnosis as a measure of the severity of mental illness. The comparison group was people who only used outpatient services.

For the breast cancer cohort, 129/401 people with a history of recent mental health service use had used inpatient services (32%), of whom 65% had a Group A diagnosis. Demographic and other features of the inpatient group were similar to Group A (full information is given in Appendix Two, page 304).

For the colorectal cancer cohort, 48/174 people with a history of recent mental health service use had used inpatient services (28%), of whom 29% had a Group A diagnosis. The difference between inpatient and outpatient groups in demographic and other features was less marked than between Groups A and B, although comorbid illness was more common amongst those who had been treated as inpatients. (See Appendix Two, page 304).

Table 49 and Table 50 show the results from running the main models using this alternative measure of severity. For breast cancer, the results were similar using either measure of severity, with a large difference between the more severe and less severe group in terms of survival. For colorectal cancer, there was no difference in

cancer survival apparent between those using inpatient services and those using only outpatient services prior to adjustment. However, following adjustment for potential mediators, those using outpatient services only appeared to do worse (HR 1.63 compared to HR 1.13 for those using inpatient services).

Table 49 Hazard ratio estimates (from Cox regression models) for breast cancer mortality according to mental health service use history and type, unadjusted and adjusted for confounders/mediators

	MHS use inpatient		MHS use outpatient	
Model*	HR	95% CI	HR	95% CI
0	2.55	1.52 - 4.27	1.74	1.14 - 2.64
1	2.40	1.43 - 4.02	1.62	1.07 - 2.47
2	1.79	1.06 - 3.01	1.63	1.07 - 2.49
3	1.76	1.05 - 2.97	1.60	1.05 - 2.44
4	1.51	0.89 - 2.55	1.46	0.96 - 2.24

*0 = crude survival; 1 = adj for age + ethnicity; 2 = 1 + SEER stage at diagnosis; 3 = 2 + NZ Deprivation Index score; 4 = 3 + C3 comorbidity index score

Table 50 Hazard ratio estimates (from Cox regression models) for colorectal cancer mortality according to mental health service use history and type, unadjusted and adjusted for confounders/mediators

	MHS use inpatient			MHS use outpatient		
Model*	HR	95% CI		HR	95% CI	
0	1.46	0.88	2.43	1.51	1.08	2.11
1	1.44	0.86	2.41	1.46	1.05	2.04
2	1.42	0.85	2.38	1.79	1.28	2.50
3	1.38	0.82	2.30	1.76	1.26	2.46
4	1.13	0.67	1.91	1.63	1.16	2.29

*0 = crude survival; 1 = adj for age + ethnicity + sex; 2 = 1 + SEER stage at diagnosis; 3 = 2 + NZ Deprivation Index score; 4= 3 + C3 comorbidity index score

5.7.3 Alternative measures of comorbidity

The Charlson index was used as an alternative to the C3 index, to estimate the proportion of cancer survival differences attributable to comorbidity. Table 51 and

Table 52 show the results for the main models rerun using the Charlson index (compare to Table 35 and Table 42). The proportion of the survival difference explained by comorbidity is less using Charlson than it was using the C3 measure.

Table 51 Hazard ratio estimates (from Cox regression models) for cancer mortality in breast cancer patients according to mental health service use history and diagnosis, adjusted for confounders/mediators, comparing using Charlson and C3 to measure comorbidity

	MHS use Group A		MHS use Group B	
model	HR	95% CI	HR	95% CI
Full model* C3	1.64	0.95 - 2.83	1.40	0.93 - 2.13
Full model# Charlson	1.72	1.00 - 2.96	1.51	1.00 - 2.28

*adj for age + ethnicity + sex + SEER stage at diagnosis + NZ Deprivation Index score + C3 comorbidity index score; #adj for age + ethnicity + sex + SEER stage at diagnosis + NZ Deprivation Index score + Charlson comorbidity index score

Table 52 Hazard ratio estimates (from Cox regression models) for cancer mortality in colorectal cancer patients according to mental health service use history and diagnosis, adjusted for confounders/mediators, comparing using Charlson and C3 to measure comorbidity

	MHS use Group A		MHS use Group B	
model	HR	95% CI	HR	95% CI
Full model* C3	1.89	1.13 - 3.17	1.32	0.93 - 1.86
Full model# Charlson	2.01	1.20 - 3.36	1.38	0.98 - 1.95

*adj for age + ethnicity + sex + SEER stage at diagnosis + NZ Deprivation Index score + NMDS comorbidity index score; #adj for age + ethnicity + sex + SEER stage at diagnosis + NZ Deprivation Index score + Charlson comorbidity index score

5.7.4 Including mental health service use on a single day

For breast cancer, when people using mental health services on a single day were included as mental health service users, this resulted in an additional three people being classed as Group A and an additional 179 being classed as group B. Crude analyses were rerun, and for Group B the hazard ratio was reduced to 1.47 (1.02-2.12), compared to 1.74 (1.16-2.63) when this group were not included as mental health service users, while the HR for Group A was very slightly reduced (HR 2.57 (1.51-4.38) compared to 2.61 (1.53-4.45)).

For colorectal cancer, including this group of mental health services resulted in an additional two people being included in Group A and 47 additional people being included in Group B. Crude survival differences between Group A and those without mental health service use were unchanged (HR 2.85 (1.74-4.68) compared to 2.84 (1.7-4.73) when this group were not treated as mental health service users), while for Group B, the estimate of survival difference between this group and those without mental illness was reduced HR 1.18 (0.87-1.60) compared to 1.25 (0.9-1.75)).

Rerunning full analyses was not felt to be warranted.

5.8 SUMMARY AND CONCLUSIONS

This chapter investigated the relationship between mental health service use in the five years prior to diagnosis with breast or colorectal cancers and survival after cancer diagnosis. It demonstrates that there are clear differences in survival after cancer diagnosis when people are compared based on previous mental health service contact.

Much of the overall survival difference between people using mental health services and others was driven by much worse survival for people with schizophrenia and bipolar disorder diagnoses. However, there were also survival differences evident for other mental health service users.

A similar pattern was seen in the two cancers examined, with worse survival for people with schizophrenia and bipolar disorder, and with stage and comorbidity both playing important roles in survival differences. Nonetheless, differences were evident between the results for breast and colorectal cancers. In particular, there was some evidence that people with contact with mental health services for conditions other than schizophrenia and bipolar disorder have a more favourable distribution of stage at diagnosis for colorectal cancer than people without history of mental health service use.

Late stage at diagnosis plays an important role in explaining poor survival from both cancers in people with schizophrenia and bipolar disorder, and for women with breast cancer with a history of using inpatient services. Comorbid physical illness also plays an important role in explaining survival differences, for all of those with a history of recent mental health service use.

There are residual differences unexplained by the available information, and these differences may relate to differences in cancer treatment receipt. It was not possible to examine treatment receipt in a reliable way using routine data.

Chapter Six: DISCUSSION: STUDY STRENGTHS AND LIMITATIONS

6.1 INTRODUCTION

The usefulness of any study is dependent on the appropriateness of the methods used. This chapter considers the strengths and limitations of the study design and execution, and the way in which methodological decisions may impact on the study results and interpretation. It is the first of two discussion chapters. The second discussion chapter (Chapter 7) focuses on the interpretation and implications of study findings.

This chapter begins with a discussion of the data sources used, namely mental health service use data, the Cancer Registry, mortality data and hospitalisation data. Other possible data sources which were not used are also identified.

The epidemiological issues relating to the design of each of the studies are then explored, firstly the study of cancer burden (Study One), and secondly the study of cancer survival and its determinants (Study Two). For each study, potential sources of error are identified, including the role of bias, confounding and chance. The merits of alternative methods are discussed where appropriate.

6.2 DATA SOURCES

6.2.1 Possible sources of data to identify a history of mental illness

There are several sources of information which can be used to identify a population of people with experience of mental illness. Health surveys, in particular mental health surveys, collect information from a representative sample of the population on self-reported experience of mental health symptoms and diagnoses, sometimes combined with diagnostic interview data. Health service data provides information on people who have accessed care recorded as being for mental health problems: such care can be identified either through the diagnosis given (for example the

ICD10 devotes a chapter to mental health diagnoses, or specific diagnoses of interest can be identified), or the type of service provided (looking specifically at access to specialist mental health services). Health care insurance records can also be used to examine access to mental health services in some countries, such as the United States, where insurance is a major funder of health care.

Surveys identify the prevalent cases of mental disorder in the population. Prevalent cases or past diagnoses of physical health conditions such as cancer can also be identified. Survey results are useful for exploring the co-occurrence of conditions in the population, and recent work from the World Mental Health Surveys has demonstrated that the presence of chronic physical conditions is associated with an elevated likelihood of mental conditions, while mood and anxiety disorders are also associated with an elevated burden of a wide range of physical conditions (Gureje, 2009). However, investigation of the links between mental and physical health problems is limited to the data collected in the survey, as the data are generally anonymised and cannot be directly linked with other sources. This means that, in general, only cross sectional investigations are possible, which do not show the temporal relationship between physical and mental health problems that would allow us to consider causal conclusions. Interpretation of such results is difficult because of the known bidirectional relationship between mental and physical health. Moreover, where prevalent cases are identified, the cases with the longest duration are over-represented (known as length-biased sampling (Rothman et al., 2008)) and so estimates of burden, and of aetiological relationships, can be biased. This is a particular problem for conditions such as cancer, where there can be high early mortality but also many cases with a very long duration. Therefore estimates of cancer burden in people with experience of mental illness cannot be reliably drawn from survey data.

Health service use data, on the other hand, identifies a population who can be followed up over time, which allows for the investigation of the incident rate of cases, and of potential causal associations. However, unlike health surveys which will identify all (or most) cases in a representative population (if the questions ask about symptoms and not previous medical diagnoses), health service use data

depends on contact with health services, and so will systematically exclude people who do not present to services but nonetheless live with symptoms of mental illness. Where there are problems with access to health care, this may mean that certain groups of the population such as ethnic or socioeconomic groups are differentially missing from the people identified through these sources. Moreover, if psychiatric diagnosis is used as an identifying feature, this relies on a specific diagnosis having been made and documented, which is not always the case, particularly where contact with mental health services is brief. Therefore health service data will not identify everybody with experience of mental illness. It will however identify everyone with mental illness disruptive enough to bring them into contact with health services.

A cohort of people with experience of mental disorders can be identified from health service use data from primary care (by identifying care for which the main diagnosis recorded was a mental disorder) or from secondary care (by identifying the type of health service used, or the diagnosis given). Primary care data will identify the many people in the population diagnosed with common mental disorders. For example, each year approximately 9% of the New Zealand population visit a general medical health provider for a mental health problem (Oakley Browne et al., 2006). Secondary care data, on the other hand, will identify the smaller group with the most severe and disruptive disorders. In New Zealand, this is approximately 3% of the population in a given year (Wilson, 2000). This is the group whose illness is most socially stigmatised, and also the group more likely to be on psychiatric medications such as antipsychotics with physical side-effects, more likely to live in disadvantaged conditions, and more likely to experience premature mortality (Mitchell and Lawrence, 2011; Pope, 2011; Chang et al., 2011; Handiside, 2004).

Therefore, using the mental health service use data source allows identification of a national cohort of people among those most affected by mental illness, and with the mental health problems likely to be most disruptive to their lives. Further restriction by mental health diagnosis would have resulted in exclusion of a large proportion of the identified population.

6.2.2 Strengths and weaknesses of mental health services data used (PRIMHD)

This study focussed on people using secondary mental health services. In terms of practicality, this approach allows straightforward identification of a large group of people from anonymised routine health records as maintained by mental health services. Routinely collected national-level data on physical health status, including hospitalisations, cancer diagnosis, and mortality, can be linked to this mental health information using the health services unique identifier (the National Health Index - NHI).

This dataset allows identification of a complete national cohort of people in contact with public secondary mental health services. As the gate keepers of public secondary mental health services are clinicians, this group consists of those who have mental health troubles severe enough to be deemed by clinical staff to warrant mental health care.

There is very little private mental health care in New Zealand, and because private insurance provides little cover for mental health care, most of the private care is paid for by individuals (Wilson, 2000). The cost barriers to private care, coupled with the association between mental disorders and poverty, mean that people with more disruptive mental illness are seldom cared for privately. Moreover, care for the most severely unwell, notably compulsory care under the Compulsory Care and Treatment Act 1992, is provided exclusively in public services. Therefore, the group under the care of public health services will include all those whose mental illness is most disruptive of their lives.

Using routine data has some additional limitations. Secondary care data were not complete for those aged 65 or over, because of different reporting practices across the country (with psychogeriatric care reported as part of geriatric care in some places and as part of psychiatric care in others). This means that it was not possible to use PRIMHD to identify people in contact with mental health services aged 65 or older. Physical health problems, especially cancer, will be much more common in an older population. However, other work suggests that the physical health disparities

associated with mental illness are more pronounced at younger ages (Mortensen and Juel, 1993; Chang et al., 2010). Moreover, comparisons are being made to the general population at the same younger ages. This younger cohort is also more likely to be amenable to interventions to improve health outcomes and reduce the burden of premature death.

The available data on mental health service use combine assessment and treatment contacts, and it is not always easy to establish the purpose or outcome of contact from routine reporting. Routine data on mental health service use will include people with fleeting contacts with services, which may have been prompted by protocol rather than symptoms of mental illness (for example, psychiatric assessment is required before certain medical procedures such as organ or bone marrow transplant). The large amount of missing diagnosis information meant it was not sensible to limit this study to those with a recorded psychiatric diagnosis in order to limit the heterogeneity of the group identified as in contact with mental health services (as some studies have done, for example (Chang et al., 2014)). However, it was possible to limit by service contact length, by excluding people with contact only on a single day, and therefore to remove people who had contact for a single assessment only.

The PRIMHD dataset is designed for contractual and financial reporting, rather than for research, and very few studies have used this mental health service dataset for epidemiological research in New Zealand. In particular it is somewhat complex to extract information on contact with services, because a multitude of different types of contact are recorded, often with many different contacts recorded on a single day. This is in contrast to the hospital service use data more usually used in research, which is arranged around discrete admission episodes. Therefore, it was difficult to extract the relevant information from the data. Missing data were also a problem, partly due to the novelty of the dataset, with not all DHBs reporting all information in the study period. Psychiatric diagnosis was missing for a large proportion of the cohort. This was partly due to gaps in reporting, but also to the requirement for diagnosis to be recorded only after three months of service contact (unlike general hospital data where diagnosis is mandatory for all discharges). This meant that only

limited information on diagnosis could reliably be included. Other information, such as HoNOS (Health of the Nation Outcome Scale) scores which measure the health and social functioning of people using services, was not complete enough to use for this study.

Despite these limitations, it was possible to identify a national cohort up to the age of 64, limited by service length (>1 day), with some diagnostic information. It was also possible to link this cohort to other relevant data health including Cancer Registry, mortality, and other secondary care data sources.

6.2.3 Strengths and weakness of other data sources used

Other health service data sources were linked to the PRIMHD dataset using the National Health Index.

The New Zealand Cancer Registry was used to identify incident cases of cancer in the New Zealand population. Cancer registration by laboratories and health services is compulsory in New Zealand, and the Cancer Registry is widely used for research. Audits suggest that data quality is high and comparable to other cancer registries internationally (Stevens et al., 2008a; Cunningham et al., 2008).

The National Mortality Register was used to identify deaths from cancer. All deaths occurring in New Zealand are recorded; therefore it is likely to capture the majority of deaths from cancer in the population (with the exception of a small number of deaths among migrants who return to their home country prior to their death). Moreover, it is unlikely that deaths from cancer would be differentially missing in people with severe mental illness.

The NMDS hospital discharge database was used to provide information about comorbidities and cancer treatment. Routine hospitalisation data have been shown to provide reasonable information for comorbidity assessment in a cancer population (Sarfati et al., 2010b; Sarfati et al., 2014b). On the other hand, for assessment of cancer treatment, this data source has been shown to produce biased estimates of treatment rates (mainly because of missing private treatment data), and the bias is

differential on axes such as ethnicity (Gurney et al., 2013). Treatment records from this data source are therefore likely to produce differentially biased estimates of cancer treatment in mental health service users compared to people without a history of mental health service use. However, no other population-based data on cancer treatment is available. In order to validly estimate cancer treatment rates it would be necessary to manually extract information from both public and private clinical records, as was done in recent studies into ethnic inequalities in cancer treatment (Swart et al., 2013; Signal et al., 2014). This is, however, a very resource intensive process.

6.3 STRENGTHS AND WEAKNESSES OF CANCER INCIDENCE AND MORTALITY ANALYSES (STUDY ONE)

6.3.1 Summary of main issues for Study One

The main strength of this study was the use of linked national data to identify a complete cohort of adults in contact with mental health services and estimate cancer burden in this population. Methods were used to ensure a comparable comparison population and minimise selection bias, particularly bias due to invulnerable time.

Misclassification of a history of mental health problems was minimised by limiting the cohort to those who had had mental health service contact of greater than one day, and through the use of a sensitivity analysis restricted to people who had been diagnosed with schizophrenia or bipolar disorder. However for mortality analyses the population in contact with mental health services will include people who had contact with mental health services after cancer diagnosis which may result in an overestimate of cancer mortality. Misclassification of cancer diagnosis and cause of death was not likely to have affected the results. Good quality information on the main confounders (age and sex) was available.

Sufficient numbers were included to allow for precise estimates of cancer incidence and mortality, including for major cancer sites.

6.3.2 Study design – Study One

Choice of outcome for Study One

Cancer incidence was chosen as the primary outcome for the assessment of cancer burden. The New Zealand Cancer Registry provides a near complete dataset for estimation of cancer incidence, including information on date of diagnosis. In contrast, public health service use datasets (for example identifying all admissions for cancer) may miss some cases of cancer which are managed privately or in primary care, and not accurately allow estimation of time of diagnosis. The use of a health services dataset may also result in selection bias, because the probability of using hospital services for cancer may be related to the exposure (experience of mental illness).

Incidence and mortality for all cancers combined were used as the main outcome measures. This was done for two reasons. Firstly, small numbers limited the power to examine cancers separately (except for the most common cancers). Secondly, it was then possible to compare the results with other studies, and therefore test the hypothesis that the apparent low burden of all cancer combined found in many studies is related to the methods employed by these studies. Nevertheless, different cancers have different aetiologies and therefore different patterns in populations. Combining all cancers together can obscure the relationship between the exposure and individual cancers, where different relationships are present for different cancers. For example, Māori ethnicity is associated with low rates of colorectal and prostate cancers, but high rates of breast and lung cancers (Blakely et al., 2010; Cunningham et al., 2010). Combining all cancers together will obscure these different patterns and may result in a misleading overall association. In addition, the association between any exposure and all-cancer incidence and mortality will be heavily influenced by the distribution of cancers within the population and which cancers are more or less common. Therefore wherever possible, the relationship between experience of mental illness and cancer risk was also examined separately for individual cancers.

Choice of design for Study One

This study is a cohort study, where a group of people in contact with mental health services are identified and followed up for cancer diagnosis. The use of a cohort study design is appropriate, as the exposure under study (mental illness leading to contact with mental health services) is relatively rare (<3% annually) in the population. The comparison cohort is the general population, as identified from the census (denominator) and the Cancer Registry (numerator). It was not possible to identify a direct comparison cohort of non-mental health service users where all person time could be accounted for. Such a cohort would allow the use of survival analysis methods to estimate differences in cancer burden, and allow time before and after mental health service use to be identified separately.

More importantly, having a direct comparison cohort would allow competing risks to be taken into account. Where there is a higher risk of death from other causes in one group than another (in this case a higher risk of death from heart disease and from suicide in the group in contact with mental health services) this means there is less time at risk of developing cancer in this group (Rothman et al., 2008). This can be overcome by using rate measures which account for changes in population at risk or using time stratified rate comparisons. Full time stratification is survival analysis, but this requires information on the population at risk at each point in time and this is not available for the comparison population. Therefore time was stratified on an annual basis for both the population in contact with services and the general population. This will slightly overestimate the person time at risk (and therefore underestimate rates of disease) because deaths occurring during each year are not accounted for. This underestimation is likely to be differential as there will be higher death rates at each age in the mental health service use population. However, because rates are calculated on an annual basis and the number of deaths will be small, this will only result in a very slight underestimation of rates in the group with mental illness, and so will not markedly affect the comparison.

Choice of analysis method for Study One

As noted above survival analysis methods would have been preferable because they would allow for more accurate estimation of person time at risk. However by creating five one-year periods of risk in the exposed population it was possible to compare the annual risk between this population and the general population in an unbiased way using standardisation methods.

Indirect standardisation was used to allow comparison of cancer incidence and mortality rates in the group in contact with mental health services and the general population. The observed cancer incidence or mortality in those using psychiatric services was divided by the cancer incidence or mortality that would have been expected if those using psychiatric services had had the same patterns of cancer incidence or mortality by age and sex as the total New Zealand population. This method can be used for comparing rates of disease between a small sub-population and a larger national population, and takes into account the differences in the age and sex structure of these populations (which would cause confounding) (Rothman et al., 2008). It is preferable to direct standardisation in this case because the small numbers of cancers and deaths at each age in the mental health service use population mean that the age-specific rates of these outcomes (needed for direct standardisation) would be unstable.

6.3.3 Selection bias - Study One

Selection biases are distortions that result from the way cohorts are selected and the factors that influence participation in the study, where the relationship between the exposure and outcome is different in the population under study and the source population (Rothman et al., 2008). In this case, cohorts were selected by identification of all people with recorded contact with mental health services and all people with cancers registered over a certain time period. Some restrictions were placed on these selections, principally by age (restricted to age 20 to 64) and gender (restricted to those identified as female or male). The use of a complete national dataset minimises the chances of selection bias influencing the results.

Characteristics of cohorts as selected

Biases can occur when criteria that determine cohort selection result in differences in characteristics between exposed and unexposed cohorts that are also associated with the outcome. For example, the selection of the exposed cohort to exclude people with prior cancer, where this exclusion is only applied to the exposed group and not the control group, creates an association between prior cancer and the exposure. Prior cancer is also associated with the risk of subsequent cancer, and so unless this restriction is also applied to the unexposed cohort, the estimate will be biased. This bias (referred to earlier as "invulnerability bias" because the exposed population is required to be invulnerable to cancer) is likely to result in an underestimate of the rate of disease in the exposed cohort because a group with a higher risk of cancer have been excluded from this cohort. Where this exclusion was applied, in the sensitivity analysis using Design A (see chapter 4, page 140), a lower estimate of the cancer burden in people with mental illness compared to the general population was obtained. This bias does not apply in the main analyses, where cohort entry criteria did not specify prior cancer status.

Other possible selection bias

Immortality bias occurs when cohort selection requires having survived for a specified period of time, such as where mental illness is defined on the basis of contact with services at a specific point in time. This was identified as a potential problem in studies of cancer incidence in people with experience of mental illness in Chapter 3. However, this only causes bias where the time spent meeting the exposure criteria is included as time at risk of the outcome. In the main analyses for this study, no assessment was made of cancer burden prior to mental health service use, and so this problem did not arise.

This study identified a prevalent cohort of mental health service users, i.e. a cross-section of people in contact with services at a particular time. This cohort was then followed forward in time to estimate the risk of the outcome (cancer diagnosis or cancer death). The alternative is to identify an incident cohort of mental health service users (that is, a cohort of people who are followed up from the point at which

they are diagnosed with mental disorder, or from the point at which they first come into contact with mental health services) (Kisely et al., 2012). However, because information was only available back to 2000, it was not possible to identify the date of first-ever service contact from this dataset.

It has been argued that studies that use a prevalent cohort to examine the health of people using mental health services will be subject to survivorship bias (Kisely et al., 2013). Survivorship bias occurs when both the exposure and unmeasured risk factors for the outcome influence the chances of dying (Rothman et al., 2008). In this case, if having a mental illness influences mortality, and factors associated with the outcome (cancer), such as smoking rates, also influence mortality, then people who are selected into the study when selection is of a prevalent cohort (the survivors) will be less likely to smoke, and so will have a lower risk of the outcome than people not selected for the study because of premature death. This bias may therefore result in an underestimate of the association between the exposure and the outcome.

The choice between using a prevalent and an incident cohort to examine health outcomes which take a long time to occur requires balancing the problems of left censoring and right censoring (Vandenbroucke and Pearce, 2015). That is, a prevalent cohort will be left censored, in the sense that information on outcomes will be missing before the start of the study, and only those who survived to the study start date will be included. An incident cohort is usually right censored, in that the follow up time is limited by the availability of information for a long time period after the inception of the cohort, and so many of the outcomes of interest will not have occurred by the study's end. For outcomes with a long lead-in time (such as cancer) the problem of right censoring (and therefore missing outcomes) is a more concerning one, with more potential to bias the results than the problem of left censoring. Therefore, prevalent cohorts (such as used here) may be preferable to incident cohorts if follow up time is limited (Vandenbroucke and Pearce, 2015). A recent study of mortality in people using mental health services in Sweden compared the results from either including or excluding prevalent cases from the sample, and found that excluding prevalent cases results in a biased overestimation of mortality

results (Crump et al., 2013a). Therefore, the use of a prevalent cohort was the best option in this case.

6.3.4 Misclassification bias – Study One

Misclassification of individuals in the study with respect to any variables in the study can cause bias. Misclassification can be either differential (varying by exposure and /or outcome status) or non-differential (not related to the exposure or the outcome). Non-differential misclassification tends to bias results towards the null (in this case towards no difference between groups), while differential misclassification has less predictable results and needs to be carefully examined (Rothman et al., 2008).

Misclassification of exposure

The exposure in this study is current severe mental illness. Recent contact with mental health services is used as a proxy for this exposure. Misclassification could result if those identified as having experienced mental illness had not in fact had mental health problems, but had been in contact with services for another reason. This might be the case for administrative reasons, for example where a psychiatric assessment was required as part of the preliminaries for a medical procedure such as an organ transplant, or for legal purposes by the courts. It might also be the case because of misdiagnosis: where symptoms of a physical ailment (such as cancer) were mistaken for a psychiatric illness and a psychiatric consult was requested. In both of these cases, short term contact with mental health services would not indicate the presence of mental illness. In order to minimise this kind of misclassification, and thereby improve the positive predictive value of the exposure assessment, people who had contact with mental health services only on a single day were removed from the mental health services cohort. In fact, sensitivity analysis showed that inclusion of people in contact on a single day made no appreciable difference to the estimate, suggesting that the inclusion of people with one day service contact would not have biased the analysis.

Some misclassification due to misdiagnosis may still be occurring, for example where physical illness misdiagnosed as mental illness results in greater than one day

of service contact. Assessment of the burden of cancer in mental health service users who had been diagnosed with schizophrenia or bipolar disorder or schizoaffective disorder was therefore carried out, on the basis that this group would have less misclassification (that is, would be less likely to have something other than mental illness as the cause of their contact with mental health services). This analysis showed a slightly higher cancer incidence in this group, which may suggest that the estimate for the full cohort is an underestimate because of misclassification. However, the group with diagnoses of schizophrenia and bipolar disorder may also have a different risk of cancer from others in contact with mental health services. This may relate to differences in risk factors, such as smoking rates or childbearing patterns, as well as disruption of health service interactions including cancer screening. This result does, however, suggest that misclassification is not masking a low risk of cancer in people with mental illness.

Misclassification of exposure is more of a problem in cancer mortality assessment, because some people who used mental health services after cancer diagnosis will have been included in the calculation of cancer mortality for the mental health service use population. This is misclassification, as here we are interested in the cancer mortality in a population who have mental health problems which are not secondary to cancer. As was noted in Chapter Three, the inclusion of people who have only been in contact with mental health services after cancer diagnosis in cancer mortality calculations will result in an overestimate of cancer mortality in people in contact with mental health services. People diagnosed with schizophrenia or bipolar disorders are less likely to have mental health problems only secondary to cancer, and so the assessment of cancer mortality in this subset of mental health service users will be less subject to this bias. This analysis showed a slightly lower estimate of relative cancer mortality in this group (SMR 1.95 compared to 2.21 when all mental health service users were included), which suggests that the estimate for the full cohort is an overestimate because of this misclassification. As with incidence, the differences between those with diagnoses of schizophrenia or bipolar disorder and others in contact with mental health services may also be due to differences in factors associated with cancer mortality. However, these factors would

be expected to lead to a higher risk of death from cancer than for other service users, not a lower one.

The general population is used as a proxy for the unexposed cohort in this study. This is generally accepted as reasonable when the exposure is sufficiently rare that only a small proportion of the general population would be exposed, and so the outcomes in the general population serve as a reasonable proxy for the outcome in the unexposed (Rothman et al., 2008). In this case, the proportion with recent contact with mental health services represent 6% of the total New Zealand population aged 20 to 64 (150,000 out of 2.5 million) and so any misclassification of the unexposed cohort will only represent a very small proportion of the total and will not affect the results substantially. To the extent that the results are affected, the bias will be towards slightly more conservative estimates. It should be noted that this is a higher proportion than the annual estimate of 3% of the population in contact with services (Wilson, 2000) because it includes five years' worth of service contacts.

Misclassification of outcome

The main outcome in this study is cancer incidence measured as the rate of cancer diagnosis. Misclassification (recording someone as having cancer when they in fact did not or vice versa) is unlikely, because reporting of malignant tumours to the Cancer Registry is compulsory and comes from multiple sources (pathology reports, radiological reports, clinician reports and death certificates). Audits suggest that the New Zealand Cancer Registry includes at least 97% of diagnosed cancers eligible for registration (Seneviratne et al., 2014; Dockerty et al., 1997; Stevens et al., 2008a).

Cancer may, however, go undetected. For subclinical cancers such as prostate cancer detected by PSA testing in the absence of symptoms, or slow growing breast cancers which are detected by screening, the probability of cancer diagnosis and registration may be differential by exposure group. That is, people in contact with mental health services may be more or less likely to be tested/screened and therefore more or less likely than the general population to have these cancers detected. Further, the bias may be in either direction. People with comorbid conditions, including mental illness, may have more contact with health services and be more likely to be

screened for disease, or their comorbid condition may inhibit contact with health services or overshadow other conditions and lead to less likelihood of screening or early detection of cancers (Fleming et al., 2005). Therefore, the incidence results for cancers where subclinical cancers make up a substantial proportion of cancer burden should be interpreted with caution. This bias is likely to explain the apparently low burden of prostate cancer in people using mental health services found in this and other studies.

Misclassification of cancer deaths can also occur. Cause of death data are recorded on the National Mortality Register, based on information as to the underlying cause of death recorded on the death certificate. Death certificates are filled out by medical practitioners who may or may not have looked after the individual concerned during their life, and may or may not have had a thorough knowledge of the person's medical history and the circumstances over the weeks and months before their death. Therefore, while efforts are made to ensure that the information recorded is accurate, there will inevitably be some inaccuracies in the information recorded. When it comes to whether or not a death was caused by any cancer, there is probably reasonable accuracy. Cancer diagnoses usually result in multiple medical contacts and so are usually well documented, making information available to the person certifying the death. Where cancers were undiagnosed but lead to death, the accuracy of recording these deaths as due to cancer would depend on the rates of post-mortems conducted. However the proportion of deaths misattributed due to undiagnosed cancers is likely to be small.

Where the mortality from individual cancers is being estimated, misclassification may be more of a problem, as the metastatic sites of cancers may be mistakenly reported as the primary sites on death certificates. Deaths from cancers at sites which are common metastatic sites, such as liver, bone and lung may therefore be overestimated. Deaths from cancers in which the primary site is not necessarily found without investigation, such as prostate and colorectal cancers, may be underestimated. In this case, mortality from lung, breast, prostate and colorectal cancers was estimated. If cancers were less well investigated in people with more severe mental illness, as some studies have suggested (Bergamo et al., 2014), then

misclassification of cause of death may be more likely in people using mental health services. It may therefore be that lung cancer mortality is overestimated and prostate and colorectal cancer mortality are underestimated. However, the proportion of deaths misclassified is likely to be small and not likely to make a material difference to the large increase in the risk of mortality found for all these cancers.

Misclassification of confounders

Misclassification of confounding can also occur, resulting in over- or underestimation of the impact of confounding. Possible misclassification of confounders is discussed below in the section on the role of confounding in study results.

6.3.5 Confounding and mediation in Study one

Confounders and mediators identified

Confounding occurs when a third factor, related to both the exposure and the outcome and not on the causal pathway between the two, creates an apparent (spurious) relationship between the exposure and the outcome. In this case age, sex, and ethnicity were the main confounders identified (see the Directed Acyclic Graph, page 105). Socioeconomic deprivation was also identified as a potential confounder, although, as noted in Chapter 5, social deprivation can also be a consequence of mental illness and so on the causal pathway between mental illness and cancer.

Other factors were also identified as potentially related to both mental illness and cancer incidence, including health behaviours such as smoking status and diet, and access to primary care services such as screening and health promotion. The decision on whether to treat these factors as confounders or mediators depends on the pathway between mental health and cancer being explored. Because the relationship between mental illness and cancer mediated by social context is being examined, these factors are on the causal pathway of interest and so are better considered mediators than confounders.

The method used to compare cancer incidence and mortality in people with recent mental health service use and the general population was indirect standardisation using routinely reported annual data on the general population. This means that only information on age, sex and ethnicity was available for both the exposed and comparison populations. Age, sex and ethnicity were therefore the only factors controlled for in the cancer incidence and mortality analyses. Age and sex were controlled for by stratification in the standardisation process. Ethnicity was controlled for by a separate stratified analysis, where age and sex standardised incidence and mortality ratios were calculated for Māori and non-Māori mental health service users compared to Māori and non-Māori in the general population.

Misclassification of confounders can lead to incomplete adjustment and residual confounding. Age is calculated based on date of birth recorded on the Cancer Registry, which uses information from the National Health Index (NHI) file. The NHI record is checked and updated at each secondary or tertiary care contact. It is therefore likely to be accurate for people in regular contact with the health system, including people in contact with the mental health services and the vast majority of people diagnosed with cancer. Moreover, five year age bands were used for adjustment, further reducing the effect of any misclassification. Likewise, sex was based on the NHI record and is likely to be accurate in most cases. It seems unlikely that the accuracy of estimation of either of these two confounders would be related to the exposure or outcome, and so that any misclassification would affect the study results. Therefore, there is unlikely to be substantial residual confounding by age and sex.

Different patterns in cancer incidence by ethnicity are seen for individual cancers. For example, breast, stomach and lung cancers are more common amongst Māori than New Zealanders of European origin, while colorectal, prostate, and melanoma skin cancers are less common. Therefore, it is not clear what the overall effect of any confounding by ethnicity would be on total cancer incidence estimates. The high rate of lung cancer found may be partly due to confounding by ethnicity, because Māori are overrepresented in the mental health service use population, and the rate of lung cancer among Māori has been estimated at 3 to 4 times the rate among European

New Zealanders (Blakely et al., 2010). Stratification of cancer incidence ratios by ethnicity shows a slightly increased rate of cancer diagnosis in Māori men using mental health services compared to general population rates for Māori men for all cancers combined, which may be an indication of particularly high lung cancer rates amongst these men. No such patterning was seen for Māori women. However, stratification revealed that overall standardised cancer incidence ratios for mental health service users compared to the general population were similar for Māori and non-Māori, indicating that confounding by ethnicity is not contributing substantially to the overall cancer incidence results.

The relationship between ethnicity and cancer *mortality* is stronger and more uniform than the relationship between ethnicity and cancer incidence, with higher rates of death from cancer at almost all sites in Māori compared to European New Zealanders (Soeberg et al., 2015). The ethnic distribution of the population using mental health services may therefore be making the risk of cancer death appear higher than it actually is. Stratified mortality analysis showed that cancer mortality was less elevated in Māori mental health service users than in non-Māori mental health service users, indicating that confounding by ethnicity was not a factor in the high rates of cancer death in mental health service users overall. Stratification by ethnicity also tested for effect modification, and this is discussed in the following chapter interpreting study results (see 251).

Misclassification of ethnicity was also a potential problem. Māori ethnicity was identified using information from health service data sets (the Cancer Registry, Mortality collection and mental health service use records) which all use the National Health Index file, recorded by health service providers based on patient self-report of their ethnic identity. This information may not be recorded accurately, or may not be elicited during health service interactions, and can result in under-identification of Māori (Ajwani et al., 2003). This can result in underestimation of cancer diagnoses in Māori (Shaw et al., 2009), however this would be the case for both mental health service users and the general population and so would not bias the results of the comparison.

There are, however, differences in the data sources for the denominators used. Ethnicity information for the denominator population used for calculation of cancer incidence and mortality rates in the general population came from the 2006 census, while for the mental health service use group it came from health service data. The census ethnicity information comes from direct self-report, not mediated by health service providers, and so gives a better representation of ethnic identity. There is therefore the potential for numerator-denominator bias, where the different ways of identifying ethnicity in the numerator and denominator mean that the rate of the cancer in the Māori population is underestimated (Ajwani et al., 2003; Shaw et al., 2009). This would mean that the rate of cancer for Māori in the general population may be underestimated. Estimates from 2001-2004 suggest approximately 15% undercounting of Māori on cancer registration records (Shaw et al., 2009), while more recent work suggests 4% misclassification of Māori patients on hospitalisation records (Rumball-Smith and Sarfati, 2011). In contrast, for the mental health service use population, health services data was used to identify ethnic group for the numerator and denominator populations and so this is not a problem. Therefore, the comparison between Māori mental health service users and Māori in the general population may show a higher rate of cancer in mental health service users because of this bias. However the degree of misclassification expected would not be enough to explain the 21% increased risk of cancer among Māori men using mental health services.

Residual confounding

As noted above, age, sex and ethnicity were the only confounders adjusted for in the assessment of cancer incidence and mortality. Residual confounding due to unmeasured confounders may still be present. Socioeconomic position is a potential confounder, being related to mental health service use and cancer incidence and mortality. The relationship between socioeconomic position and cancer incidence in New Zealand varies by cancer, with some cancers having a higher incidence in less deprived groups (such as melanoma, breast and prostate cancers), some cancers having a higher incidence in more deprived groups (such as lung and stomach cancers), and some having little evidence of a social gradient (such as colorectal

cancer) (Blakely et al., 2010). As with ethnicity, the relationship between socioeconomic position and cancer mortality is more uniform across cancer sites, with higher rates of death from cancer at almost all sites in more deprived New Zealanders (Soeberg et al., 2015). The relatively deprived situation of people using mental health services may therefore have made the risk of cancer death in this group appear higher than it actually was. Because national annual cancer incidence and mortality reports were used for comparison, it was not possible to stratify comparisons by deprivation. However, the magnitude of the cancer mortality difference between people using mental health services and others is substantially greater than that seen between the least and most deprived groups of New Zealanders, and so the high rates of mortality among mental health service users cannot be entirely due to socioeconomic differences. Moreover, deprivation can also be considered a mediator of the relationship between mental illness and cancer.

Risk factors for cancer, such as smoking rates or reproductive history, are also factors associated with both the exposure and the outcome, and are on the causal pathway of interest and so are better considered mediators than confounders. In this case no information on these factors was available, and so adjustment was not possible. However, as these factors are mediators of the relationship between mental illness and cancer, they should not be considered to have confounded the estimates presented.

6.3.6 Study power and role of chance

This is a large population based study including complete national data on cancer registration, mental health service use and mortality to explore the occurrence and outcomes of cancer in the context of significant mental illness. Because the study is limited to those under 65, the outcomes (cancer diagnoses and cancer mortality) were relatively rare. There were, however, sufficient numbers for all cancers combined, and for major cancers, to compare rates between the groups, and detect differences with reasonable precision. Where differences were not detected (such as for cancer incidence for all cancers combined), this was unlikely to have been due to

lack of power to detect a difference. The fact that results were similar for each year examined provides reassurance that the findings were not due to chance.

There were sufficient numbers to examine major cancers separately, although there were insufficient numbers to examine less common cancers of interest such as cervical cancer. Where subgroups were compared, such as stratification by ethnicity or by mental health diagnosis, all cancers were combined in order to preserve precision of estimates.

6.3.7 Generalisability for Study One

Overall this study had good internal validity, that is, the findings are unlikely to be explained by errors due to chance, bias or confounding, as discussed above. Therefore its findings can be considered valid for the population from which the study sample was drawn. Once a study's internal validity is established, it is important to consider how its results might apply to other populations. The choice of other populations to which it may be appropriate to generalise the findings depends on the hypothesis about the relationship between the exposure and the outcome. Where the hypothesis is that a biological relationship drives the association between mental health problems and cancer, then results are expected to be generalizable to people with similar disorders in other populations and settings. However, when the interest is in exploring the way in which the social consequences of mental illness are responsible for the association between mental illness and certain cancers, then it would be expected that these consequences would vary over time and place, and generalisability will be less straightforward. In societies sharing certain characteristics, including similar health and social welfare systems, similarities in patterns of the association between mental illness and cancer might be seen, but differences would also be expected. For example, breast cancer burden is related to reproductive history, and the relationship between experience of mental illness and reproductive patterns will vary over time and place. Where those with mental illness are confined to hospital for long periods from a young age, or are routinely provided with long term contraception, birth rates may be low, while where women with experience of mental illness are less constrained in their choices, birth rates may be

much higher. These two examples would manifest in different breast cancer incidence patterns in women using mental health services.

The findings of Study One describe cancer incidence and mortality in people with experience of severe mental illness, as identified by contact with mental health services, in New Zealand at a particular point in time. They are also limited to people under 65, and may not be generalisable to older people with experience of mental illness. While the results are similar to the findings of other studies of cancer in people with experience of mental illness, there are also important differences. For example, breast cancer burden was not found to be elevated, as it has been in other studies (Bushe et al., 2009). It is likely that the reasons for this variation can be understood by considering the social context of living with mental illness in New Zealand over the past three or four decades (the time over which cancer causing exposures may have occurred), as well as by the age of the cohort in this study. These possible reasons are explored further in the next chapter.

In summary, these findings are relevant to considering cancer incidence and mortality in people with severe mental illness and people in contact with health services in other countries and health systems. Firstly, the methodological considerations presented here could be tested in other settings for their impact on estimates of cancer incidence. Secondly, where health systems and societies are similar, there are likely to be similar drivers of cancer in the context of mental illness, and therefore a similar burden of cancer.

6.4 Strengths and weaknesses of cancer survival analyses (Study Two)

6.4.1 Summary of main issues for Study Two

Study Two also benefited from including a complete national cohort of people in contact with public mental health services, linked to complete national cancer registrations and death registrations. Another major strength was the availability of information on possible mediators of the relationship between mental illness and

cancer survival. It is also likely that the exposure and outcome are free of major misclassification.

However reliable information was not available on cancer treatment timing or receipt which are likely to be important mediators. The use of routine data also means that there will have been some misclassification of confounding and mediating variables, which may have resulted in underestimation of the proportion of survival differences explained by these factors.

6.4.2 Study design – Study Two

Choice of outcome for Study Two

Cancer-specific survival was chosen as the main outcome of interest for survival analyses, rather than all-cause survival. People using mental health services have higher rates of premature mortality from all causes (see Appendix Three, page 307)) (Chang et al., 2011). The population using mental health services would therefore be expected to have a higher rate of mortality for reasons that are unrelated to cancer diagnosis and treatment. Using all-cause mortality as the outcome would not provide information specifically relevant to managing cancer in the context of mental illness. However, cancer-specific survival relies on having accurate cause of death information. This issue is discussed further under misclassification bias below.

Choice of design for Study Two

This study was a retrospective cohort study. This design allowed assessment of the impact of a relatively uncommon exposure (mental health service use). It also allowed the use of survival methods to compare outcome between the exposed and unexposed cohorts.

Choice of analysis method for Study Two

Kaplan Meier survival models, and Cox proportional hazards regression which has the same methodological challenges introduced by censoring, were chosen as the main methods for comparing survival between people with and without a history of

recent mental health service use. Both of these methods censor at the occurrence of competing outcomes. This requires the assumption that people who have the competing outcome (for example, die of something other than cancer) would have had the same risk of the outcome of interest as people who did not have the competing outcome, if they had not died of the competing outcome before they could have the outcome of interest. This random censoring assumption is the same assumption on which survival analysis is predicated – that the probability of being censored is not related to the hypothetical chance of getting the outcome. When other predictors are included in the model, analysis is predicated on the weaker assumption of independent censoring: that the risk is the same as others within the same strata of predictors (for example, others of the same age, ethnicity, gender, and socioeconomic status and with the same level of comorbidity).

The Kaplan Meier and Cox methods may therefore overestimate the probability of the outcome, because deaths from competing causes are treated as censored and therefore the people who had these competing events are treated as though they would have had the same risk of the outcome as people who remained at risk (uncensored). As noted above, this will be less of a problem in fully adjusted models, where the risk of the outcome in censored individuals (subsequent to censoring) is assumed to be the same within strata of other predictors.

Competing risk methods are an alternative approach to this particular problem. These methods treat outcomes which compete with the main outcome (that is prevent people from ever getting the main outcome) as competing events rather than treating them the same as an example of incomplete follow up. These methods estimate cumulative incidence fractions by treating people who had a competing event as still in the risk set but never able to have the event, and so the probability of the outcome is more realistically estimated. However, competing risk methods may not be appropriate in the current study. To understand why, we have to consider the counterfactual world that each model is based on.

Kaplan Meier methods estimate survival in a counterfactual world where no one gets any competing outcomes (i.e. it is impossible to die of other causes) within the study time period. Where the outcome of interest is death from any cause then this is not a

problem, as everyone will die eventually. However, this may be more of a problem where the outcome is death from a particular cause (such as cancer), or some other non-inevitable outcome (such as hospitalisation or cancer remission). Where the absolute probability is the outcome of interest (such as where wanting to advise patients on the probability of an outcome with or without treatment), this counterfactual world may not be a reasonable proxy for the real world, particularly where competing outcomes are common (such as in elderly cancer patients). However, where the outcome of interest is the relative difference between two groups, such as whether people using mental health services and others have different outcomes after being diagnosed with cancer, this counterfactual may be more useful. It may be that estimating the difference in the probability of surviving for five years after cancer diagnosis, in a hypothetical world where people do not die of anything else, is meaningful, where people using mental health services have a higher risk of dying from other causes but you do not want this higher risk of dying from other causes to overshadow the risk of dying from cancer.

In the current study, where the population is limited to people under 65 with cancer, the probability of dying from another cause is so low that the counterfactual world modelled may actually be very close to the real world. Moreover, where the relative differences in experiencing the outcome rather than the absolute probability of the outcome is of interest, then Kaplan Meier methods may give more useful information about the difference between the two groups, as the information is restricted to outcomes from cancer and not muddied by different probabilities of having other outcomes.

Competing cause regression methods were used as a sensitivity analysis. Because of the very low rates of deaths from other causes in the cohort, there was very little difference in the magnitude of difference found using this method versus traditional methods, and no difference in the direction of the difference between the cohorts.

6.4.3 Selection bias in Study Two

As with Study One, the use of complete national datasets including the entire population of interest reduced the likelihood of selection bias in this study.

However, this population is assumed to represent a group of people with experience of mental illness disruptive enough to lead to contact with mental health services. It is possible that the relationship between experience of mental illness and cancer survival is different in the population selected and in the total population with experience of mental illness. For example, it may be that being in contact with mental health services results in improved cancer survival compared to those with experience of mental illness that have not accessed secondary mental health care. Alternatively, the group in contact with services might experience worse cancer outcomes related to the medication used to treat their mental illness or to the stigmatizing effect of being known to be receiving mental health care, or indeed to the severity of the symptoms of their mental illness. It is, therefore, important to clearly identify that the findings of this study relate to those in contact with mental health services.

If this study had included people who had contact with mental health services following cancer diagnosis, this would have resulted in clear selection bias, as those who access services following cancer diagnosis would have a period of immortal time between diagnosis and contact with mental health services, where they cannot die from their cancer because then they would not access services. Therefore, the restriction to mental health service use prior to cancer was important for avoiding selection bias.

6.4.4 Misclassification bias in Study Two

Misclassification of exposure in Study Two

The exposure was contact with mental health services for more than one day in the five years prior to cancer diagnosis, as a way of identifying a population with experience of mental illness. Those identified will include some people who had very brief contact with mental health services and who may not in fact have had experience of mental illness. The restriction to those in contact with services on more than a single day will have minimised the risk of this by excluding people who had one-off assessments, but it is likely some people from this category were still included. As with study one, misclassification of people as having had experience of

mental illness when they in fact did not will result in an underestimation of the effect of prior mental illness, biasing the results towards the null.

Although only those who had contact with mental health services prior to cancer diagnosis were included as having had experience of mental illness, it is still possible that some of those categorised as having experience of mental illness actually had cancer initially misdiagnosed as mental illness. This group may have worse cancer survival than the general population because of delays to diagnosis resulting from misdiagnosis, and so may result in an increased estimate of the impact of mental illness of cancer survival. It is unlikely that this group would form more than a very small proportion of those with contact with mental health services prior to cancer diagnosis, and so it is unlikely that this misclassification could explain the results found. Moreover, late diagnosis was only found to be an important factor in poor survival for those diagnosed with schizophrenia and bipolar disorder, diagnoses which take three months of assessment to confirm, and it is unlikely that people would have received these diagnoses when their symptoms were in fact caused by cancer.

Misclassification of outcome in Study Two

Cancer-specific survival was the outcome used, based on date and cause of death as recorded on the death certificate. Misclassification of cause of death may result in underestimation (or overestimation) of the proportion of deaths due to cancer. In this case, only a small proportion of deaths were registered as being due to causes other than the cancer diagnosed, or to metastatic tumours. Of these, more than half were recorded as being due to cancers at other sites. It is likely that the majority of these deaths recorded as due to cancers at other sites are due to metastases from the primary tumour site. For example, deaths registered as being due to bone or liver cancers in someone with breast cancer are highly likely to be deaths due to secondary tumours rather than a second primary. Therefore the proportion of deaths due to breast cancer may be underestimated. If deaths were more likely to be misclassified in people with mental health service contact, then this could result in an overestimation of cancer specific survival in this group and an underestimation of the difference between the two groups. As a sensitivity analysis all-cause mortality

was also examined as an outcome, and the same pattern of results was seen, with people using mental health services and particularly people with schizophrenia or bipolar disorder having poorer survival than the reference group. Therefore this misclassification is not likely to be resulting in substantial bias.

Misclassification of confounders and mediators in Study Two

The confounders adjusted for were age, sex and ethnicity. All are drawn from the National Health Index dataset, which is updated at each hospital contact. Misclassification of age is unlikely, as date of birth will be rechecked regularly, although data entry errors are of course always possible, and, even if present, such errors would result in non-differential misclassification. Sex is less likely to be rechecked with the individual, but biological sex is likely to be known to health providers, and misclassification is likely to be minimal and non-differential.

Ethnicity is more likely to be misclassified on heath records, as noted for Study One, due to inaccuracies in health provider recording of ethnicity. Ethnicity was categorized as Māori or non-Māori. While there will be some misclassification of who identifies as Māori or non-Māori, socially assigned Māori ethnicity is associated with worse health outcomes than self-assigned Māori ethnicity (Harris et al., 2013), and so it is likely that the group identified through such a process as Māori would have worse cancer survival than those erroneously identified as non-Māori. Therefore, the adjustment for ethnicity here may be accounting for a greater proportion of the difference in survival than is actually due to differences in ethnicity. However, other work suggests that misclassification of ethnicity is only a very minor problem in cohort studies such as this one, and almost certainly would have no important effect on the results (Simmonds, 2010).

The mediators adjusted for in the Cox regression models were stage at diagnosis, deprivation and comorbidity. Misclassification of stage at diagnosis is likely to have occurred. An audit of staging data on New Zealand colon cancers registrations found that approximately 11% of colon cancer registrations had a stage record (including cancer recorded as unstaged) which did not match with clinical notes information in 2002-3, but also noted that the accuracy of stage recording was improving over time

(Cunningham et al., 2008). A more recent audit found that in 2011 approximately 12% of breast cancers were inaccurately staged or recorded as unstaged on the NZCR (Seneviratne et al., 2014). The majority of misclassification of stage in these audits resulted in cancers being recorded on the Cancer Registry as unstaged or less advanced than clinical records suggested. Misclassification may be differential, with other work suggesting that severe mental illness is associated with less thorough investigation of cancers (Bergamo et al., 2014). Therefore, it is likely that misclassification has led to under adjustment for stage in the models. The proportion of the difference in survival in men and women with schizophrenia or bipolar disorder diagnoses accounted for by late stage at diagnosis may therefore be greater than suggested in the models. For other mental health service users, where stage was not found to be important in explaining the difference in cancer survival, it is possible that later stage at diagnosis may be being masked by misclassification, although it is unlikely that this is a major effect.

A degree of misclassification of the level of deprivation is also likely. The level of deprivation was measured using the New Zealand Deprivation Index which is an area-based measure, based on a person's residential address and the composite level of multiple measures of deprivation in census data on their area of residence. Misclassification can be due to errors in data collection or data entry, where the residential address recorded is not correct. Amongst a population with cancer, who will have had multiple contacts with health services and therefore multiple opportunities for any errors in address to be corrected, this is unlikely to be a major problem. Misclassification can also occur where the average level of deprivation in the area where people live is not relevant to the specific individual concerned. This can occur in areas with very diverse populations, such as inner city areas, but also when a person's residence is a supported care facility or a hospital and so the usual barriers to entry to that residential area (such as house prices or rents) do not apply. This is likely to be more often the case for people using mental health services than for other people with cancer, and so there may be more misclassification of deprivation for this group which may reduce the apparent difference in deprivation levels between the two groups resulting in an underestimation of the role of deprivation in explaining survival differences. In fact, deprivation was not found to

be an important mediator after accounting for stage differences, and so any underestimation is unlikely to have made a great deal of difference to the estimates.

Misclassification of the measure of comorbid physical illness is also a potential problem. Two different measures of comorbidity were used (Charlson and C3), both based on conditions recorded in hospital records in the five years prior to cancer diagnosis. Conditions were therefore only included if they had been diagnosed by a doctor at the time of cancer diagnosis, and so people with undiagnosed disease will be misclassified as having no comorbid disease. This is likely to result in non-differential misclassification resulting in underestimating the amount of mediation on this pathway. It is possible that differential misclassification of comorbidity also occurred, but it is not clear whether this would result in increased or decreased diagnosis of comorbid diagnoses in people using mental health services. A history of mental illness could result in overshadowing and less documentation of other disorders, or surveillance and more documentation of other disorders. These effects may also vary by the severity of the mental illness, with overshadowing more likely to occur in people with schizophrenia and bipolar disorder. Therefore it is possible that the effect of comorbidity on survival differences is being underestimated particularly for people with more severe mental disorder.

6.4.5 Confounding in Study Two

Adjustment for confounders

Confounding and mediating factors were identified using the Directed Acyclic Graph (see Figure 5, page 106). Age, sex and ethnicity were identified as the principle potential confounders, as they are related to the exposure (mental illness leading to mental health service contact) and the outcome (cancer survival), and these are not on the causal pathway. These factors were treated as confounders in main analyses. For breast cancer survival, adjustment for age and ethnicity explained approximately 10% of the survival disadvantage for women with a history of mental illness (see Table 34). This was likely to be due to poorer survival in younger women. For colorectal cancer, adjustment for age, sex and ethnicity did not substantially change the estimated association (see Table 47).

Residual confounding

Geographical region and year of diagnosis were also possible confounders. However neither of these factors was strongly associated with mental health service use or cancer survival in descriptive analyses. In order to minimise the number of factors in the model these factors were not included. It is unlikely that there is substantial residual confounding due to these factors or that inclusion of these factors would have changed the results.

6.4.6 Mediators in Study Two

Other covariates were considered as mediating variables or factors on the pathway between mental illness history and cancer survival differences. Mediators included in the model were cancer stage at diagnosis, deprivation and comorbidity. As noted above, some misclassification of each of these mediators is possible, and so mediation via these pathways may not be fully accounted for.

Sequential adjustment of hazard ratios, comparing people with and without prior contact with mental health services, was conducted in order to estimate the contribution of mediating variables to survival disparities. The apparent contribution of any factor will be influenced by the order in which factors are added to the model. For example, if comorbidity had been added prior to stage at diagnosis, a greater proportion of the survival difference would appear to be explained by comorbidity. Therefore it is important to recognise that what is being assessed in the model is the contribution of an individual factor such as comorbidity independent of the factors already in the model.

Mediation by cancer stage at diagnosis was assessed. Amongst the colorectal cancer cohort, adjustment for stage reduced the hazard ratio estimates for people with diagnoses of schizophrenia or bipolar disorder, and slightly increased the estimate for people using mental health services for other conditions. It is possible that the crude stage categories used did not capture all the relevant variation in stage at diagnosis between people with and without a history of mental illness. It is also possible, as noted above, that stage at diagnosis was less well investigated or

documented for people with a history of mental illness. For both of these reasons the role of cancer stage may be being underestimated, and there may be some residual mediation by stage. However, it is not likely that this would change the direction of the mediation found.

The impact of comorbid physical illness on cancer survival differences will have been incompletely captured by the use of routine data and there may therefore be some residual or remaining mediation after adjustment for comorbidity. Moreover, no data was available for health behaviours such as smoking or the use of psychiatric medications. Both of these factors are likely to be on the causal pathway from mental illness to comorbid physical illness, and so missing data on these factors is only a problem to the extent that these factors have an effect on cancer survival independent of their effect on comorbid conditions. Information on these variables would have allowed for a more thorough investigation of the impact of other physical health problems and their risk factors on differences in survival outcomes.

Information on other mediating factors, in particular receipt of cancer screening and cancer treatment, was not available. It is likely that a greater proportion of the survival difference would have been explained by the addition of information on these factors to the survival models.

6.4.7 Study power and role of chance in Study Two

This study used a complete national dataset of cancer registrations over a five year period, combined with information on a complete national cohort of people in contact with public mental health services, both inpatient and outpatient. It had sufficient power to detect differences with reasonable precision between those in recent contact with mental health services and others.

When people with schizophrenia and bipolar disorder were examined as a separate group, the numbers of people in the exposed (mental health service use) cohort was small, especially for colorectal cancer, and the estimates for this group were much less precise. However, the magnitude of the difference in survival between people with these diagnoses (Group A) and people without a history of recent mental health

service contact was large, and so despite wide confidence intervals it is unlikely that the finding of worse cancer survival associated with schizophrenia and bipolar disorder was due to chance.

Follow up time was limited to up to five years, which provided sufficient time to examine differences in survival. Differences emerging later in the course of cancer treatment may have been missed. However, greater survival differences were apparent early in the course of cancer, and so it is unlikely that longer follow up time would have changed the results.

6.4.8 Generalisability

As with cancer burden, the population to which results might be generalized will depend on the hypothesis about the relationship between cancer survival and mental illness. If the hypothesis is to do with some intrinsic or biological independent relationship between mental illness and cancer survival, then generalisation would be to all people with comparable mental illness, regardless of their context, and all other contextual factors would be treated as confounder of the 'real' relationship.

If, however, the hypothesis is that contextual and social factors such as health services, drug prescription, social deprivation and discrimination form the basis of the association between mental illness and cancer survival, then the results found would be expected to be specific to the local context, and liable to change with time and place. Generalisation would therefore be more circumspect, but similarities would be expected between places with similar health services and societies.

In this case, the latter hypothesis forms the basis of the current study, and so the results found are considered to be specific to people in contact with mental health services in the current New Zealand context. However, the mechanisms by which experience of mental illness influences cancer outcomes, such as the impact of psychiatric medication and of stigma related to mental illness, will be similar in countries with similar cultures and health systems.

As with the results from Study One, examining differences and similarities between the findings from this study and other studies undertaken in different contexts is likely to be useful in enhancing our understanding of the mechanisms by which mental illness is associated with poor cancer outcomes. Similarities and differences with the results from other studies are explored in the next chapter.

This study focused on people under 65 using mental health services, and so the results are not generalizable to older people. However it is likely that many of the same factors are important in determining cancer survival in older people with a history of mental illness.

6.5 SUMMARY – MAIN STRENGTHS AND WEAKNESSES OF THIS WORK

This research presents the results from two studies of cancer in the context of mental illness severe enough to lead to contact with mental health services. Both studies use a full national cohort of adults in contact with public mental health services, limited to those who have had contact for greater than a single day, linked to national cancer registrations and deaths.

The public secondary sector in New Zealand provides the majority of care for mental health problems which are unable to be managed in primary care. Therefore, the cohort studied is a nearly complete national cohort of people receiving specialist mental health care. The New Zealand Cancer Registry and Mortality Register are both compulsory data collections which aim to capture complete national information.

Study One explored the impact of common methodological issues in cancer incidence studies, with sufficient power to examine major cancers separately. Methods for the main estimates were carefully selected to reduce the biases impacting on the findings of similar studies.

Study Two had sufficient power to examine survival from two of the most commonly diagnosed cancers, and to a limited extent to explore differences by

mental health diagnosis. Data were also available on some of the potential pathways mediating worse cancer survival.

Follow up data was available for up to five years following cancer diagnosis, although for some individuals follow up time was much shorter. However, substantial survival differences were apparent from these data, and it is very unlikely that these differences could be explained by errors due to chance, bias or confounding.

The main weaknesses were the due to missing data on key variables, and the restriction of the study to those under 65. There was limited information on psychiatric diagnosis and no useable information on cancer treatment receipt or other aspects of cancer care including waiting times, referral patterns and screening receipt. More complete information would have allowed a more thorough investigation of the factors associated with differences in cancer survival. This study was also limited to those under 65, and so the majority of cancers diagnosed in people with experience of severe mental illness in New Zealand are not captured.

Overall, this study provides reliable information on cancer incidence and cancer survival in adults using mental health services in New Zealand. It also provides important information about the potential impacts of bias in other similar studies of cancer incidence.

Chapter Seven: **DISCUSSION OF FINDINGS**

7.1 INTRODUCTION

This second discussion chapter explores the findings of the two studies in detail, and how these findings might be interpreted. The findings of each study are compared to the international literature.

7.1.1 Summary of findings

This is one of the first pieces of research to use the PRIMHD dataset on mental health service use in New Zealand and link it to other routine data sources. Although the dataset had missing information on key variables such as psychiatric diagnosis, this work has demonstrated that it is possible to use the dataset to identify a population in contact with mental health services and explore the physical health burden of this population. Despite the shortcomings of the available routine data, it is possible to produce robust and reliable information from PRIMHD.

The incidence of cancer in people with a history of recent contact with mental health services in New Zealand was found to be comparable to that of the rest of the New Zealand population, once methodological problems were dealt with appropriately to minimise bias. Cancer incidence varied by cancer, with mental health service users having higher rates of lung cancer and lower rates of prostate cancer compared to the general population. In contrast, cancer mortality was higher, both for all cancers combined and across individual cancer types. Cancer mortality results are however harder to interpret because of the use of consultant liaison services in terminal cancer.

Cancer survival was investigated for breast and colorectal cancers, and men and women with a history of recent psychiatric service use in New Zealand were found to have poorer survival after diagnosis compared to those who did not have such a history. People who had been diagnosed with schizophrenia, schizoaffective disorder or bipolar disorder prior to cancer diagnosis had two and a half times (breast) to three times (colorectal cancer) the risk of dying from their cancer within five years,

after adjusting for confounding. After adjustment for factors which might explain this association, there remained a survival disadvantage for this group, with 1.3 to 1.8 times the risk of mortality after cancer diagnosis. A similar pattern was seen for both breast and colorectal cancers.

For both cancers, those with a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder were more likely to have their cancers diagnosed at an advanced stage. Stage at diagnosis was an important factor in explaining survival differences for this group, with more than a third of crude survival differences being attributable to stage. However late stage at diagnosis was not a factor in poor survival for service users with other diagnoses.

Comorbid illness was more common among those using mental health services than among those without a history of recent mental health service contact, particularly those with diagnoses of schizophrenia and bipolar disorder. These differences in the burden of other physical health problems played an important role in explaining survival disparities for all those with a history of recent mental health service use.

It was not possible to investigate the contribution of treatment receipt to the survival disparities, because of missing private treatment data (Gurney et al., 2013). However, given the evidence from other health systems that a history of mental illness makes guideline-concordant cancer treatment less likely (Baillargeon et al., 2011; Goodwin et al., 2004; Kisely et al., 2013; Boyd et al., 2012; Mahabaleshwarkar et al., 2015), it is probable that treatment differences are at least part of the explanation for the remaining survival difference.

7.1.2 This chapter

This chapter puts these findings in the context of other research and the local health system. It is structured in three parts.

In the first part, the results of study one, into cancer incidence and mortality, are discussed in detail and compared to the findings from international research in this

area. Possible reasons for similarities and differences in findings are discussed, particularly as they relate to the New Zealand context.

In the second part, the results of study two, into cancer survival and its determinants, are discussed and compared to findings from other research. Possible reasons for similarities and differences are explored.

The final section discusses the implications of the findings for health service providers, policy makers, and researchers, and for those using mental health services.

7.2 THE BURDEN OF CANCER – FINDINGS FROM STUDY ONE

Cancer is an important cause of morbidity and mortality among adults in contact with mental health services in New Zealand. The overall incidence of cancer in this group was found to be similar to the incidence in the New Zealand population, with some variation by cancer type, while cancer mortality was higher than for the general population. These findings are in keeping with the international literature, which suggests that the burden of cancer is either slightly lower or similar to the local population rate, while mortality is higher (Bushe and Hodgson, 2010; Kisely et al., 2013). An Australian study using similar data to those used in this study to compare cancer incidence in people with a history of mental health service use in Western Australia with general population rates estimated the rate ratio of cancer incidence in men using mental health services at 1.05 (95%CI 1.02-1.09) and in women using mental health services at 1.02 (0.98-1.05) (Lawrence et al., 2000a). A recent UK study of cancer incidence in people with severe mental illness on primary care registers found an incidence rate ratio of 0.98 (0.88-1.09), adjusted for age, sex, period and deprivation (Osborn et al., 2013). A meta-analyses of the relationship between schizophrenia and cancer incidence found a pooled overall standardised incidence ratio of 1.05 (95%CI 0.95-1.15) from eight studies (Catts et al., 2008).

Studies which have compared cancer incidence and mortality in the same population have consistently found disparities between the two, with mortality higher than incidence. For example, a study from Nova Scotia compared cancer incidence and mortality in people in contact with mental health services to local population rates

and found rate ratios of 1.21-1.31 for incidence and 1.59-1.72 for mortality (Kisely et al., 2008). A more recent study from Queensland Australia found an SIR for cancer in people using mental health services of 0.94 and an SMR of 1.41(Kisely et al., 2015).

The differences in findings among studies are likely to be attributable, at least in part, to methodological differences. Whitley pointed out that the usual approach of excluding people with cancer prior to mental illness diagnosis may be overly conservative (Whitley et al., 2012). This thesis has built on Whitley's work by exploring the possible biases present in four possible study designs and demonstrating that categorisation of studies in this way is useful for explaining differences in findings. Possible "best" approaches to minimise bias and produce reliable findings on cancer burden are recommended. This typology could be extended to similar studies looking at cancer burden in the context of other neurological conditions, or in fact any condition for which there is variation in status over time independent of the time of cancer diagnosis. The application of this study typology may demonstrate that the apparent low burden of cancer in the context of conditions such as Parkinson's disease or Alzheimer's disease (Catalá-López et al., 2014) is in fact related to the methods used to assess the burden.

Small numbers meant it was not possible to assess the relative burden of each cancer separately, to look for different patterns between cancers, except in the case of the most common cancers. It would have been useful to be able to assess the burden of cancers such as cervical cancer for which disparities are known to occur between ethnic or socioeconomic groups (Soeberg et al., 2012). It was however possible to assess lung, breast, colorectal and prostate cancers separately and the findings are discussed below.

7.2.1 Lung Cancer in Study One

This study found a high burden of lung cancer amongst people in contact with mental health services, despite it being limited to people under 65 (in New Zealand in 2011 70% of lung cancers were diagnosed in people aged 65 and older) (Ministry of Health, 2014a). This is likely to be related to high rates of smoking in those in

contact with mental health services. While smoking rates have not been formally measured in the population in contact with mental health services in New Zealand, there is evidence to suggest that smoking rates are much higher than in the general population. The New Zealand Mental Health Survey Te Rau Hinengaro found that nearly one third of adults meeting the criteria for mental disorders in the twelve months prior to the survey smoked daily, approximately 50% higher than the general population (Tobias et al., 2008). Based on these findings, one third of cigarettes were estimated to be consumed by the one fifth of the population with active mood, anxiety and substance use disorders. Surveys from Australia and the United States have found similar results, with one third of adults who met ICD-10 criteria for mental disorders in the 12 months prior to the survey smoking, almost twice the rates of adults without mental disorders, and higher rates for those with disorders such as schizophrenia (Lawrence et al., 2009). In New Zealand, a 2009 survey of 404 adults in contact with Auckland mental health services found that this group were more likely to be current smokers than the general population (41.6% compared to 19.9%), and those who did smoke were more likely to smoke heavily (Wheeler et al., 2013). The low response rate for this survey (28%) means that its generalisability is limited, but it does give an indication of the high prevalence of smoking among those in contact with mental health services in New Zealand.

Other studies have also found higher rates of lung cancer among those with mental illness (Lichtermann et al., 2001; Goldacre et al., 2005), although it has been suggested that the increased burden of lung cancer is not as great as would be expected given smoking rates (Catts et al., 2008). Current lung cancer incidence reflects historical rather than current smoking patterns, because of the long time over which cancer develops. Therefore, current rates of cancer reflect patterns of smoking between twenty and fifty years ago (or longer in studies which include older people). Rates of smoking among those using mental health services, or those who would go on to have contact with services, will have been different in the 1960s and 70s from the rates seen today. While smoking rates in the general population have been falling over the past half century, smoking rates have peaked later in some segments of the population, including people of lower socioeconomic status and indigenous peoples (Shaw et al., 2005). Similarly, rates have remained persistently high for people with

experience of mental illness, and may even have increased with the use of cigarettes as inducements in mental health services and the increased freedoms of deinstitutionalisation. Therefore, it cannot be assumed (as it has been in some analyses) (Catts et al., 2008), that historical smoking rates in people with mental illness can be estimated from current rates, or from historical rates for the general population. It may be that the peak of the lung cancer epidemic for this population has not yet been reached. Analyses which adjust lung cancer incidence for estimated historical smoking rates should therefore be viewed with caution.

Lung cancer incidence and mortality were both raised to a similar degree in people using mental health services compared to the general population, indicating that while lung cancer is more common, there are not major disparities in survival. Lung cancer is a cancer with a high case fatality rate and poor survival (Janssen-Heijnen and Coebergh, 2001). Early diagnosis and treatment make less difference to prognosis than in some other cancers. There is, therefore, less room for differences in outcomes between groups, and this may explain the lack of disparity between relative incidence and mortality found. Other work suggests that comorbid illness has less impact on cancer survival in cancers with a poor prognosis (Sarfati et al., 2014a). Changes in lung cancer incidence over time could also explain this pattern, if recent smoking rates were higher than historical ones and incidence patterns reflected more recent higher smoking rates while mortality rates reflected lower rates of smoking in an earlier period.

7.2.2 Breast Cancer in Study One

This study found a similar incidence of breast cancer in women in contact with mental health services and the general population. This result is similar to the findings from a number of recent studies (Lawrence et al., 2000a). However many studies have found elevated breast cancer incidence in women with severe mental illness. A recent meta-analysis looking at the relationship between schizophrenia and breast cancer risk found great variation in the estimated risk, but found that studies with more than 100 cases of breast cancer, women aged over 50 for a significant period of follow up, and person-time at risk >100,000 years consistently found an

elevated risk of breast cancer (Bushe et al., 2009). Again, methodological differences as discussed above may help to explain the differences in findings between studies. There are also a number of reasons why the burden of breast cancer in people using mental health services may change over time and place, and so the differences between studies may reflect real differences in the populations studied.

It has been suggested that older anti-psychotic medication may increase the risk of breast cancer through hormonal effects (Schyve et al., 1978). Several newer antipsychotics are also associated with causing elevated levels of prolactin, a hormone which has been associated with breast cancer risk (Bushe et al., 2008). Changes in antipsychotic prescribing over time may therefore explain some of the differences between studies, if older or new drugs are more likely to promote cancer, given the variation in timing and cohort age of the studies. This study had a relatively young cohort and so will be most affected by more recent prescribing. However, when breast cancer rates in women on potentially hormone disrupting drugs are compared to rates in women on other antipsychotic medications, or to rates in women who have not used anti-psychotic medications, no difference in breast cancer risk has been found between groups, suggesting that medication may not be a key factor in explaining differences in study findings (Dalton et al., 2006; Azoulay et al., 2011).

Rates of breast cancer are also related to reproductive factors, in particular age at first birth and number of children (Kelsey et al., 1993). Experience of significant mental illness could make early childbearing and multi-parity more or less likely, depending on the nature of the illness and the health system's response in terms of contraception and long term hospitalisation. For example, findings from the US National Comorbidity Survey in the 1990s suggested that early onset mental health problems were associated with an increased risk of subsequent teenage pregnancy (Kessler et al., 1997). On the other hand, in Denmark, 41% of women hospitalised with schizophrenia who were born between 1935 and 1973 had not had any children by the age of 40, compared to 10% of the general female population (Dalton et al., 2003). Breast cancer rates in the older women in this cohort will be related to their reproductive behaviour in the 1960s and 1970s. The deinstitutionalisation of

psychiatric care in New Zealand occurred over this period, changing the reproductive opportunities of women in psychiatric care from very limited to much greater between the 1960s and 1980s. It may be that the high breast cancer rates among women with mental illness found in some studies with older cohorts reflect the very limited childbearing in women under the care of mental health services historically, when long term gender segregated care was the norm. Lower rates in more recent and younger cohorts (such as this one) may reflect changes to reproductive patterns with deinstitutionalisation.

Breast cancer risk factors also vary with age. In particular, obesity is associated with a decreased risk of pre-menopausal breast cancer but an increased risk of post-menopausal cancer (Carmichael and Bates, 2004). Antipsychotic and other psychiatric medications are associated with weight gain and obesity, and so may lead to a reduced rate of breast cancer in younger women on psychiatric medication, but an increased rate for older women. It is therefore important to consider the age of women studied, and if possible to assess pre- and post-menopausal breast cancer rates separately. When women aged over 50 were examined separately in this study, a slightly increased risk of breast cancer was found, although this did not reach statistical significance (SIR 1.13, 95%CI 0.99-1.29). This finding of a higher rate of breast cancer in older women is in keeping with obesity being a factor in variation in cancer rates by menopausal status. Variation in the relationship between parity and breast cancer risk with age (with nulliparous women having a lower risk at younger ages and higher risk at older ages) could also be a factor in these findings. However, other factors (such as changing reproductive factors as noted above) may also be important in explaining higher relative rates in older women.

Breast cancer screening has been shown to increase breast cancer incidence by detecting cancers earlier and by detecting cancers that would never have presented clinically (Independent U. K. Panel on Breast Cancer Screening, 2012). Breast cancer screening uptake in New Zealand has been high, with 70% coverage for women aged 50-64, but uptake has not been equal across ethnic and socioeconomic groups (Robson et al., 2014). International evidence suggests lower breast screening rates in women with experience of mental illness, particularly for women with

diagnoses of schizophrenia and bipolar disorder (Aggarwal et al., 2013; Lord et al., 2010). It is, therefore, possible that breast screening is less common among women using mental health services than in other New Zealand women. Lower screening rates would result in women with mental health problems having apparently lower rates of breast cancer than the general population (particularly in a screening age cohort). Without information on screening rates it is not possible to know whether this is impacting on the breast cancer rates found in this study. Evidence of late stage at diagnosis of breast cancer for women with schizophrenia or bipolar disorder in the second study does however indicate that screening receipt may be low for this group.

This study found much higher mortality from breast cancer in women with recent contact with mental health services than the general population. Other studies which have examined both breast cancer incidence and mortality in people with severe mental illness have also found relative mortality to be substantially higher than incidence (Lawrence et al., 2000a; Kisely et al., 2013). This disparity between similar incidence and higher mortality suggests worse survival, which was shown to be the case in full survival analysis. Moreover, despite concerns about the impact of women referred to psychiatric services after breast cancer diagnosis being included, the magnitude of difference between incidence and mortality rates was similar to the survival disadvantage found.

7.2.3 Colorectal cancer in Study One

This study found a similar incidence of colorectal cancer in people using mental health services and the general population. The results of other studies have been mixed, with some studies finding similar incidence (Lawrence et al., 2000a), but most studies have found slightly lower incidence of colorectal cancer in people with a history of mental illness compared to the general population (Kisely et al., 2013; Kisely et al., 2015; Goldacre et al., 2005; Dalton et al., 2005). As noted above, study design has a major impact on results, and may explain the diverse findings.

Changes in risk over time and place may also result in different findings between studies. New Zealand has one of the highest rates of colorectal cancer in the world (Center et al., 2009). Colorectal cancer incidence is not clearly socioeconomically

patterned in New Zealand, with rates uniformly high across socioeconomic groups, although lower in the indigenous Māori population (Soeberg et al., 2012). In contrast, there is evidence of variation in the risk of colorectal cancer by socioeconomic status in England, with lower rates in more deprived groups (Cancer Research UK and National Cancer Intelligence Network, 2014). This difference may relate to historically greater differences in diet between socioeconomic groups in the UK than in New Zealand. Colorectal cancer screening has potential to reduce incidence by detecting premalignant lesions, and so may exacerbate or create socioeconomic and other differences between groups based on access to care (von Wagner et al., 2009). New Zealand does not yet have a colorectal screening programme in place. Therefore, it is possible that the relatively similar rates of colorectal cancer in New Zealanders using mental health services and others in the population reflect a lack of socioeconomic variation in diet and a lack of colorectal screening, and these factors may be driving the low rates of colorectal cancer seen in people using mental health services in other countries. As colorectal cancer becomes more widespread, a reversal of this pattern may be seen, with higher rates of colorectal cancer among people with mental illness, if screening uptake is lower in this group.

Higher rates of mortality from colorectal cancer in the context of similar incidence again indicated the need for the subsequent survival study, which confirmed survival differences.

7.2.4 Prostate cancer in Study One

Rates of prostate cancer were found to be lower in men in contact with mental health services than in the general population. This finding is in keeping with other studies (Lawrence et al., 2000a; Lichtermann et al., 2001; Grinshpoon et al., 2005; Goldacre et al., 2005). It is likely that this is due to low rates of PSA testing (the test used to screen for prostate cancer) amongst those using mental health services, as prostate cancer screening detects cancers earlier and detects which would not otherwise have presented, and so increases the rate of prostate cancer diagnosis (Etzioni et al., 2002). PSA testing in New Zealand is currently offered by general practitioners on

an individual basis, with no universal offer of screening (Durham et al., 2003). Prostate cancer in New Zealand is strongly patterned by socioeconomic status and ethnicity, due to lower rates of prostate screening in people living in deprived areas and of non-European ethnicity (Blakely et al., 2011). It is, therefore, not surprising that prostate cancer incidence is low in men in contact with mental health services in New Zealand. The high rates of prostate cancer mortality found among men using mental health services suggest survival disparities which may relate to later diagnosis, as well as to health care after diagnosis.

7.2.5 Differences by ethnicity and diagnosis in Study One

Cancer incidence and mortality were also examined separately for Māori and non-Māori mental health service users, and for people with a diagnosis of schizophrenia or bipolar disorder.

Cancer incidence in Māori women with a history of recent mental health service use was no different from cancer incidence in Māori women without a history of recent mental health service use [SIR 1.00 (0.87-1.14)]. This was the same finding as for non-Māori women [SIR 1.03 (0.96-1.10)], indicating that ethnicity was not acting as an effect modifier for women. For Māori men, using mental health services was associated with an increased risk of developing cancer [SIR 1.21 (1.04-1.41)], whereas for non-Māori men this was not the case [SIR 0.99 (0.92-1.07)]. Therefore, the association between mental health service use and total cancer incidence was different for Māori and non-Māori men.

It is likely that this difference was related to the mix of cancers differing by ethnicity. In other words, the total cancer burden in Māori men is made up of a slightly different mix of cancers from the total cancer burden in non-Māori men. It is likely that within cancers, the relationship between a history of mental illness and cancer incidence would be roughly the same for Māori and non-Māori men, but it was not possible to examine individual cancers separately to ascertain this. The top five most commonly diagnosed cancers among Māori men are lung, prostate, colorectal, stomach and liver cancers, while for non-Māori men they are prostate, colorectal, melanoma, lung and bladder cancers (Cormack et al., 2007). Prostate

cancer is a more significant contributor to the total cancer burden in non-Māori men than Māori men (30% vs 20% of cancers diagnosed); while lung cancer is a more significant contributor in Māori men (24% of cancer diagnosed vs 10% for non-Māori men). Therefore, the observed pattern (higher cancer incidence among Māori men using mental health services compared to other Māori men, but no difference among non-Māori men) could be explained by the high rates of lung cancer and low rates of prostate cancer amongst men using mental health services. Amongst both Māori and non-Māori women breast cancer is the most commonly diagnosed cancer (Cormack et al., 2007).

Cancer incidence was also explored in men and women who had recorded diagnoses of schizophrenia, schizoaffective disorder, or bipolar disorder. For both women and men cancer incidence was slightly higher among people with these diagnoses compared to those with no history of mental health service use (SIR 1.15 and 1.12 for women and men respectively). Again, this may be related to the mix of cancers, with higher rates of smoking in people with psychosis diagnoses compared to other mental health service users and therefore likely higher rates of lung cancer in men and women with these diagnoses.

7.2.6 Study One Conclusions

A similar cancer incidence was found amongst those using mental health services compared to the general population. Those with experience of mental illness are therefore a group with equal importance to the rest of the population for cancer prevention initiatives, for timely recognition of cancers, and for provision of cancer services. Tobacco cessation support is particularly important, given the high incidence of lung cancer and the possibility that this may continue to increase.

The finding of higher cancer mortality suggests unequal outcomes for this group. This finding may partly reflect the inclusion of people who had contact with mental health services only after cancer diagnosis (who are not included in the denominator for cancer incidence). This is especially the case because it was not possible to distinguish those using mental health services by diagnosis, and a large number of people with no recorded diagnosis were included (assuming that many people who

only had contact with services after cancer diagnosis would have no mental health diagnosis assigned). Nevertheless, when the analysis was restricted to those with diagnosed schizophrenia or bipolar disorder, cancer mortality remained increased compared to incidence, although less so than for the entire population of people using mental health services. It is probable that most people with these diagnoses will have had mental health service contact prior to cancer diagnosis (and so will be in the denominator for both incidence and mortality), and so these restricted results suggest that the high mortality rates are not due to misclassification, but reflect a real difference in the risk of death from cancer for people with severe mental illness. Moreover, when cancer survival was directly examined for breast and colorectal cancers, clear survival disparities were demonstrated.

This study focused on a relatively young population from the perspective of cancer diagnosis, as cancer incidence and mortality increase markedly over the age of 65. The results therefore may not be representative of the total burden of cancer among those who have been in contact with mental health services at any age. Risk factor distributions also change over time, and cancer patterns in an older cohort will reflect exposure to risk factors in an earlier time period, and so it is not possible to reliably extrapolate the cancer burden in older adults using mental health services from these results. However, this younger population has great potential to benefit from interventions, especially those aimed at cancer prevention, and so it is important to understand cancer patterns in this population.

Cancer is a common cause of morbidity and mortality in people in contact with mental health services, just as it is for the general New Zealand population. While most research on physical health in the context of severe mental illness has focused on the high burden of heart disease, cancer research in this population is also important. Comparing incidence and mortality rates suggests disparities in cancer outcomes after diagnosis for this group. Therefore it was important to also examine survival.

7.3 CANCER SURVIVAL – STUDY TWO

The second study, examining survival after diagnosis with breast and colorectal cancers in those using mental health services, clearly demonstrated poor survival for this group. The survival disparity was especially large for people with diagnoses of schizophrenia, schizoaffective disorder and bipolar disorder, but there was also evidence of poor survival for others in contact with mental health services.

7.3.1 Study Two findings in context

The finding of worse cancer survival associated with a history of mental illness is consistent with the small number of other studies that have examined this question, both for specific cancers or mental disorders (Bergamo et al., 2014; Boyd et al., 2012), and for cancers or mental disorders combined (Baillargeon et al., 2011) (Chang et al., 2014). The estimated increase in the risk of dying from cancer for those using mental health services or with diagnoses of mental illness has varied considerably between studies, and direct comparisons are difficult because of differences in cancers examined, mental health populations examined, and factors adjusted for in estimates. Differences between health systems are also to be expected, particularly between systems with universal free health care and user-pays or co-pay systems. However, comparing estimates among studies, and exploring the reasons for any differences, may shed light on the reasons for the disparities in cancer outcomes themselves.

The magnitude of the difference in cancer survival between those using mental health services and the rest of the population will depend both on the characteristics of those using mental health services and on cancer survival in the local population. Although in most countries the majority of those with psychotic disorders will have some contact with specialist mental health services, for other diagnoses the likelihood of contact with services will vary over time and place, depending on resources and capacity of services. Therefore the average severity of mental illness amongst those in contact with services will vary from place to place and over time. For example, the study by Chang and colleagues (2014) is set in South London, a community with a very high level of physical and mental health needs (Woodhead et

al., 2014), where mental health services will be catering to a higher level of mental health problems than services in provincial areas. Services in South London also act as a tertiary referral centre, accepting people with very high needs from other centres. It might then be expected that the group of people in contact with such services would have worse physical health than people in contact with mental health services in other regions. Equally, it may be that those being cared for in a large teaching and academic centre would be receiving the best possible service from health care providers and so would do better than those receiving care in smaller centres. Therefore this group may have better or worse cancer survival than those being cared for in smaller centres, and empirical comparisons are necessary.

Differences in cancer survival between people diagnosed with different mental disorders will also vary by setting, because of the different thresholds for care among those with non-psychotic illnesses in different places. It is likely that in an area with very high mental health needs there will be less difference in physical health, health care access, levels of discrimination, and other determinants of cancer survival between those with psychotic illness and those with other reasons for contact with mental health services than in areas with lower overall psychiatric morbidity. This may partly explain why a larger difference in cancer survival between those using mental health services for schizophrenia and bipolar disorder and those using them for other causes (for example depression) is found in this New Zealand study than in the methodologically comparable study in South London (Chang et al., 2014).

The patterns of cancer survival for the background population will also vary from place to place. Cancer survival for all those living in a deprived area of South London (the reference population for the above study) may be worse than in New Zealand as a whole. The additional disadvantage of experience of mental illness leading to contact with specialist services may potentially be less in London than in New Zealand, as starting at a low base may leave less room for doing worse.

Beyond establishing the importance of cancer as a cause of morbidity and mortality among people using mental health services, this study has begun to identify the causes of the unequal burden of cancer mortality in this population. This is important for prioritising areas for intervention. It is also relevant for understanding and acting

on other health disparities for this population. For example, similar factors such as access to primary care, the high level of physical comorbidity, and receipt of appropriate treatment in secondary care, are also relevant for disparities in cardiovascular outcomes associated with mental illness.

The factors potentially contributing to cancer survival disparities include clinical factors such as comorbidity, and health service factors, including access to screening and early diagnosis, and access to timely treatment. In this study we were able to investigate the impact of stage at diagnosis and comorbidity. Other pathways, in particular treatment receipt, are likely to be important in explaining survival differences but were not able to be assessed through these routine data.

7.3.2 The role of stage at diagnosis

Differences in stage at diagnosis were important for explaining cancer survival disparities in those with diagnoses of schizophrenia and bipolar disorder, but not for others in contact with mental health services. Other studies that have examined the role of cancer stage at diagnosis in survival disparities for people with a history of mental illness have produced conflicting findings, with some studies finding that mental illnesses are associated with late diagnosis (Boyd et al., 2012; O'Rourke et al., 2008; Kisely et al., 2013) while others finding an association with early diagnosis (Bergamo et al., 2014; Koroukian et al., 2015), or no association (Chang et al., 2014; Goodwin et al., 2004).

It is well recognised in the comorbidity literature that pre-existing physical illness can influence the stage at which cancers are diagnosed in a variety of ways, sometimes overshadowing cancer symptoms resulting in late diagnosis, but in other cases leading to increased surveillance resulting in earlier cancer diagnosis, depending on factors such as the severity of the illness, the type of cancer, and the health system context (Fleming et al., 2005). This could also explain the findings of cancer stage in the context of mental illness.

More severe illness may distract attention from cancer symptoms resulting in late diagnosis, while less severe illness may result in earlier diagnosis through increased

contact with the health system and hence increased opportunities for detection (Fleming et al., 2005). The problem of diagnostic overshadowing of physical illness by mental illness is well recognised, with physical health symptoms being mistakenly attributed to mental illness (Jones et al., 2008; Thornicroft et al., 2007; Shefer et al., 2014). In this study, the delayed diagnosis of cancer in people with schizophrenia and bipolar disorder may relate to this overshadowing of physical complaints by known mental illness. For colorectal cancer, there was also some evidence of early cancer diagnosis in people using mental health services for non-psychotic conditions, which may relate to increased contact with health services resulting in the surveillance effect, described in the comorbidity literature as occurring with less severe comorbid illness (Fleming et al., 2005).

The relationship between mental illness and cancer diagnosis may also depend on the type of cancer. For example, diagnosis of cancers with more insidious onset, such as pancreatic cancer, has been found to be delayed in people with mental illness (Boyd et al., 2012). Another study of lung cancer among Medicaid beneficiaries found that people with schizophrenia were more likely to have their lung cancers diagnosed earlier, which may relate to the high index of suspicion for this particular cancer in this population with high smoking rates (Bergamo et al., 2014). Where all cancers are examined together, the different stage distribution for different cancers may be obscured, and result in no apparent relationship (Chang et al., 2014). In this thesis, late diagnosis was found for both breast and colorectal cancer among those with schizophrenia and bipolar disorder, while evidence of early diagnosis was only found for colorectal cancer in other mental health service users.

Differences in the health system setting are also important. For example, in the study of Medicare patients mentioned above (Bergamo et al., 2014), it is likely that early diagnosis of lung cancer relates to Medicare patients with schizophrenia having frequent contact with health providers and possibly undergoing a high degree of surveillance of the type likely to pick up lung cancer (such as chest X-rays) in the Medicare system. In New Zealand primary care is provided by private practitioners (although largely publicly funded) and co-payments are charged for primary care visits and prescriptions. Cost barriers may therefore be a factor in the late stage at

diagnosis for those with more severe mental illness seen in this study. It is notable that stage disparities have generally not been found in settings in which there are no co-payments for primary care, including the UK (Chang et al., 2014), and the US Medicare (Bergamo et al., 2014) and Veteran's Affairs (Wadia et al., 2015) systems, although there are exceptions (Baillargeon et al., 2011).

In addition to cost barriers, confusion among providers about responsibility for the physical health care of people with severe mental illness may contribute to delays in diagnosis (Handiside, 2004; Robson and Gray, 2007). Problems of role ambiguity and care boundaries may be more pronounced in people with diagnoses such as schizophrenia who tend to have prolonged contact with mental health services.

7.3.3 The role of physical comorbidity

Coexisting physical illness (referred to as comorbidity) is an important factor in cancer survival disparities in other contexts, such as ethnic disparities in New Zealand (Hill et al., 2010; Sarfati et al., 2009). Comorbidity can impact on cancer stage at diagnosis as explained above, but independently can also impact on survival through influencing treatment options, and the survivability of both treatments and the cancer itself (Bradley et al., 2014; Sarfati et al., 2009). However there is limited information from previous studies about the role of comorbidity in cancer management in the context of mental illness. Most studies of cancer survival in the context of mental illness have either had no information on comorbidity (Chang et al., 2014), treated comorbidity as a confounder (Chang et al., 2013), or included comorbidity in models together with stage so that its individual contribution could not be assessed (Baillargeon et al., 2011). In a notes review study of 29 patients with schizophrenia and lung cancer at the Mayo Clinic in Minnesota, USA, comorbid illness was the reason for not receiving treatment in two out of the five patients who did not receive state of the art therapy for potentially curable cancer (Mateen et al., 2008). However, there was no comparison group for this study, and so it is not possible to know whether comorbidity is a contributor to unequal treatment or unequal outcomes for people with schizophrenia.

The current study found that comorbidity, after accounting for stage at diagnosis, was an important factor in understanding survival disparities, particularly for those using mental health services for reasons other than psychotic illnesses. Examining the impact of comorbid illness as a mediator of survival differences, as was done in this study, highlights the importance of not considering mental illness in isolation. People with mental illness are often also living with physical illness as well, and cancer treatment needs to be considered in this complex context. Moreover, the impact of comorbidity on treatment decisions is not inevitable, and in fact there is evidence that treatment may at times be inappropriately withheld on the basis of comorbid illness (Bradley et al., 2014; Sarfati et al., 2009). For example, in a cohort study of 589 people diagnosed with colon cancer in New Zealand, people with stage III colon cancer and a high degree of comorbid illness (a Charlson score ≥ 3) were less likely to be offered chemotherapy than those with no recorded comorbid illness (19% compared to 84%) (Sarfati et al., 2009). This is despite such therapy being associated with around a 60% reduction in excess mortality in these patients. Therefore, comorbidity is a cause of mental health related survival differences that is potentially amenable to intervention.

7.3.4 The role of treatment receipt

Beyond the effect of individual factors and timely diagnosis, receipt of timely cancer treatment has also been shown to play an important role in socioeconomic cancer survival disparities (Woods et al., 2006), and this is likely to also be the case for people with mental illness. Several studies have found that those with a history of mental illness are less likely to receive treatments such as surgery and chemotherapy (Chang et al., 2013; Kisely et al., 2013; Baillargeon et al., 2011). Moreover, the stigma and discrimination associated with mental illness is likely to be playing a role in these treatment disparities (Küey, 2008). After adjustment for all available factors, this study found that those using mental health services had worse survival than those without a history of mental health service use (although the differences were for the most part no longer statistically significant). It is likely that some of this remaining unexplained survival disadvantage relates to differences in treatment.

However, it was not possible to ascertain complete information on treatment receipt for this study. When receipt of treatment was examined, it appeared that those under psychiatric care were more likely to receive cancer treatments including surgery and chemotherapy than others in the population. Moreover, in the unexposed cohort only 77% received surgery for breast cancer. This indicates significant undercounting of surgery receipt in this cohort, consistent with other research on this issue (Gurney et al., 2013).

Secondary care, including mental health and cancer care, is universally available free of charge in New Zealand's public system. However, cancer treatment receipt has been shown to vary by ethnicity in New Zealand (Hill et al., 2010). Moreover, people with experience of mental illness in New Zealand report discrimination by health services including non-psychiatric services (Peterson et al., 2007). Cancer treatment receipt may well be a factor in the survival differences found.

7.4 SUMMARY – ANSWERING THE THESIS QUESTIONS

This concluding section provides a summary of the findings of this thesis by considering how the results of these two studies, into cancer burden and cancer survival, answer the four questions posed in the introduction.

1. Is cancer an important cause of morbidity and mortality among adults living with severe mental illness in New Zealand?

This research has found that cancer *is* an important cause of morbidity and mortality for adults living with severe mental illness in New Zealand.

An average of 375 cancers were diagnosed each year in people aged 20 to 64 with a recent history of mental health service use, or about 260 cancers per hundred thousand people per year. This is approximately the same rate of cancer diagnosis as occurs in other adults of this age in the New Zealand population. The most common cancers diagnosed in people using mental health services are breast, lung, melanoma and colorectal cancers.

Cancer is also an important cause of mortality, with around 150 deaths occurring annually in people under 65 with a history of recent mental health service use (116 cancer deaths per hundred thousand people per year). This represents approximately one fifth of the deaths occurring in people with recent mental health service contact annually, a similar proportion to deaths caused by cardiovascular disease in this age group. Moreover, the rate of death from cancer in mental health service users is double the death rate from cancer of other New Zealanders in the same age range.

2. Is cancer contributing to differences in health outcomes between people with severe mental illness and others in the population?

Cancer is also a contributor to poor physical health and shortened life expectancy for people with severe mental illness in New Zealand, through the high burden of lung cancer, and markedly worse survival from cancer once diagnosed.

Lung cancer was found to be twice as common in both men and women using mental health services compared to people in the general population.

For breast cancer, women with a history of mental illness had an 86% survival disadvantage, while for colorectal cancer, men and women with a history of mental illness had a 46% disadvantage, after accounting for demographic factors. When men and women with a diagnosis of schizophrenia or bipolar disorder were considered separately, the survival disadvantage was even more pronounced.

3. What are the factors that are contributing to any differences in cancer outcomes between people with severe mental illness and others in the population?

Smoking is clearly contributing to cancer inequalities in people using mental health services in New Zealand. Data on cigarette smoking behaviour was not reliably available from routine sources to allow direct assessment of the role of smoking in cancer incidence and cancer survival. However, the high rates of lung cancer found are clearly linked to cigarette smoking. Moreover, smoking is an important cause of the comorbid physical illness present in people diagnosed with cancers, including cardiac and respiratory disease, which impacts on cancer survival inequalities.

Tobacco control interventions are therefore important for reducing health inequalities for this group.

The role of social deprivation was also explored. Although there was a higher level of deprivation amongst the population using mental health services than the general population, social deprivation was not found to be a major explanatory factor in the cancer inequalities found. Social deprivation was not a major factor in the survival disparities for breast or colorectal cancers. Similarly, the excess burden of lung cancer amongst those using mental health services compared to the general population was greater than the difference in lung cancer incidence between the most and least deprived third of New Zealanders, particularly for women (Blakely et al., 2010), indicating the socioeconomic deprivation alone does not explain the high burden of lung cancer.

Late diagnosis contributed to poor cancer survival in men and women with diagnoses of schizophrenia or bipolar disorder. Access to health care is crucial for timely cancer diagnosis. Barriers to access, in particular the cost barriers to primary care in New Zealand may be important in explaining late cancer diagnosis in people with schizophrenia and bipolar disorder. A recent report for the Australian and New Zealand College of Psychiatrists looked at barriers to accessing health care for people with mental illness in New Zealand, and found that the relatively high cost barrier to accessing GP services was the most significant barrier (RANZCP, 2015). Unequal access to cancer screening may also be contributing to late diagnosis of breast cancer in women with schizophrenia or bipolar disorder.

Misdiagnosis and inadequate investigation of cancer symptoms are known to be important factors in delays in cancer diagnosis in the general population (Macleod et al., 2009). Misdiagnosis of cancer in people with mental illness can occur through diagnostic overshadowing, where symptoms of cancer are misattributed as being due to known mental illness. This is a recognised barrier to receiving appropriate physical health care and is related at least in part to the stigma attached to a mental illness diagnosis, particularly a diagnosis such as schizophrenia (Thornicroft et al., 2007).

Multimorbidity, or the high burden of multiple physical health problems, was also a factor in differences in survival inequalities for all those with a history of recent mental health service contact. Multiple factors will be contributing to the higher burden of comorbid illnesses such as heart disease and diabetes, including psychiatric medications, health behaviours, and health system factors. Therefore, interventions such as ensuring that the metabolic effects of psychiatric medications are minimised, monitored and managed will not only reduce the impact of cardio metabolic disorders, but will also help to reduce cancer inequalities in this population.

The disconnect between mental and physical health care at a system level, and confusion over responsibility for physical health care in patients being cared for by psychiatric services, may also be impacting on the high level of comorbid illness and the delays in cancer diagnosis which are in turn contributing to cancer survival.

In this study it was not possible to investigate cancer treatment as a factor in cancer survival disparities. However the remaining difference in survival after adjustment for other factors suggests treatment differences. Further investigation into this mechanism is required, including investigating the contribution of any treatment differences to survival differences, and the factors which influence treatment decision making.

4. Does the relationship between mental illness and cancer vary by mental health diagnosis or cancer type?

When those with diagnoses of schizophrenia or bipolar disorder were examined separately, a higher incidence of cancer and markedly worse survival from cancer were found. As noted above, a variety of factors are likely to be contributing to the differences between people with these diagnoses and others in contact with mental health services. It was not possible to examine these potential pathways in any detail in this type of study. Improving cancer outcomes for this most disadvantaged group needs to be a priority in considering cancer in the context of mental illness.

However, while much of the work on health disparities associated with mental illness focuses on people with schizophrenia and/or bipolar disorder, the studies presented here show that others in contact with mental health services also have a high burden of lung cancer, and are more likely to die from cancer once diagnosed than the general population. This indicates the need for a broadening of perspective in relation to physical health and severe mental illness.

Chapter Eight: **IMPLICATIONS AND CONCLUSIONS**

8.1 INTRODUCTION

This is the final chapter of the thesis and provides the concluding material. The implications for clinicians and health services, health and social policy makers, and for researchers are discussed. The implications for the people who are the subject of this study are also considered. Recommendations for each of these audiences are included. The chapter then finishes with some brief conclusions.

8.2 IMPLICATIONS

8.2.1 For clinicians and health services

For health care providers, including in mental health care, cancer care and primary care, awareness of the magnitude of cancer survival disparities associated with a history of mental illness is an important first step. Dissemination of the results of this study to health care providers is therefore required (and is already underway).

For mental health care providers, awareness that cancer is common and a major cause of death among those they care for is important for promoting timely diagnosis and cancer screening utilisation, particularly for those with psychosis diagnoses. However this research makes it clear that making the diagnosis is not enough, and that the role of mental health care providers in providing support for those under their care through the cancer care journey needs to be explored. Primary care providers also have a responsibility for ensuring access to screening and timely diagnosis of cancers in those with severe mental illness, and this has been shown to be particularly important for those with psychosis diagnoses.

The management of other conditions such as cardiovascular disease and diabetes, particularly as they relate to medications prescribed for psychiatric conditions, is also important for cancer survival, and the responsibilities of mental health and primary care services in this regard need to be clearly delineated. Collaborations between mental health and primary care services and protocols for managing physical health

in secondary mental health care services are being trialled in some parts of New Zealand. However, the current approach is fragmented and there is no national consistency. National guidance, as well as sharing of successes around the country, will be important in ensuring consistently good physical health care for people using mental health services. The Equally Well collaboration, which is still in its infancy, has the potential to support this process, as a platform for sharing ideas and as an advocacy organisation for national and systemic changes.

For cancer care clinicians, this research highlights the importance of awareness of the patient group with severe mental illness as one vulnerable to poor cancer outcomes, and one to whom particular attention may need to be paid in enabling navigation of the cancer care system. Existing initiatives such as cancer care coordinators may be useful for improving outcomes for this group. Further research into the role of treatment delays and treatment receipt in poor survival is needed to further inform cancer clinicians of the best ways in which cancer care for this group may be improved.

In the training of health professionals, educational and contact interventions have been shown to reduce the stigma of mental illness among care providers (Kassam et al., 2011; Pittman et al., 2010; Altindag et al., 2006). Such interventions have the potential to reduce the stigma and discrimination associated with mental illness and therefore facilitate better health care, including early diagnosis and appropriate management of cancer and other physical health conditions, particularly for people with more severe mental illness. The way in which health care providers are educated about and exposed to mental illness therefore needs to be reviewed in the light of existing evidence of best practice.

Training, guidance and support for managing multi-morbidity will be important for all health care professionals as chronic disease becomes more common. This training needs to recognise that the presence of mental illness, alongside multiple physical conditions, is common and has an impact on outcomes.

Finally, tobacco control interventions, both at the service level (such as provision of smoking cessation support and smoke-free inpatient facilities), and at the governance

level (including interventions to change the culture of smoking in mental health services) will be important. In New Zealand, a 2014 review of tobacco control activities funded by the Ministry of Health found that no specific services for those with mental health illness were reported by DHBs, although cessation advice was offered to inpatients in some mental health services (Casswell et al., 2014). The report recommended that the Ministry of Health should "Encourage funders and providers of mental health services to prioritise smoking cessation for clients of mental health services" (Casswell et al., 2014: p32). National smoke-free guidelines and education resources for mental health services are currently being developed, with the aim of "shifting the culture" away from normalised tobacco use (Williams, 2014).

8.2.2 For policy makers

This is the first piece of work in New Zealand to quantify the health disparities experienced by people using mental health services. It demonstrates that such quantification is possible from routinely collected data, and therefore that ongoing monitoring of the health status of this group could be instituted with minimal adaption to current data systems.

This work also demonstrates that the group of people in contact with mental health services in New Zealand experience health disparities at least as great as those experienced by other vulnerable populations. It is therefore important that people with severe mental illness are considered when designing health services and public health interventions, and the way in which such interventions will impact on the health of this group is considered.

Possible policy level interventions include tying funding for primary care to meeting physical health care targets for people with experience of mental illness, as occurs in the United Kingdom. Such targets might include annual physical health checks or offering and facilitating cancer screening. Better linking of routinely collected data, such as including a record of primary care visits on PRIMHD, could also improve coordination of care and reduce the chances of physical health care being overlooked.

8.2.3 For researchers

This work also has implications for further research. In particular, research to understand the role of cancer treatment in cancer survival disparities is needed. A detailed understanding is needed, not only of whether and when treatment is received, but also of the way in which treatment decisions are reached and the factors which influence these decisions. Specific research examining the clinical notes of those with cancer, with and without a history of mental illness, will be important in understanding variations in the clinical pathways which may be contributing to cancer survival disparities. This research will be important for a better understanding of how clinicians can work to reduce the identified disparities in cancer survival. Without this research it is difficult to provide specific advice about how cancer clinicians in particular might alter their practice to improve outcomes for this group.

Further research into cancer in the context of mental illness should also, where possible, include those over 65, as this is where the burden of cancer will be greatest. Work will need to be done on improving the quality of routinely available data about people using mental health services in this age group in order to enable future work in this area.

Research which prioritises the voices and experiences of people with mental illness is also needed, to understand and therefore address the barriers to improving physical health including cancer outcomes. Research which explores the cancer treatment journey, and other types of clinical care, from the perspective of people with experience of mental illness, is needed to better understand the causes of cancer survival disparities and how they might be addressed. Such research will allow exploration of the role of discrimination in disparities in cancer outcomes.

Any future research considering the incidence of cancer in people using mental health services or others with mental illness needs to consider the methodological issues raised here, in particular the problem of invulnerability bias. Further work to explore the implications of this bias for research into cancer incidence in other groups is also needed.

8.2.4 For people using mental health services

Finally, this work is probably of most interest and import to people with lived experience of mental illness and mental health service use, for it is information about real people and their lives and deaths. The finding of double the risk of lung cancer, and double the risk of dying from breast and colorectal cancers after diagnosis, is shocking, and is important information for ensuring that the health of this group is regarded as an important problem by society. This thesis has provided the first information on the extent of the problem of poor physical health among people in contact with mental health services in New Zealand.

For past and current users of mental health services, it is important that the potential to develop cancer is an issue of which people are aware. This group should be encouraged to access cancer screening services and to act to minimise cancer risk, including being supported to quit smoking. Moreover, people with experience of mental illness should be encouraged by services such as the Health and Disability Commission (New Zealand's independent agency charged with upholding health consumer rights) not to put up with discrimination when using health services. Involvement of people with experience of mental illness in setting the research agenda, and undertaking research, around unequal physical health outcomes, will also be important.

8.3 CONCLUSIONS

Cancer in the context of severe mental illness matters. Cancer diagnosis is equally common amongst people with severe mental illness and others in the population, but people with severe mental illness are more likely to die from their cancers. This includes not only people with diagnoses of schizophrenia and bipolar disorder, but also the wider group of people in contact with specialist mental health services.

The methods used to assess the burden of cancer matter. In particular, a number of important biases commonly effect epidemiological assessment of cancer incidence in the context of prior mental illness. Care is therefore required in the selection of methods for such studies, and in the interpretation of results.

The cancer survival disparities associated with experience of prior mental illness are large in comparison to the disparities seen for other vulnerable groups in the population. These disparities therefore demand attention from health services and policy makers. Interventions to address the stigma associated with mental illness and the consequent low priority accorded to this segment of the population, will be important for ensuring this disparity is accorded due attention.

Interventions to address the burden of cancer amongst people with severe mental illness in New Zealand are indicated at multiple levels. Cancer prevention interventions, particularly relating to tobacco control, are needed. Promotion of early diagnosis of cancers, through screening and efforts to improve awareness of cancer in both people with mental illness and their health care providers, is indicated, particularly for people with schizophrenia and bipolar disorder. Better management of the comorbid physical health conditions which can exist alongside mental illness and cancer will also be important to improving cancer outcomes. Better communication and coordination between providers of physical and mental health care has the potential to improve the health care provided to people with experience of mental illness, including the care of cancer.

Further investigation of the cancer treatment journey for those with experience of mental illness is needed to understand the reasons for the gap in cancer outcomes not

explained by comorbid illness and late stage at diagnosis. This investigation will need to explore the role of factors such as diagnostic overshadowing reported as barriers to care by people with severe mental illness. It will also need to involve people with experience of mental illness in the research process to ensure the right questions are asked.

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APPENDIX ONE: ADDITIONAL MATERIAL CHAPTER FOUR

1.1 MISSING DATA

The following tables show the patterns of missing data for each annual cohort of people with recent contact with mental health services. An X represents complete data for that variable, and a "." represents missing data on that variable. Each row represents a possible combination of missing and non-missing data across all variables. For example, the top line of Table 53 shows that 77% of the 2006 cohort of people with recent mental health service use had complete data on all variables. The second line shows that the variable with data most commonly missing was diagnosis. For 2010, 90% of the cohort had complete data on all variables (Table 57), with main change over time being in the completeness of the diagnosis variable.

Table 53 Missing data patterns: Recent mental health service use cohort 2006

Group	Ethnicity	Age	Sex	NZDep	DHB	Prioritised diagnosis	Freq. (n)	Percent
1	X	X	X	X	X	X	101426	77.38
2	X	X	X	X	X	.	21917	16.72
3	X	X	X	X	.	X	1058	0.81
4	X	X	X	X	.	.	915	0.7
5	X	X	X	.	X	X	352	0.27
6	X	X	X	.	X	.	85	0.06
7	X	X	X	.	.	X	1	0
8	X	X	X	.	.	.	4	0
9	X	X	.	X	X	X	2	0
10	X	X	.	X	X	.	1	0
11	.	X	X	X	X	X	3623	2.76
12	.	X	X	X	X	.	1548	1.18
13	.	X	X	X	.	X	26	0.02
14	.	X	X	X	.	.	90	0.07
15	.	X	X	.	X	X	21	0.02
16	.	X	X	.	X	.	8	0.01

Table 54 Missing data patterns: Recent mental health service use cohort 2007

Group	Ethnicity	Age	Sex	NZDep	DHB	Prioritised diagnosis	Freq. (n)	Percent
1	X	X	X	X	X	X	112266	82.51
2	X	X	X	X	X	.	16187	11.9
3	X	X	X	X	.	X	1074	0.79
4	X	X	X	X	.	.	843	0.62
5	X	X	X	.	X	X	397	0.29
6	X	X	X	.	X	.	72	0.05
7	X	X	X	.	.	X	1	0
8	X	X	X	.	.	.	4	0
9	X	X	.	X	X	X	2	0
10	X	X	.	X	X	.	2	0
11	.	X	X	X	X	X	4001	2.94
12	.	X	X	X	X	.	1077	0.79
13	.	X	X	X	.	X	27	0.02
14	.	X	X	X	.	.	79	0.06
15	.	X	X	.	X	X	25	0.02
16	.	X	X	.	X	.	8	0.01

Table 55 Missing data patterns: Recent mental health service use cohort 2008

Group	Ethnicity	Age	Sex	NZDep	DHB	Prioritised diagnosis	Freq. (n)	Percent
1	X	X	X	X	X	X	123076	87.05
2	X	X	X	X	X	.	10830	7.66
3	X	X	X	X	.	X	1090	0.77
4	X	X	X	X	.	.	763	0.54
5	X	X	X	.	X	X	428	0.3
6	X	X	X	.	X	.	44	0.03
7	X	X	X	.	.	X	1	0
8	X	X	X	.	.	.	3	0
9	X	X	.	X	X	X	1	0
10	X	X	.	X	X	.	1	0
11	.	X	X	X	X	X	4386	3.1
12	.	X	X	X	X	.	636	0.45
13	.	X	X	X	.	X	27	0.02
14	.	X	X	X	.	.	61	0.04
15	.	X	X	.	X	X	27	0.02
16	.	X	X	.	X	.	4	0

Table 56 Missing data patterns: Recent mental health service use cohort 2009

Group	Ethnicity	Age	Sex	NZDep	DHB	Prioritised diagnosis	Freq. (n)	Percent
1	X	X	X	X	X	X	134238	90.42
2	X	X	X	X	X	.	6800	4.58
3	X	X	X	X	.	X	1117	0.75
4	X	X	X	X	.	.	763	0.51
5	X	X	X	.	X	X	460	0.31
6	X	X	X	.	X	.	24	0.02
7	X	X	X	.	.	X	2	0
8	X	X	X	.	.	.	2	0
9	X	X	.	X	X	X	1	0
10	.	X	X	X	X	X	4639	3.12
11	.	X	X	X	X	.	316	0.21
12	.	X	X	X	.	X	24	0.02
13	.	X	X	X	.	.	51	0.03
14	.	X	X	.	X	X	27	0.02
15	.	X	X	.	X	.	1	0

Table 57 Missing data patterns: Recent mental health service use cohort 2010

Group	Ethnicity	Age	Sex	NZDep	DHB	Prioritised diagnosis	Freq. (n)	Percent
1	X	X	X	X	X	X	141295	90.28
2	X	X	X	X	X	.	7364	4.71
3	X	X	X	X	.	X	1158	0.74
4	X	X	X	X	.	.	1133	0.72
5	X	X	X	.	X	X	462	0.3
6	X	X	X	.	X	.	22	0.01
7	X	X	X	.	.	X	1	0
8	X	X	X	.	.	.	3	0
9	X	X	.	X	X	X	2	0
10	.	X	X	X	X	X	4677	2.99
11	.	X	X	X	X	.	282	0.18
12	.	X	X	X	.	X	23	0.01
13	.	X	X	X	.	.	60	0.04
14	.	X	X	.	X	X	23	0.01
15	.	X	X	.	X	.	1	0

1.2 COHORT OF MENTAL HEALTH SERVICE USERS: INDEX YEARS 2007-2010

The following tables show the characteristics of each cohort of people with recent mental health service contact, for the years 2007 to 2010. The characteristics of the 2006 cohort are shown in Chapter Four (Table 10).

Table 58 Cohort 2007

Characteristic		Women	%	Men	%
Total with MHS use in five years prior to 2007$		67530		68531	
Age (at 1/1/07)	*20-29*	18205	*27.0*	19914	*29.1*
	30-44	29591	*43.8*	29697	*43.3*
	45-64	19734	*29.2*	18920	*27.6*
Ethnicity	*European*	47012	*69.6*	44161	*64.4*
	Māori	13421	*19.9*	15001	*21.9*
	Pacific	2323	*3.4*	3428	*5.0*
	Asian	2407	*3.6*	1651	*2.4*
	other	761	*1.1*	663	*1.0*
	unknown	1606	*2.4*	3627	*5.3*
NZDep Score (quintile)^	*1 (least deprived)*	8245	*12.2*	6631	*9.7*
	2	10118	*15.0*	9154	*13.4*
	3	13273	*19.7*	12563	*18.3*
	4	17763	*26.3*	18646	*27.2*
	5 (most deprived)	17907	*26.5*	21254	*31.0*
DHB region	*North*	22179	*32.8*	23664	*34.5*
	Midland	13590	*20.1*	12350	*18.0*
	Central	15482	*22.9*	16545	*24.1*
	South	15567	*23.1*	14656	*21.4*
Prioritised diagnosis	*Schizophrenia, other psychoses*	7117	*10.5*	11267	*16.4*
	Bipolar affective disorder	4373	*6.5*	2942	*4.3*
	Depression and other mood	16842	*24.9*	9552	*13.9*
	Anxiety and stress disorders	6908	*10.2*	4802	*7.0*
	Substance use	6098	*9.0*	12910	*18.8*
	Other mental health diagnoses	2058	*3.0*	1460	*2.1*
	"no diagnosis" or "diagnosis deferred"	14703	*21.8*	16759	*24.5*
	No diagnostic information	9431	*14.0*	8839	*12.9*
Service type	*Any inpatient service use*	18323	*27.1*	19458	*28.4*
	any Mental Health Act	3639	*5.4*	5004	*7.3*

$ 4 people were of unknown sex and are not included in this table; ^ 507 (0.4%) had missing NZDep information;

Table 59 Cohort 2008

Characteristic		Women	%	Men	%
Total with MHS use in five years prior to 2008$		69533		71843	
Age (at 1/1/08)	*20-29*	19105	*27.5*	21098	*29.4*
	30-44	29743	*42.8*	30455	*42.4*
	45-64	20685	*29.7*	20290	*28.2*
Ethnicity	*European*	48182	*69.3*	45747	*63.7*
	Māori	13843	*19.9*	15988	*22.3*
	Pacific	2529	*3.6*	3954	*5.5*
	Asian	2588	*3.7*	1826	*2.5*
	other	820	*1.2*	740	*1.0*
	unknown	1571	*2.3*	3588	*5.0*
NZDep Score (quintile)^	*1 (least deprived)*	8653	*12.4*	6999	*9.7*
	2	10443	*15.0*	9561	*13.3*
	3	13640	*19.6*	13219	*18.4*
	4	18215	*26.2*	19450	*27.1*
	5 (most deprived)	18362	*26.4*	22327	*31.1*
DHB region	*North*	23811	*34.2*	26128	*36.4*
	Midland	13796	*19.8*	12726	*17.7*
	Central	15493	*22.3*	16920	*23.6*
	South	15686	*22.6*	14871	*20.7*
Prioritised diagnosis	*Schizophrenia, other psychoses*	7225	*10.4*	11477	*16.0*
	Bipolar affective disorder	4486	*6.5*	3043	*4.2*
	Depression and other mood	17676	*25.4*	10108	*14.1*
	Anxiety and stress disorders	7333	*10.5*	5053	*7.0*
	Substance use	6508	*9.4*	13700	*19.1*
	Other mental health diagnoses	2247	*3.2*	1692	*2.4*
	"no diagnosis" or "diagnosis deferred"	17661	*25.4*	20826	*29.0*
	No diagnostic information	6397	*9.2*	5944	*8.3*
Service type	*Any inpatient service use*	18676	*26.9*	19960	*27.8*
	any Mental Health Act use	3839	*5.5*	5305	*7.4*

$ 2 people were of unknown sex and are not included in this table; ^ 507 (0.4%) had missing NZDep information;

Table 60 Cohort 2009

Characteristic		Women	%	Men	%
Total with MHS use in five years prior to 2009$		72082		76382	
Age (at 1/1/09)	*20-29*	20127	*27.9*	22828	*29.9*
	30-44	30016	*41.6*	31496	*41.2*
	45-64	21939	*30.4*	22058	*28.9*
Ethnicity	*European*	49563	*68.8*	47840	*62.6*
	Māori	14506	*20.1*	17324	*22.7*
	Pacific	2786	*3.9*	4779	*6.3*
	Asian	2819	*3.9*	2122	*2.8*
	other	855	*1.2*	795	*1.0*
	unknown	1553	*2.2*	3522	*4.6*
NZDep Score (quintile)^	*1 (least deprived)*	8909	*12.4*	7536	*9.9*
	2	10749	*14.9*	10021	*13.1*
	3	14208	*19.7*	14052	*18.4*
	4	18830	*26.1*	20497	*26.8*
	5 (most deprived)	19171	*26.6*	23975	*31.4*
DHB region	*North*	25671	*35.6*	29348	*38.4*
	Midland	14107	*19.6*	13137	*17.2*
	Central	15937	*22.1*	17540	*23.0*
	South	15632	*21.7*	15133	*19.8*
Prioritised diagnosis	*Schizophrenia, other psychoses*	7288	*10.1*	11732	*15.4*
	Bipolar affective disorder	4578	*6.4*	3098	*4.1*
	Depression and other mood	18563	*25.8*	10588	*13.9*
	Anxiety and stress disorders	7876	*10.9*	5462	*7.2*
	Substance use	6784	*9.4*	14604	*19.1*
	Other mental health diagnoses	2507	*3.5*	1943	*2.5*
	"no diagnosis" or "diagnosis deferred"	20417	*28.3*	25067	*32.8*
	No diagnostic information	4069	*5.6*	3888	*5.1*
Service type	*Any inpatient service use*	18871	*26.2*	20398	*26.7*
	any Mental Health Act use	4176	*5.8*	5761	*7.5*

$ 1 person was of unknown sex and is not included in this table; ^ 516 (0.4%) had missing NZDep information;

Table 61 Cohort 2010

Characteristic		Women	%	Men	%
Total with MHS use in five years prior to 2010$		75070		81434	
Age (at 1/1/10)	*20-29*	21628	*28.8*	24965	*30.7*
	30-44	30513	*40.6*	32774	*40.2*
	45-64	22929	*30.5*	23695	*29.1*
Ethnicity	*European*	50969	*67.9*	50041	*61.4*
	Māori	15483	*20.6*	18958	*23.3*
	Pacific	3095	*4.1*	5628	*6.9*
	Asian	3065	*4.1*	2364	*2.9*
	other	939	*1.3*	880	*1.1*
	unknown	1519	*2.0*	3563	*4.4*
NZDep Score (quintile)^	*1 (least deprived)*	9243	*12.3*	8008	*9.8*
	2	11174	*14.9*	10631	*13.1*
	3	14662	*19.5*	14946	*18.4*
	4	19542	*26.0*	21671	*26.6*
	5 (most deprived)	20238	*27.0*	25877	*31.8*
DHB region	*North*	27730	*36.9*	32559	*40.0*
	Midland	14444	*19.2*	13696	*16.8*
	Central	16401	*21.8*	18271	*22.4*
	South	15614	*20.8*	15411	*18.9*
Prioritised diagnosis	*Schizophrenia, other psychoses*	7254	*9.7*	11792	*14.5*
	Bipolar affective disorder	4605	*6.1*	3122	*3.8*
	Depression and other mood	18738	*25.0*	10801	*13.3*
	Anxiety and stress disorders	8145	*10.8*	5669	*7.0*
	Substance use	6997	*9.3*	14984	*18.4*
	Other mental health diagnoses	2826	*3.8*	2222	*2.7*
	"no diagnosis" or "diagnosis deferred"	22175	*29.5*	28309	*34.8*
	No diagnostic information	4330	*5.8*	4535	*5.6*
Service type	*Any inpatient service use*	19112	*25.5*	20716	*25.4*
	any Mental Health Act use	4581	*6.1*	6280	*7.7*

$ 2 people were of unknown sex and are not included in this table; ^ 512 (0.3%) had missing NZDep information;

APPENDIX TWO: ADDITIONAL MATERIAL CHAPTER FIVE

2.1 MISSING DATA

The tables below show the patterns of missing data for each cancer cohort, by exposure status (recent mental health service use).

Table 62 Missing data patterns: Breast cancer cohort with a history of mental health service use

Group	Age	Ethnicity	NZDep	Stage	Charlson	Diagnosis	Freq.	%
1	X	X	X	X	X	X	327	81.55
2	X	X	X	X	X	.	29	7.23
3	X	X	X	.	X	X	29	7.23
4	X	X	X	.	X	.	5	1.25
5	X	X	.	X	X	X	6	1.5
6	X	X	.	X	X	.	1	0.25
7	X	.	X	X	X	X	4	1

Table 63 Missing data patterns: Breast cancer cohort with no history of mental health service use

Group	Age	Ethnicity	NZDep	Stage	Charlson	Freq.	%
1	X	X	X	X	X	7386	88.34
2	X	X	X	.	X	513	6.14
3	X	X	.	X	X	189	2.26
4	X	X	.	.	X	22	0.26
5	X	.	X	X	X	218	2.61
6	X	.	X	.	X	24	0.29
7	X	.	.	X	X	8	0.1
8	X	.	.	.	X	1	0.01

Table 64 Missing data patterns: colorectal cancer cohort with a history of mental health service use

Group	Age	Ethnicity	NZDep	Stage	Charlson	Diagnosis	Freq.	%
1	X	X	X	X	X	X	126	72.41
2	X	X	X	X	X	.	17	9.77
3	X	X	X	.	X	X	25	14.37
4	X	X	X	.	X	.	2	1.15
5	X	X	.	X	X	.	1	0.57
6	X	.	X	X	X	X	3	1.72

Table 65 Missing data patterns: colorectal cancer cohort with no history of mental health service use

Group	Age	Ethnicity	NZDep	Stage	Charlson	Freq.	%
1	X	X	X	X	X	3039	78.98
2	X	X	X	.	X	575	14.94
3	X	X	.	X	X	85	2.21
4	X	X	.	.	X	21	0.55
5	X	.	X	X	X	106	2.75
6	X	.	X	.	X	18	0.47
7	X	.	.	X	X	4	0.1

2.2 CANCER TREATMENT RECEIPT

Cancer treatment data drawn from national routine data collections was used to compare treatment receipt between people with a history of mental health services use and those without. Table 66 and Table 67 show treatment receipt for those with breast and colorectal cancers respectively. Because of the large amount of missing data on treatment, these results are likely to be biased. (Gurney et al., 2013) Specifically, it is likely that treatment receipt in people not using mental health services is underestimated, because of missing data on private cancer treatment services.

Table 66 Breast cancer treatment receipt by MHS use and diagnosis

	MHS use Group A		MHS use Group B		No MHS use	
		%	n	%	n	%
total number	112		289		8361	
local or regional disease	91		251		7522	
Surgery						
yes	80	71.4	236	81.7	6465	77.3
no	32	28.6	53	18.3	1896	22.7
Chemotherapy for local or regional disease						
yes	28	30.8	78	31.1	2703	35.9
no	63	69.2	173	68.9	4819	64.1
Radiotherapy						
yes	34	30.4	76	26.3	2358	28.2
no	78	69.6	213	73.7	6003	71.8
Surgery for local or regional disease						
yes	76	83.5	228	90.8	6283	83.5
no	15	16.5	23	9.2	1239	16.5

Table 67 Colorectal cancer treatment receipt by MHS use and diagnosis

	MHS use Group A		MHS use Group B		No MHS use	
	n	%	n	%	n	%
total number	33		141		3848	
local or regional disease	17		84		2393	
Surgery						
yes	21	63.6	84	59.6	2412	62.7
no	12	36.4	57	40.4	1436	37.3
Chemotherapy for regional disease						
yes	6	46.2	16	34.0	766	51.0
no	7		31		736	
Radiotherapy						
yes	2	6.1	22	15.6	702	18.2
no	31	93.9	119	84.4	3146	81.8
Surgery for local or regional disease						
yes	15	88.2	70	83.3	1907	79.7
no	2	11.8	14	16.7	486	20.3

2.3 INPATIENT SERVICE USE DESCRIPTIVE

The following tables show the characteristics of people in the breast and colorectal cancer cohorts based on their history of inpatient or outpatient service use.

Table 68 Descriptive analysis of inpatient and outpatient service use and no mental health service use cohorts for breast cancer

	MHS use Inpatient		MHS use Outpatient		No MHS use	
	n	%	n	%	n	%
total number	129		272		8361	
Age at diagnosis						
18-44	30	23.3	79	30.4	1757	21
45-64	99	76.7	193	69.6	6604	79
Ethnicity						
NZ Māori	32	24.8	55	19.4	1205	14.4
Non-Māori	95	73.6	234	80.6	7156	85.6
NZDep Quintile						
1	15	11.6	39	15.2	1681	20.1
2	15	11.6	39	14.9	1515	18.1
3	20	15.5	52	19.0	1604	19.2
4	38	29.5	65	23.9	1708	20.4
5	38	29.5	73	25.6	1633	19.5
C3 comorbidity score						
0	60	46.5	199	68.2	7291	87.2
1-2	56	43.4	58	25.3	944	11.3
3+	13	10.1	15	6.6	126	1.5
Stage						
Local	64	49.6	137	51.2	4481	53.6
Regional	41	31.8	100	35.6	3041	36.4
Distant	11	8.5	14	4.8	279	3.3
Unstaged	13	10.1	21	8.3	560	6.7

Table 69 Descriptive analysis of inpatient and outpatient service use and no mental health service use cohorts for colorectal cancer

	MHS use Inpatient		MHS use outpatient		No MHS use	
	n	%	n	%	n	%
Total number	48		126		3848	
Age at diagnosis						
18-44	9	18.8	29	23.0	458	11.9
45-64	39	81.3	97	77.0	3390	88.1
Sex						
Female	27	56.3	63	50.0	1765	45.9
Male	21	43.8	63	50.0	2083	54.1
Ethnicity						
NZ Māori	6	12.5	19	15.1	332	8.6
Non-Māori	42	87.5	107	84.9	3516	91.4
NZDep Quintile						
1	5	10.4	15	11.9	754	19.6
2	8	16.7	23	18.3	660	17.2
3	6	12.5	20	15.9	793	20.6
4	13	27.1	39	31.0	831	21.6
5	16	33.3	28	22.2	700	18.2
NMDS comorbidity score						
0	18	37.5	69	54.8	3332	86.6
1-2	25	52.1	43	34.1	390	10.1
3+	5	10.4	14	11.1	126	3.3
Stage						
Local	10	20.8	31	24.6	891	23.2
Regional	20	41.7	40	31.7	1502	39
Distant	13	27.1	33	26.2	841	21.9
Unstaged	5	10.4	22	17.5	614	16

APPENDIX THREE: PREMATURE MORTALITY IN ADULTS USING NEW ZEALAND PSYCHIATRIC SERVICES

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Premature mortality in adults using New Zealand psychiatric services

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Abstract

Aims People with experience of mental illness, in particular those accessing mental health services, have increased mortality compared to the general population, but no studies have examined the situation in New Zealand. This study uses a complete national dataset to estimate mortality rates from natural and external causes for adults using psychiatric services compared to the general New Zealand population.

Methods Routinely collected data on adults aged 18–64 using secondary mental health services between January 2002 and December 2010 were linked to death registrations over the same period. Indirect standardisation was used to estimate the mortality ratio (SMR) for those with any contact with mental health services over this period compared to the New Zealand population.

Results Both men and women using mental health services in New Zealand have more than twice the mortality rate of the total population [combined SMR 2.14 (95% CI 2.09–2.19)], with an increased risk of death from cancer and cardiovascular disease [SMRs=1.31(1.24–1.37), and 1.69 (1.60–1.79) respectively], and external causes (suicide and accidents) [SMR 3.11 (3.00–3.23)]. People with a diagnosis of a psychotic disorder had three times the overall death rate of the population.

Conclusions This study confirms that those using mental health services in New Zealand are dying prematurely from both natural and external causes, and provides evidence which supports calls for coordinated action on this issue.

It has been called the "scandal of premature mortality"[1]: people who experience mental health problems, in particular those whose illness is severe enough to lead to contact with psychiatric services, are dying prematurely.[2]

While this is in part due to higher rates of suicide, chronic medical conditions such as heart disease and cancer are also important contributors to premature deaths in this population.[3] There is also evidence that the difference between the mortality of those using psychiatric services and that of the general population has not diminished over time despite major changes to psychiatric care in the past century.[4,5]

Studies in multiple countries including Australia,[6] the United Kingdom,[7] and the United States[8] have demonstrated this inequality in health outcomes. However, most published studies have been restricted to subnational data, either collected regionally or by specific mental health services (for example[3]), whereas in New Zealand national level data are available on public inpatient and community psychiatric service use, providing an opportunity to investigate mortality on a complete national dataset. Despite this, mortality amongst those using mental health services in New Zealand has not been explored.

New Zealand has a public health care system in which primary care attracts a part-charge at the point of access, but all public secondary services, including mental health care, are provided free of charge.

Most mental health care, particularly for those with more severe illness, is provided by the public and not for profit sectors, and is increasingly provided in the community. Public services are designed to cater for the 3% of the population with the highest mental health needs.[9]

This study examines mortality rates and causes of death for adults using psychiatric services in New Zealand from 2002 to 2010 and compares them to the total New Zealand population.

Methods

This study examines mortality in a cohort of adults in contact with specialist adult public psychiatric services, both community and inpatient, over a 9-year period.

Participants

Adults who had any recorded contact with New Zealand adult public psychiatric services between January 2002 and December 2010, and who were aged 18–64 at the time of contact with services, were eligible for inclusion. People were excluded if they had a recorded principal psychiatric diagnosis of dementia or another organic disorder, without a diagnosis of a non-organic psychotic disorder, or a principal psychiatric diagnosis of intellectual disability without another principal psychiatric diagnosis.

On the assumption that some psychiatric service use is secondary to terminal illness, people were also excluded if their first recorded psychiatric service use was within 3 months prior to their death from a natural cause (excluding psychiatric causes), if they did not have a diagnosis of schizophrenia or bipolar disorder (as these diagnoses imply a longer standing mental illness).

Data on mental health service use in 2001 were used to provide a look-back period for the purposes of establishing whether there was mental health service use more than 3 months before a person's date of death for those who died in 2002.

Data sources

All data were extracted from collections held by the New Zealand Ministry of Health, which were linked using the National Health Index (NHI) (a unique health identifier), and subsequently anonymised. Data on psychiatric service use came from the Ministry of Health data sets on mental health service use. The MHINC (Mental Health Information National Collection) was established in July 2000. In July 2008 this was superseded by PRIMHD (Project for Integration of Mental Health Data) and all MHINC data mapped into this new system.

Data on mortality and cause of death were drawn from the New Zealand Mortality Data Collection. The 2006 New Zealand Census was used for the national denominator population for comparisons.

Variables

Demographic variables: age, sex, ethnicity and area of residence were drawn from the NHI master record. For all analyses presented by sex, those with unknown sex (n=6) were excluded. Prioritised ethnicity as recorded on the NHI record was grouped into the four principal ethnic groups in New Zealand: Māori (the indigenous population), Pacific, Asian and European (including New Zealand European). For the analyses presented here, these were collapsed into Māori and non-Māori (all other) ethnic groups. The New Zealand Deprivation Index 2006 (NZDep2006)[10] was used to assign a deprivation score to the area of residence.

Prioritised diagnosis—Multiple psychiatric diagnoses can be recorded for each individual on psychiatric service records, including principal, secondary and provisional diagnoses, using ICD 9, ICD 10AM or DSMIV. Nevertheless, many individuals have no diagnostic information or "no diagnosis" recorded. There is a requirement that some diagnostic information is entered after a person

has been in contact with services for 30 days, with the result that many of those with no diagnostic information are those with short term contact with services.

In order to identify a single primary diagnosis for each individual to allow comparisons of mortality between diagnostic groups, a prioritisation process was used. The prioritised order of diagnoses was:

1. Schizophrenia, schizoaffective disorder and other non-organic psychoses;
2. Bipolar affective disorder and other affective psychosis;
3. Organic disorders and dementia (excluded from the current study);
4. Depression and other mood disorders;
5. Anxiety and stress disorders;
6. Substance use disorders;
7. Mental retardation (excluded);
8. Other mental health diagnoses (includes personality disorders, eating disorders, etc); and
9. "No diagnosis" or "diagnosis deferred" recorded.

Principal diagnosis was used if available, otherwise provisional diagnosis information was used.

Mental health service type and extent: Those with any inpatient service use recorded in the 9-year study period were categorised as having received inpatient care. The number of calendar years in the time period in which contact with mental health services was recorded (not necessarily continuous) was categorised into three levels: 1 year, 2 to 4 years, and 5 or more years.

Cause of death—Underlying cause of death is recorded using ICD10, based on information from death certificates and coroners reports. Cause of death was grouped into categories based on the underlying cause of death– natural causes of death (all deaths not from external causes), split into cardiovascular causes (ICD10 I chapter), cancer (ICD10 C chapter), psychiatric causes (ICD10 F chapter, includes deaths attributed to dementia, eating disorders and other psychiatric conditions) and other natural causes; and external causes of death, split into self-inflicted and other external (accident and assault and undetermined intent).

Analysis

A descriptive analysis of those using adult mental health services between 2002 and 2010 was performed to provide context for the study.

Standardised mortality ratios (SMRs) were calculated by dividing the observed mortality in those using psychiatric services by the mortality that would be expected if those using psychiatric services had the same patterns of mortality as the total New Zealand population.

The national mortality data for 2005 to 2007 (the mid-point of the study), by cause and 5-year age groups, were used for the comparison. Deaths in those under 20 were excluded from the SMR calculations as their small numbers could lead to unstable results. Only deaths prior to age 65 were included in the calculations, for the purposes of comparison to the New Zealand population. As a sensitivity analysis, the overall SMR was estimated both with and without the exclusion of those with service use only in the 3 months prior to death.

SMRs were calculated for all those using adult mental health services, and then separately for (a) those with a diagnosis of schizophrenia and other non-organic psychoses or bipolar disorder (psychotic disorders) and (b) those with substance use disorders. SMRs for other diagnoses were not calculated because of the large amount of missing diagnostic information.

To examine cause of death, SMRs were also calculated for natural and external causes of death, and for deaths from cancer and cardiovascular disease as the two most common causes of death other than suicide. Standardised mortality ratios for Māori and non-Māori mental health service users, compared to all Māori and non-Māori in the New Zealand population, were also examined separately.

All analysis was performed using SAS software (version 9).

Ethical approval for this study was granted by the New Zealand Multi-region Ethics Committee (reference number MEC/12/05/046).

Results

393,444 people who had had contact with services between 2002 and 2010 were identified from the Ministry of Health PRIMHD data set. After exclusions, 266,093 people were eligible for the study and were included in the final data set.

Figure 1 shows the numbers at each step.

Figure 1. Cohort selection process

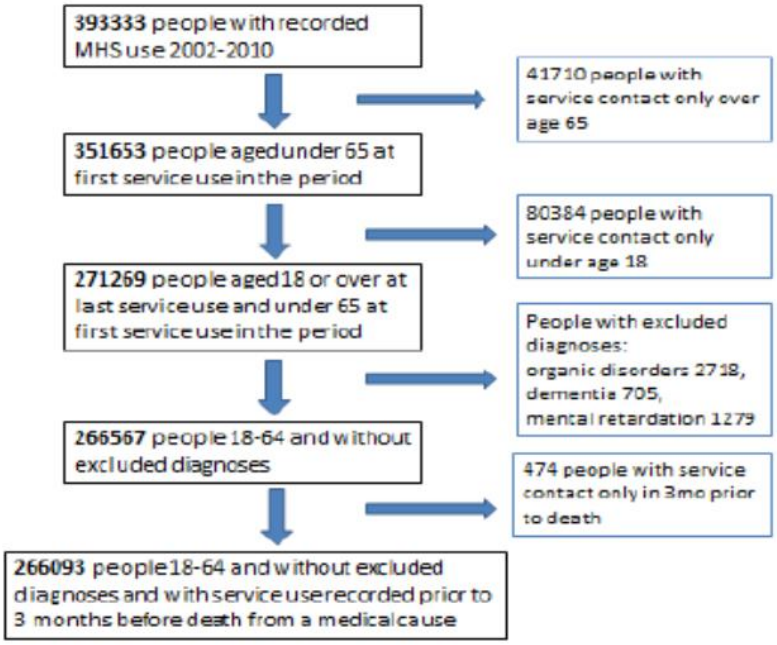

Table 1 shows the demographic and service use characteristics and the prioritised psychiatric diagnosis of the study population. Both men and women were relatively young, with 70% under the age of 45.

The majority was of European ethnicity, and 20% were identified as Māori. Those using psychiatric services commonly lived in relatively deprived areas with around 30% living in the most deprived quintile. Approximately half of those using psychiatric services had no diagnostic information available, and this was related to the length of service use (30% of those with service contact only in 1 year had diagnostic information available, while 92% of those with 5 or more years of service use and 87% of people who had been inpatients had a diagnosis).

One-fifth of those using psychiatric services had inpatient stays during the study period. Nearly half of those seen by psychiatric services had contact with services in only one calendar year over the 9-year study period.

Table 1. Cohort characteristics: adults using mental health services in New Zealand between 2002 and 2010

Characteristic		Women	%	Men	%
Total with MHS use 2002–2010*		128450	48.3	137637	51.7
Age (at 1/1/06)#	18–29	37835	29.5	43199	31.4
	30–44	49858	38.8	51885	37.7
	45–64	32394	25.2	32721	23.8
Ethnicity	European	86840	67.6	84456	61.4
	Māori	25855	20.1	31009	22.5
	Pacific	5222	4.1	8992	6.5
	Asian	5780	4.5	4186	3.0
	other and unknown	4753	3.7	8994	6.5
NZDep Score (quintile)^	1 (least deprived)	16502	12.1	13935	9.7
	2	19272	14.2	18445	12.9
	3	25119	18.5	25337	17.7
	4	32897	24.2	36320	25.3
	5 (most deprived)	34228	25.2	43038	30.0
Prioritised diagnosis	Schizophrenia, other psychoses	8973	7.0	14075	10.2
	Bipolar affective disorder	5881	4.6	4042	2.9
	Depression and other mood	26443	20.6	15621	11.4
	Anxiety and stress disorders	12546	9.8	8734	6.4
	Substance use	4484	3.5	3415	2.5
	Other mental health diagnoses	9631	7.5	21747	15.8
	"no diagnosis" or "diagnosis deferred"	38295	29.8	47078	34.2
	No diagnostic information	22197	17.3	22925	16.7
Service type	Any inpatient service use	24025	18.7	25683	18.7
Years of service use	1 year	62056	48.3	66950	48.6
	2–4 years	47418	36.9	49528	36.0
	5+ years	18976	14.8	21159	15.4

* 6 were of unknown sex and are not included in this table.

5.7% were under 18 years of age at the midpoint and 1.1% were over 65 years.

^ 994 had missing NZDep information.

Table 2. Standardised mortality ratios (SMRs) by cause of death for adults (aged 18–64) using mental health services in New Zealand 2002–2010 compared to the New Zealand population

Cause of death	Women (n)	SMR	95% CI	Men (n)	SMR	95% CI	Combined SMR	95% CI
All natural causes	2092	1.89	1.81–1.97	2611	1.78	1.72–1.85	1.83	1.78–1.88
Cancer	805	1.26	1.18–1.35	759	1.29	1.20–1.38	1.27	1.21–1.34
Cardiovascular	399	1.95	1.76–2.15	816	1.59	1.48–1.70	1.69	1.60–1.79
Mental health	56	9.58	7.37–12.45	81	5.13	4.12–6.38	6.33	5.35–7.48
Other natural causes	832	0.75	0.70–0.80	955	0.65	0.61–0.69	0.69	0.66–0.73
All external causes	832	4.27	3.99–4.57	1864	2.78	2.65–2.91	3.11	3.00–3.23
Intentional self-harm	489	5.97	5.46–6.52	1075	3.90	3.67–4.14	4.37	4.16–4.59
Other external causes	343	3.04	2.74–3.38	789	2.00	1.86–2.14	2.23	2.10–2.36
All causes	**2924**	**2.23**	**2.15–2.32**	**4475**	**2.08**	**2.02–2.14**	**2.14**	**2.09–2.19**

Table 2 shows numbers of deaths and standardised mortality ratios by cause of death. Over 7000 adults who had used mental health services died before the age of 65 during the study period.

The majority of deaths for both women and men were due to natural causes (71% and 58% respectively), with cancer and cardiovascular disease accounting for most deaths in this category. Suicide accounted for 15% of deaths in women and 22% of deaths in men, and other external causes (mainly accidents) were also common.

Overall those using mental health services had an SMR of 2.14, more than twice the risk of death compared to the general population. This difference was greatest for intentional self-harm and other external causes (SMR=4.4 and 2.2 respectively), but was also substantial for all natural causes combined (SMR=1.83), and for both cancer (SMR=1.27) and cardiovascular disease (SMR=1.69).

When those with psychiatric service use only in the last 3 months of their life were not excluded, the overall SMR was slightly higher at 2.26 (95% CI 2.21–2.31: sensitivity analysis not displayed in Table 2).

Table 3. Standardised mortality ratios (SMRs) by diagnosis and setting for adults using Mental Health Services in New Zealand 2002–2010 compared to the New Zealand population

Diagnosis/ Setting	Female (n)	SMR	95% CI	Male (n)	SMR	95% CI	Combined SMR	95% CI
Psychotic disorders	630	3.00	2.78–3.25	938	2.94	2.76–3.14	2.97	2.82–3.12
Substance use	308	3.48	3.12–3.90	733	2.32	2.16–2.50	2.58	2.43–2.74
Any inpatient care	1081	3.84	3.62–4.07	1569	3.52	3.35–3.70	3.64	3.51–3.79
Outpatient care only	1843	1.79	1.71–1.88	2906	1.70	1.64–1.77	1.74	1.69–1.79

Table 3 shows standardised mortality ratios by psychiatric diagnosis and psychiatric service setting. Both men and women with psychotic disorders had mortality rates three times that of the general population (combined SMR=2.97). Women with a

principle diagnosis of substance use had an even higher mortality rate relative to the population as a whole (SMR=3.48).

Men and women who had accessed any inpatient care over the 9-year study period had much higher mortality relative to the whole population than that observed for those who had only accessed outpatient care (combined SMRs=3.64 and 1.74 respectively).

Māori mental health service users had a mortality rate one third greater than that of the whole Māori population assuming the same age structure [combined SMR 1.36 (95% CI 1.30–1.43)], while non-Māori service users had an SMR of 2.39 compared to the non-Māori New Zealand population (95% CI 2.33–2.45).

The difference between Māori using mental health services and the whole Māori population was more marked for women than men [SMR 1.50 (1.38–1.62) vs. 1.29 (1.21–1.37) respectively].

Discussion

This study is the first to examine the mortality of those using mental health services in New Zealand, and demonstrates that those with mental illness are experiencing premature mortality here just as they are in other countries. Men and women using mental health services in New Zealand have more than twice the risk of death when compared to the New Zealand population after adjusting for age. Men and women with psychotic disorders have even higher mortality, three times that of the whole population.

While suicide and accidents were important contributors to the high death rates, both men and women using mental health services also had a significantly raised risk of death from natural causes such as cancer and cardiovascular disease. Māori using mental health services also have higher mortality compared to the Māori population as a whole, but the magnitude of the difference was less for Māori than for non-Māori.

A large body of international literature points to multiple reasons for the high mortality of those using mental health services.[11,12] The patterns of mortality found are important for understanding possible causes. For example the elevated risk of death from cardiovascular disease for those using mental health services in New Zealand is likely to be caused, at least in part, by the use of antipsychotic medications, which have adverse metabolic and cardiac effects.[13] A recent international review found that monitoring of the side effects of psychiatric drugs tends to be inadequate.[14]

In addition, smoking rates remain high amongst those using mental health services,[15] in part because mental health services have in the past facilitated smoking.[16] Smoking is likely to impact both on rates of cardiovascular disease and cancer. There is also evidence from other countries that those who use mental health services are less likely to receive appropriate treatment for their cardiac disease,[17] and this may also be contributing to unequal outcomes in New Zealand.

The metabolic effects of antipsychotic medications are also likely to be a cause of the higher mortality seen in people with psychotic disorders. The effect of discrimination may also help explain the higher mortality of people with psychotic disorders.

Experience of discrimination by health service providers has been reported by people using mental health services internationally including in New Zealand,[18] and discrimination is thought to be related to a lack of adequate preventative care or treatment for physical health problems for people with mental illness.[19]

Moreover discrimination in wider society can lead to difficulties securing long-term employment and housing, which in turn impact on health.[20] While such discrimination can occur against anyone with mental illness, there is some evidence that discrimination is more commonly experienced by people with psychotic disorders compared to other mental illness diagnoses.[21]

The high mortality of those with substance use diagnoses is likely to be related to the impacts of the substances themselves, in particular alcohol. Alcohol is the most commonly used recreational drug in New Zealand and has a major impact on health and mortality.[22]

Social deprivation will also be contributing to the reported mortality gap. Mental illness is both caused by social disadvantage, and also a cause of such disadvantage through social selection.[23] We found that those using mental health services were more likely to live in more deprived areas, and thus social circumstances will be driving some of the increased mortality risk for this group.

Māori in New Zealand have higher rates of morbidity and premature mortality when compared to non-Māori.[24] It might be expected that Māori using mental health services would bear a double burden of disadvantage– experiencing both the disadvantage of ethnicity and of mental health status. However these findings show that the additional burden of mortality experienced by those using mental health services compared to those of the same ethnicity in the New Zealand population was not greater for Māori than for non-Māori. Similarly, Piatt[25] found that African Americans (who also have a higher base line mortality) with severe mental illness did not have increased premature mortality compared with white decedents with severe mental illness.

Our findings are consistent with other studies of mortality in people using mental health services, which have almost universally found excess mortality across all psychiatric diagnoses, settings and ages, and both natural and unnatural causes of death.[2] However as far as we are aware, this is the first study to look at the impact of excluding those whose psychiatric service use is likely to be secondary to a terminal illness. People who are referred to consultant liaison psychiatry by medical or hospice services have a very high mortality rate, and so their inclusion can bias the results of this type of study.

In a recent Australian study, a high and increasing risk of death from cancer was found in those with diagnoses of stress and adjustment disorders [3]. It is likely that this finding reflects stress and adjustment disorders secondary to cancer rather than the reverse. Because we were not able to specifically identify those accessing consultant liaison services or accessing care because of a physical illness, contact with psychiatric services only in the last 3 months of life (excluding those who died from external or psychiatric causes) was used as a way of identifying those likely to be in this group. It is notable that removing this group from the analysis reduced the SMR estimate slightly but the large gap remains.

A particular strength of this study is that it used routine national data about all people using public mental health services, as well as some NGO services, in New Zealand over a 9-year period. It is likely that virtually all deaths in this group are recorded in the national mortality data, as reporting is mandatory and the emigration rate for this group is likely to be low. However using routine data has limitations in terms of data completeness.

No psychiatric diagnosis information was available for half of those included in the study, which limited the examination of the mortality of people with specific diagnoses. However most of those with no diagnostic information had brief contact with services, and it is likely that people who did have the primary diagnoses examined (psychotic disorders or substance use) would have more prolonged contact with services and have diagnostic information recorded.

There are also no outpatient mental health service use data prior to 2001, and so the use of psychiatric services in earlier periods could not be examined. Information on psychiatric service use for those aged 65 and older is not universally included in the national mental health service use collection. The age of those included in a study of this type will impact on the results, as deaths from unnatural causes typically occur earlier in life while deaths from medical causes occur later in life.[2]

There are two sources of bias that may result in this study in fact underestimating the differences in mortality between those using mental health services and those who are not. First, it was not possible to exclude those who have used mental health services from the comparison population. This means we are not comparing those who have used mental health services with those who are not, but with a group that includes people with the high mortality related to mental illness. Second, the study examines a cross section of people using mental health services (a prevalent cohort), and because those who access mental health services have the highest risk of death, particularly from suicide, in the first year after diagnosis,[26] it is likely that the mortality for those using mental health services is underestimated with this method. However using a prevalent cohort enables inclusion of those who have long-term experience of psychiatric illness and therefore may be more likely to suffer the chronic physical effects of medication use, substance use and socioeconomic deprivation.

There have been numerous calls to action on the physical health and mortality of people with mental illness internationally (for example[27]), and as well as in New Zealand,[28,29] and many health services are working to address this inequality.[30]

Primary care providers have a particularly important role as they treat the majority of those with mental illness, including those who also have contact with secondary services. However more evidence about the causes of the mortality gap and the effectiveness of interventions, including interventions in primary care, is needed. In particular more research to illuminate the causes of unequal outcomes for natural causes of death including cancer and cardiovascular disease is needed to inform appropriate action. Moreover, very little research has examined this issue from the perspective of those using mental health services.

As we have shown, adults using mental health services in New Zealand experience at least twice the mortality rate of the total population, information not previously available.

The present study provides a baseline for ongoing monitoring of the physical health of people with mental illness, and will inform the policy and research needed to address these highlighted inequalities.

Competing interests: Nil.

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APPENDIX FOUR: CANCER SURVIVAL IN THE CONTEXT OF MENTAL ILLNESS: A NATIONAL COHORT STUDY

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Psychiatric-Medical Comorbidity

The Psychiatric–Medical Comorbidity section will focus on the prevalence and impact of psychiatric disorders in patients with chronic medical illness as well as the prevalence and impact of medical disorders in patients with chronic psychiatric illness.

Cancer survival in the context of mental illness: a national cohort study

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ABSTRACT

Objective: To explore the reasons for worse cancer survival in people with experience of mental illness, including differences by cancer type and psychiatric diagnosis.
Method: New Zealand breast and colorectal cancer registrations (2006–2010) were linked to psychiatric hospitalization records for adults (18–64 years). Cancer-specific survival was compared for recent psychiatric service users and nonusers using Cox regression. The contributions of deprivation, comorbidity and stage at diagnosis were assessed for those with schizophrenia or bipolar affective disorder (Group A) and others using mental health services (Group B).
Results: Of 8762 and 4022 people with breast and colorectal cancer respectively, 440 (breast) and 190 (colorectal) had recent contact with psychiatric services. After adjusting for confounding, risk of death from breast cancer was increased for Group A [Hazard Ratio (HR) 2.55 (95% confidence interval 1.49–4.35)] and B [HR 1.62 (1.09–2.39)] and from colorectal cancer for Group A [HR 2.92 (1.75–4.87)]. Later stage at diagnosis contributed to survival differences for Group A, and comorbidity contributed for both groups. Fully adjusted HR estimates were breast: Group A 1.65 (0.96–2.84), B 1.41 (0.95–2.09); colorectal: Group A 1.89 (1.12–3.17), B 1.25 (0.89–1.75)].
Conclusions: The high burden of physical disease and delayed cancer diagnosis in those with psychotic disorders contributes to worse cancer survival in New Zealand psychiatric service users.

1. Background

Experience of mental illness is associated with adverse physical health outcomes. People with mental illness have higher rates of many physical illnesses than others in the population and also fare worse once diagnosed with physical conditions [1–3]. Understanding the pathways that lead from experience of mental illness to worse outcomes from physical health conditions is crucial in enabling health services to improve outcomes for this group.

Cancer is a leading cause of death in those with mental illness in developed countries [4,5], and while cancer incidence rates have generally been found to be comparable between people with and without a history of mental illness, cancer mortality is higher [6]. Cancer mortality depends on cancer incidence and cancer survival. The small number of studies which have examined the impact of mental illness on cancer survival has found disparities across cancer types, mental health diagnoses and settings [7–11]. There is some evidence to suggest that these survival disparities may be due to later diagnosis [10] and being less likely to receive treatment for cancer [11]. However few studies have had the power to investigate the contribution of specific factors to cancer survival disparities.

There are a number of possible pathways to apparently worse cancer survival. The difference in survival may be due to confounding – the age, sex and ethnicity of those with experience of mental illness may explain the differences seen in cancer survival. The higher burden of physical illnesses such as diabetes, heart disease and liver disease among those with mental illness compared to those without may impact on survival both directly and through ability to tolerate cancer treatments. People with mental illness may be less likely to access primary care services, or their mental illness may overshadow their cancer symptoms when they do, resulting in cancers being diagnosed later with worse prognosis. Finally, health care quality, or the likelihood of receiving appropriate and timely treatment once diagnosed, may impact on subsequent survival.

This study uses information from a national mental health service dataset linked to a national cancer registry to answer two questions: first, what is the relative importance of the different drivers of cancer survival (particularly stage and comorbid illness) in explaining differences in survival after diagnosis with common cancers for those with

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mental illness, and second, how does the role of these drivers differ by psychiatric diagnosis and cancer type?

2. Methods

We examined 5-year survival in a cohort of adults diagnosed with breast or colorectal cancers between 1/1/2006 and 31/12/2010 and compared those in contact with public psychiatric services in the 5 years prior to cancer diagnosis to those without such a history. Breast and colorectal cancers were chosen as the two most commonly registered cancers in New Zealand (aside from prostate cancer) [12].

2.1. Participants

Adults, usually resident in New Zealand, who were diagnosed with incident breast cancer (ICD10 codes: C50x) or colorectal cancer (ICD10 codes: C18x C19x C20x) between 1/01/2006 and 31/12/2010, and were aged 18–64 at cancer diagnosis.

2.2. Data sources

All data were extracted from collections held by the New Zealand Ministry of Health, which were linked using the National Health Index (a unique identifying number that is assigned to all individuals who use health services in New Zealand) and subsequently anonymised. Data on cancer diagnosis came from the New Zealand Cancer Registry, a population-based register of all malignant cancers diagnosed in New Zealand (except nonmelanoma skin cancers), with mandatory reporting by laboratories and clinicians. Data on psychiatric service use came from the Mental Health Information National Collection (1/1/2001–30/6/2008) and Project for Integration of Mental Health Data (1/7/2008–31/12/2010) data collections, which record data on all public inpatient and outpatient mental health service use in those aged under 65. Data on mortality and cause of death were drawn from the New Zealand Mortality Data Collection, which records all deaths occurring in New Zealand. Data on comorbid diagnoses were drawn from the National Minimum Data Set, which records all inpatient public secondary care contacts.

2.2.1. Exposure

Recent mental illness was defined as mental illness that has been disruptive enough to lead to contact with adult secondary mental health services (for assessment and/or treatment) in the 5 years prior to cancer diagnosis. In order to separately investigate the pathways for different types of mental illness, participants with mental health service use were divided into those with any diagnosis of schizophrenia, schizoaffective disorder, bipolar affective disorder, or other nonorganic psychosis (ICD10 codes: F20, F25, F28, F29, F30, F31) (Group A) and those with any other recorded psychiatric diagnoses or no psychiatric diagnosis recorded (Group B). The remainder of the cohort (with no recorded contact) was treated as the reference group for calculation of hazards ratios. Contact with inpatient psychiatric services over the 5 years prior to cancer diagnosis was also used as an alternative measure of severity as a sensitivity analysis.

2.2.2. Outcomes

Cancer-specific survival (where cancer was identified as the underlying cause of death on the death certificate) was used as the primary outcome (those dying of noncancer causes were censored at time of death). All-cause survival was also estimated with mortality for any cause being treated as the event of interest. Participants who were still alive at the end of the follow-up period were treated as censored in both analyses.

2.3. Variables

Age at cancer diagnosis was calculated from date of diagnosis and date of birth. Age was modeled in the survival analyses using a restricted cubic spline function with three knots (knots at 10th, 50th and 90th percentiles). Sex was used as recorded on the Cancer Registry (male or female), and this information was complete for all of those identified in the cohort.

Ethnic group, as recorded on the Cancer Registry, was used. There are four main ethnic groups in New Zealand: the indigenous Maori population (14%) and European (70%), Pacific (7%) and Asian (11%) groups [13]. Multiple ethnic identities can be recorded on the Cancer Registry, but for reporting, a single prioritized group is used, with the prioritization order of Maori, then Pacific, then Asian and then a residual group. For the analyses reported here, the indigenous Maori population was compared with all other (non-Maori) groups. Those with missing ethnicity information were included in the non-Maori group. Further analysis by ethnic group was limited by small numbers.

Level of deprivation was measured using the NZDep (2006) index, which is a small area measure of deprivation based on data from the 2006 Census [14]. Deprivation level was missing where information on area of residence at the time of cancer diagnosis was not available (about 2%), and these data were imputed using values from multiple other variables [age, sex (for colorectal cancer), ethnicity, cancer stage, comorbidity score and whether the person died] to predict likely deprivation score. The Proc MI (multiple imputation) procedure was used in the analytic programme SAS, and five output datasets were created. Deprivation quintiles were used in survival analysis.

The C3 comorbidity index [15] was used to estimate level of comorbid illness present at the time of cancer diagnosis. This index, specifically developed to measure comorbidity in the context of cancer using administrative hospitalization data, includes up to 42 conditions. For the C3 index, conditions are identified from ICD-10 coded diagnoses recorded for any hospitalization event for a given patient in the 5 years prior to cancer diagnosis. Each condition is weighted according to its impact on a 1-year noncancer mortality (as a mark of severity). The weights are summed to give an overall index score for each patient, with a higher score indicating a higher level of comorbidity. The index was adapted for the current study to exclude psychiatric diagnoses. Comorbidity was modeled using a restricted cubic spline function using three knots for the survival analysis (for breast cancer knots at 0, 0.5 and 1.3; for colorectal cancer knots at 0, 0.5 and 2.0) [16]. For the descriptive analysis C3 scores were divided into three categories: 0, 1–2 and 3+.

Stage at diagnosis is recorded on the Cancer Registry based on all available information on staging within 3 months of diagnosis. The SEER (Surveillance Epidemiology and End Results Programme) summary staging system is used, and this was converted into local, regional and distant disease for analyses. Those with missing stage data were treated as having unstaged disease, and this was used as a stage category.

2.4. Analysis

Breast and colorectal cancer cohorts with a history of recent mental health service use (in the 5 years prior to cancer diagnosis) were compared to those without such a history in terms of demographics, cancer characteristics and comorbidity. Kaplan Meir survival curves for cancer-specific mortality were estimated for those with and without a history of mental health service use and visually compared to assess proportionality of hazards. Cox proportional hazards modeling was used to compare cancer-specific and all-cause survival between those with recent mental health service use and those without and to investigate the contribution of demographic confounders (age, sex, ethnicity) and factors likely to be on the causal pathway (deprivation, comorbidity and stage at diagnosis). Survival estimates were also produced using the Fine Gray method which takes into account deaths from competing causes [17] to check for any bias due to analysis method selection. A directed acyclic graph (DAG) was used to plot the assumed causal

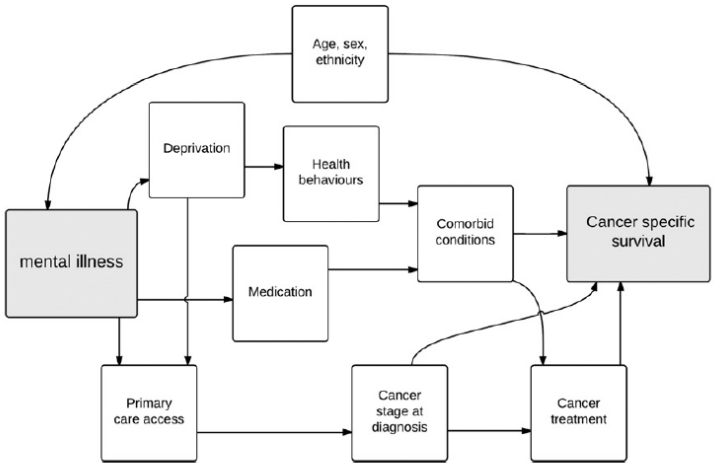

Fig. 1. DAG, demonstrating assumed causal and confounding relationships.

relationships investigated (see Fig. 1). The maximum postdiagnosis follow-up time for the survival analysis was 5 years.

All analysis was performed using SAS version 9.3.

Ethical approval for this study was granted by the New Zealand Multi-region Ethics Committee (reference number MEC/12/05/046).

3. Results

We identified 8762 women with a diagnosis of breast cancer, of whom 440 had had contact with mental health services in the 5 years prior to cancer diagnosis [112 had a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder (Group A)]. There were 4022 people identified with colorectal cancer diagnosed before age 65, of whom 190 had contact with psychiatric services in the 5 years prior (33 in Group A). For both cancers, compared to people without any recent mental health service use, those with a history of recent mental illness (both Group A and Group B) were more likely to be of indigenous (Maori) ethnicity, live in deprived areas and have a higher level of physical comorbidity. These patterns were most marked for mental health service users in Group A. People in Group A also had a less favorable distribution of stage at diagnosis (Tables 1 and 2) for both cancer cohorts.

Women with breast cancer and a history of mental health service use (both Groups A and B) were more likely to die from their breast cancer compared to other women (Fig. 2). Women in Group A had two and half times the risk of death after adjusting for confounding by age and ethnicity [adj. HR 2.55 (95% CI 1.49–4.35)], while women in Group B had a 60% increased risk of death [adj. HR 1.62 (1.09–2.39)] (Table 3). The factors contributing to poor survival were different for these two groups, as shown in Table 3. After adjusting for age and ethnicity, stage accounted for 45% of the remaining survival difference for Group A but did not account for any of the survival difference for Group B. Comorbidity accounted for 25–30% of the remaining difference after adjusting for stage and deprivation for both Group A and Group B. After adjustment for all available factors, a substantial survival difference remained and was similar in magnitude for Group A (fully adj. HR 1.65 (0.96–2.84) and Group B (fully adj. HR 1.41 (0.95–2.09). The results were not substantially different when all-cause survival was used as an outcome measure.

A similar picture was seen for colorectal cancer survival, although the differences between the diagnostic groups were more marked (Table 4) (Fig. 3). Those in Group A were nearly three times as likely to die from their cancer after adjusting for demographic confounders [HR 2.92 (95% CI 1.75–4.87)], while those in group B did not have a significantly elevated risk of death [HR 1.15 (0.84–1.59)]. As for breast cancer, stage was an important contributor to survival differences for Group A. After adjusting for age and ethnicity, stage accounted for 39% of the remaining survival difference for Group A but did not account for the survival difference for Group B. After adjusting for stage and deprivation, comorbidity accounted for 10% of the remaining difference for Group A and around 50% of the remaining difference for Group B. Full adjustment for stage, deprivation and comorbidity reduced the estimate for Group A [HR 1.89 (1.12–3.17)], while adjustment for these factors increased the estimate for Group B [HR 1.25 (0.89–1.75)]. As with breast cancer, similar results were found for all-cause survival.

Using competing cause methods instead of Cox regression methods did not alter the estimates (changes to hazard ratios at the second

Table 1
Breast cancer cohort (n=8772) description of sociodemographic and clinical characteristics by mental health service use groups.

Factor/Characteristic	Group A People with a diagnosis of functional psychosis		Group B People in contact with mental health services for other reasons		No MHS use	
	n	%	*n*	%	*n*	%
Total number	112		328		8322	
Age at diagnosis						
18–44	21	18.75	99	30.18	1746	20.98
45–54	48	42.86	139	42.38	3367	40.46
55–64	43	38.39	90	27.44	3209	38.56
Gender						
Female	112	100.0	328	100.0	8322	100.0
Ethnicity						
NZ Maori	31	27.7	67	20.4	1194	14.3
Non-Maori	81	72.3	261	79.6	7128	85.7
NZDep quintile						
1	10	8.9	48	14.6	1677	20.2
2	11	9.8	47	14.3	1511	18.2
3	17	15.2	67	20.4	1592	19.1
4	34	30.4	78	23.8	1699	20.4
5	37	33.0	83	25.3	1624	19.5
Missing	3	2.7	5	1.5	219	2.6
Comorbidity score						
0	64	57.1	231	70.4	7382	88.7
1–2	38	33.9	67	20.4	775	9.3
3+	10	8.9	30	9.1	165	2.0
Stage						
Local	53	47.3	162	49.4	4467	53.7
Regional	38	33.9	123	37.5	3021	36.3
Distant	11	9.8	16	4.9	277	3.3
Unstaged	10	8.9	27	8.2	557	6.7

Table 2
Colorectal cancer cohort (n=4022) description of sociodemographic and clinical characteristics by mental health service use groups.

Factor/Characteristic	Group A People with a diagnosis of functional psychosis		Group B People in contact with mental health services for other reasons		No MHS use	
	n	%	*n*	%	*n*	%
Total number	33		157		3832	
Age at diagnosis						
18–44	4	12.1	38	24.2	454	11.8
45–54	13	39.4	38	24.2	999	26.1
55–64	16	48.5	81	51.6	2379	62.1
Gender						
Female	17	51.5	77	49.0	1761	46.0
Male	16	48.5	80	51.0	2071	54.0
Ethnicity						
NZ Maori	3	9.1	28	17.8	326	8.5
Non-Maori	30	90.9	129	82.2	3506	91.5
NZDep quintile						
1	3	9.1	17	10.8	754	19.7
2	5	15.2	28	17.8	658	17.2
3	1	3.0	29	18.5	789	20.6
4	9	27.3	50	31.8	824	21.5
5	15	45.5	32	20.4	697	18.2
Missing	0	0.0	1	0.6	110	2.9
Comorbidity score						
0	15	45.5	85	54.1	2922	76.3
1–2	13	39.4	45	28.7	743	19.4
3+	5	15.2	27	17.2	167	4.4
Stage						
Local	4	12.1	45	28.7	883	23.0
Regional	13	39.4	48	30.6	1501	39.2
Distant	13	39.4	39	24.8	835	21.8
Unstaged	3	9.1	25	15.9	613	16.0

decimal place only — results not shown). Using inpatient versus outpatient service use as an alternative measure of severity of psychiatric illness (instead of the grouping by psychiatric diagnosis reported above) gave similar results, with those with a history of inpatient service use having significantly worse survival than those who had used outpatient services only (results not shown).

4. Discussion

Men and women with a history of recent psychiatric service use in New Zealand had poorer survival after diagnosis with breast or colorectal cancer than those who did not have such a history. Those who had been diagnosed with schizophrenia, schizoaffective disorder or bipolar disorder prior to cancer diagnosis had two and half times (breast) to three times

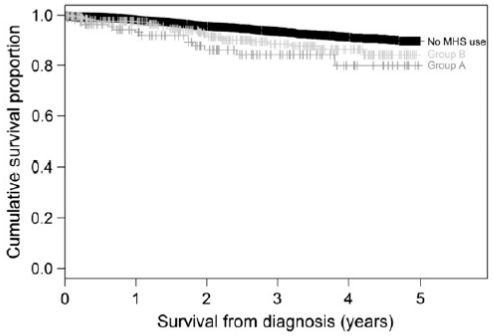

Fig. 2. Breast cancer survival (unadjusted Kaplan–Meier estimates of cancer-specific survival) by mental health service (MHS) use history [Group A (psychosis diagnosis) n=112, Group B (other MHS use) n=328 and no history of service use n=8322].

Table 3
Hazard ratio estimates (from Cox regression models) for breast cancer mortality according to mental health service use history, unadjusted and adjusted for confounders/mediators.

	Group A		Group B	
Model*	HR	95% CI	HR	95% CI
0	2.62	1.54–4.46	1.72	1.17–2.54
1	2.55	1.49–4.35	1.62	1.09–2.39
2	1.85	1.08–3.17	1.63	1.10–2.41
3	1.81	1.05–3.11	1.60	1.08–2.36
4	1.65	0.96–2.84	1.41	0.95–2.09

* 0=crude survival; 1=adj for age+ethnicity; 2=1+SEER stage at diagnosis; 3=2+NZ Deprivation Index score; 4=3+C3 comorbidity index score.

(colorectal cancer) the risk of dying from their cancer within 5 years, after adjusting for confounding. Late stage at diagnosis explained more than a third of the survival difference for this group, but was not a factor for service users with other diagnoses. Comorbid illness also played an important role in explaining survival disparities for both groups. After adjustment for available factors, a 30 to 80% survival disadvantage remained unexplained, although this was no longer significant except in the case of colorectal cancer in people with schizophrenia or bipolar disorder. A similar pattern was seen for both breast and colorectal cancers.

The finding of worse cancer survival associated with a history of mental illness is consistent with the small number of other studies that have examined this question, both for specific cancers or mental illnesses [11,18], and for cancers or mental disorders combined [7,8]. It is also consistent with the wider literature suggesting that cancer mortality is disproportionately increased compared to incidence in people with a history of mental illness [6,19]. The factors potentially contributing to cancer survival inequalities include clinical factors such as comorbidity and health service factors including access to screening and early diagnosis and access to timely treatment. In this study we were able to investigate the impact of stage at diagnosis and comorbidity.

Other studies which have examined the role of cancer stage at diagnosis in survival disparities for people with history of mental illness have produced conflicting findings, with some studies finding that mental illnesses are associated with late diagnosis [10], while others finding an association with early diagnosis [20], or no association [7]. Preexisting illness (including mental illness) can influence the stage at which cancers are diagnosed in a variety of ways, sometimes overshadowing cancer symptoms resulting in late diagnosis, but in other cases leading to increased surveillance resulting in earlier cancer diagnosis, depending on factors such as the severity of the illness, the type of cancer and the health system context [21]. For example, more severe illness may distract attention from cancer symptoms resulting in late diagnosis (as may have occurred with schizophrenia and bipolar disorder in this study), while less severe illness may result in earlier diagnosis through increased contact with the health system and hence increased opportunities for detection. Where all cancers and/or all mental illnesses are examined together, the different stage distribution for different cancers and mental illnesses may be obscured, resulting in no apparent relationship (for example [7]). Differences in findings for the same mental illness diagnosis (e.g., schizophrenia) are likely to relate

Table 4
Hazard ratio estimates (from Cox regression models) for colorectal cancer mortality according to mental health service use history, unadjusted and adjusted for confounders/mediators.

	Group A		Group B	
Model*	HR	95% CI	HR	95% CI
0	2.84	1.70–4.73	1.21	0.88–1.67
1	2.92	1.75–4.87	1.15	0.84–1.59
2	2.17	1.30–3.63	1.47	1.07–2.04
3	2.01	1.20–3.36	1.47	1.06–2.03
4	1.89	1.12–3.17	1.25	0.89–1.75

* 0=crude survival; 1=adj for age+sex+ethnicity; 2=1+SEER stage at diagnosis; 3=2+NZ Deprivation Index score; 4=3+C3 Comorbidity Index score.

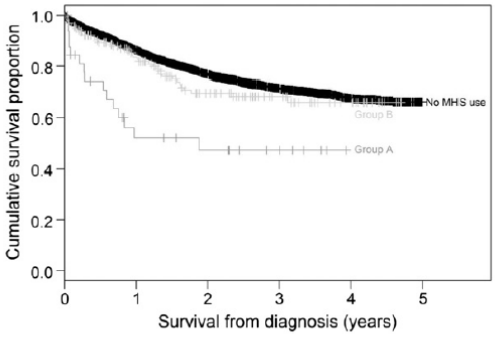

Fig. 3. Colorectal cancer survival (unadjusted Kaplan–Meier estimates of cancer-specific survival) by mental health service use history (Group A (psychosis diagnosis) $n=33$, Group B (other MHS use) $n=157$ and no history of service use $n=3832$).

to the cancer and the health system setting — for example, the finding of earlier lung cancer diagnosis in Medicare patients with schizophrenia than others [20] suggests that these patients undergo a high degree of surveillance of the type likely to pick up lung cancer (likely chest x-rays) in the Medicare system.

Late diagnosis of breast cancers in people with schizophrenia and bipolar disorder in New Zealand may relate to poorer access to screening for breast cancer. In New Zealand, free population-based screening is offered for breast cancer, and coverage rates across the population are high but vary by ethnicity [22]. Screening coverage for people with experience of mental illness in New Zealand is not known, but most studies in other countries have found lower screening coverage rates in people with severe mental illness [23]. Population-based screening for colorectal cancer was not offered at the time of this study. Access to primary care is also important for early cancer diagnosis. The New Zealand health system provides public secondary and tertiary care, including cancer and mental health care, free of charge. However primary care is provided by private practitioners (although largely publicly funded), and copayments are charged for primary care visits and prescriptions. These copayments have been significantly reduced in recent years but continue to present a barrier to access for some groups [24]. In addition to cost barriers, other factors such as overshadowing of physical by psychiatric symptoms and confusion among providers about responsibility for the physical health care of people with severe mental illness may contribute to delays in diagnosis. However as the large linkage studies of cancer survival disparities in Denmark have shown, ready access to primary care and screening for early detection, as is provided by the Danish health system, is not a solution by itself to survival disparities associated with deprivation or diagnoses such as schizophrenia [25].

Coexisting illness (referred to as comorbidity) is also known to be an important factor in cancer survival disparities [26]. Comorbidity can impact on cancer stage at diagnosis as explained above, but independently can also impact on survival through influencing treatment options, and the survivability of treatments and the cancer itself. Most studies of cancer survival in the context of mental illness have either had no information on comorbidity (e.g., [7]), treated comorbidity as a confounder (e.g., [8]) or included it in models together with stage so that its individual contribution could not be assessed (e.g., [27]). Examining the impact of comorbid illness on survival as a mediator draws attention to the fact that the impact of mental illness cannot be considered in isolation — those with mental illness are often also living with physical illness, and cancer treatment needs to be considered in this complex context. In this study we found that comorbidity, after accounting for stage at diagnosis, is an important factor in understanding survival disparities, particularly for those using mental health services for reasons other than psychotic illnesses. Moreover, the impact of comorbidity on treatment decisions is not inevitable, and in fact there is evidence that treatment may at times be inappropriately withheld on the basis of comorbid illness [28,29]. Therefore comorbidity should be considered a cause of mental health-related survival differences that is potentially amenable to intervention.

Beyond the effect of individual factors and timely diagnosis, receipt of timely cancer treatment has also been shown to play an important role in cancer survival disparities, and this is likely to also be the case for people with mental illness [30]. Several studies have found that those with a history of mental illness are less likely to receive treatments such as surgery and chemotherapy [8,27,11]. Moreover, the stigma and discrimination associated with mental illness is likely to be playing a role in these treatment disparities [31,32]. It was not possible to ascertain complete information on treatment receipt in this study. However after adjustment for all available factors, those using mental health services had worse survival than those without a history of mental health service use (although the differences were for the most part no longer statistically significant), and some of this remaining unexplained survival disadvantage may relate to differences in treatment. While secondary care, including mental health and cancer care, is universally available free of charge in New Zealand's public system, evidence of differences in treatment receipt by ethnicity [33], as well as reports of experience of discrimination by health services from people with experience of mental illness [31], suggests that treatment receipt may be a factor in the survival differences found.

4.1. Strengths and weaknesses

This is a population-based study, using complete national data, which allowed longitudinal observation of all New Zealanders using mental health services who subsequently developed common cancers, and comparison to all other New Zealanders with these cancers. This study focused on those under 65, as data on mental health service use for those over 65 are not uniformly or universally collected in New Zealand. Many of the other studies on this topic have been limited to the US Medicare population (over 65). The younger group reported on in the current study is more amenable to interventions to improve cancer survival, and furthermore prevention of premature cancer mortality is an important policy goal, so investigation of this group provides important information for health services and policy makers. It is likely that there was little loss to follow up, as all deaths occurring in New Zealand were captured. It was possible to separately examine breast and colorectal cancer outcomes and the pathways leading to them for people with a diagnosis of schizophrenia, bipolar disorder or schizoaffective disorder, and all others in contact with mental health services, with sufficient power to investigate differences. There was reasonable completeness of data, including cancer stage. Multiple imputation was performed to augment deprivation status completeness.

There was limited information available on psychiatric diagnosis (around 50% had no diagnosis recorded or had “no diagnosis” recorded on their record), so it was not possible to investigate differences in cancer survival and pathways between types of mental illness in more detail. However, it was possible to identify those with schizophrenia and bipolar disorder, conditions generally regarded as the most severe mental illnesses, and it is likely that people with these diagnoses would have this information correctly recorded. It was not possible to obtain reliable information on cancer treatment for this study, and it is likely that treatment differences would explain some of the remaining survival differences. Data on lifestyle factors such as smoking status were not available, but their potential impacts on cancer survival are likely to be at least partially accounted for by including a measure of comorbidity. There is some imprecision in the measurement of each pathway examined. Stage at diagnosis is based on Cancer Registry records, and it is possible that the quality of staging data might vary by mental health status. For example if those with mental illness were less thoroughly investigated, then the Cancer Registry records might incorrectly report disease at a lower stage, resulting in an underestimation of the difference between those with and without mental illness. Comorbidity

may also be mismeasured. Comorbid physical illness was ascertained from previous diagnoses recorded on hospital records, using an index that predicts the relationship between these diagnoses and mortality risk [15]. Not all preexisting illness will be diagnosed, and not all diagnosed illnesses will necessarily be recorded on hospital medical records, and there could be a bias in either direction for those using mental health services (i.e., diagnoses may be more or less likely to be made and more or less likely to be recorded, and this would be likely to vary by the severity and type of mental illness). The comorbidity index used here which is designed specifically for use in cancer populations explains a larger proportion of the difference in survival than the commonly used Charlson comorbidity index, and it is possible that a better measure of comorbidity (if that were possible) would explain even more of the survival difference.

4.2. Implications

These findings add to the limited body of research examining cancer survival in adults with experience of mental illness. Consistent with other work, we have found worse breast and colorectal cancer survival in this group, and in particular much worse survival among those diagnosed with schizophrenia or bipolar disorder. Comorbidity is a contributor to the survival differences found for all those using mental health services, while late stage at diagnosis is an important contributor for those with the most severe psychiatric illnesses. Ensuring timely cancer diagnosis for those with schizophrenia and bipolar disorder is therefore important in improving survival, but on its own will not be enough. Preventive and treatment interventions to reduce the physical disease burden in those with mental illness and treatment guidelines to ensure that comorbid illness does not unnecessarily impede cancer treatment also have the potential to improve cancer survival. The gap in outcomes that remains unexplained may be partly due to imprecision in measuring other factors. However it is also likely that timely access to appropriate treatment and less tangible factors on the treatment pathway such as communication and the relationships between clinicians and patients play an important role in cancer outcomes for those with mental illness. Further investigation of the cancer treatment journey for those with experience of mental illness is needed to understand the reasons for the remaining unexplained gap in outcomes.

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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