The Influence of Comorbidity on Breast Cancer Care and Outcomes in New Zealand

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Abstract

BACKGROUND: Patients with breast cancer and concomitant comorbidity have poorer prognosis, which may be related to a reduction in the receipt and efficacy of cancer treatment. The primary aims of this thesis were to: (1) evaluate the influence of comorbidity on standards of treatment for breast cancer; and (2) determine the survival benefits of treatments in relation to comorbidity burden.

METHODS: Incident cases of primary breast cancer, diagnosed between 2000 and 2015, were identified from 2 prospectively-collected New Zealand breast cancer registers. Comorbidity severity was measured by C3 index score; derived via linkage with national hospitalisation data. Study 1 provided a descriptive analysis of comorbidity burden amongst the cohort. Study 2 modelled the impacts of comorbidity on breast cancer diagnosis and standards of treatment. In Study 3, propensity scores for the conditional probability of treatment were used to create weighted samples balanced with respect to baseline confounding variables. Treatment effects were estimated from weighted Cox proportional hazards and competing risks regression analyses modelling all-cause and breast cancer mortality. Treatment effect heterogeneity by comorbidity severity was evaluated through interaction tests and subgroup analyses.

RESULTS: The study population comprised 12 834 women, with 21.5% possessing at least 1 comorbid condition. Comorbidity was associated with poorer survival, with greatest impact on all-cause mortality. Individuals with comorbidity were more likely to have higher stage disease and less likely to receive all treatment modalities. Comorbid patients derived mortality benefits from surgery, adjuvant radiotherapy, and endocrine therapy but not adjuvant chemotherapy. Heterogeneity in treatment effects by comorbidity severity was noted for surgery and endocrine therapy, with reduced benefits at higher levels of comorbidity.

CONCLUSIONS: Comorbid women with breast cancer receive less treatment than their non-comorbid counterparts, with reduced mortality benefits for those who do. Inferior survival amongst the comorbid is therefore mediated through mechanisms additional to reduced receipt of treatment.

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Glossary

ACE-27	Adult Comorbidity Evaluation-27
AIC	Akaike information criterion
ALND	Axillary lymph node dissection
AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists'
ATE	Average treatment effect
ATT	Average treatment effect on the treated
BCS	Breast conserving surgery
BMI	Body mass index
BreastSurgANZ	Breast Surgeons of Australia and New Zealand
BSA	Breast Screen Aotearoa
C3	Cancer, Care, and Comorbidity Index
CALGB	Cancer and Leukaemia Group B
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
CHF	Congestive heart failure
CIRS	Cumulative Illness Rating Scale
CMF	Cyclophosphamide, methotrexate, and 5-fluorouracil
COPD	Chronic obstructive pulmonary disease
DCIS	Ductal carcinoma in situ
DHB	District health board
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen receptor
FCT	Faster Cancer Treatment
FNA	Fine needle aspiration
Gy	Gray
HER2	Human epidermal growth factor receptor-2
HR	Hazard ratio
ICD-10-AM	*International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australasian Modification*
ICED	Index of Co-existent Disease
IHC	Immunohistochemistry
IPT	Inverse probability of treatment
IQR	Interquartile range
KFI	Kaplan-Feinstein Index
KPI	Key performance indicator

LHRH	Luteinising hormone-releasing hormone
LVI	Lymphovascular invasion
MAR	Missing at random
MCAR	Missing completely at random
MI	Myocardial infarction
MNAR	Missing not at random
MPR	Medication possession ratio
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NHI	National Health Index
NMDS	National Minimum Dataset
NST	No special type
NZCR	New Zealand Cancer Registry
NZDep2013	New Zealand Index of Deprivation 2013
OARS	Older Americans Resources and Services
OR	Odds ratio
PHARMAC	Pharmaceutical Management Agency
Pharms DM	Pharmaceutical Claims Data Mart
PR	Progesterone receptor
PRR	Prevalence risk ratio
RCS	Restricted cubic spline
Ref	Reference category/value
RR	Risk ratio
SEER	Surveillance, Epidemiology, and End Results
SERM	Selective estrogen receptor modulator
sHR	Subdistribution hazard ratio
SLNB	Sentinel lymph node biopsy
SMR	Standardised mortality ratio
TIBI	Total Illness Burden Index
TNM	Tumour-node-metastasis
WBI	Whole breast irradiation
WHO	World Health Organization

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Co-Authorship Form

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Please indicate the chapter/section/pages of this thesis that are extracted from a co-authored work and give the title and publication details or details of submission of the co-authored work. Chapter 3, Sections 3.4.1-3. Citation: Edwards MJ, Campbell ID, Kuper-Hommel MJ. The influence of comorbidity on chemotherapy use for early breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat. 2017; 165 (1): 17-39. DOI: 10.1007/s10549-017-4295-4.

Nature of contribution by PhD candidate	Concept development, study design, data collection and synthesis, statistical analysis, interpretation of results, preparation of manuscript.
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Marion Kuper-Hommel	Advice on study design, review of manuscript.

Certification by Co-Authors

The undersigned hereby certify that:

- the above statement correctly reflects the nature and extent of the PhD candidate's contribution to this work, and the nature of the contribution of each of the co-authors; and
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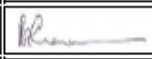
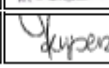
Ross Lawrenson		13/08/2019
Marion Kuper-Hommel		16/08/2019

Chapter 1. Introduction

Is cure possible? Is cure necessary? Is cure possible only when it is not necessary?

—Willett Whitmore

Breast cancer is the most frequently diagnosed cancer and cause of cancer death amongst women worldwide.[1] Like many cancers, the cumulative risk of developing and dying from breast cancer increases with age.[2,3] In parallel with increased vulnerability to breast cancer, advancing age confers higher risk for the development of a number of other chronic health conditions. Chronological age alone however is a poor surrogate for comorbidity burden,[4] with independent impacts on treatment and outcomes from breast cancer.[5-11]

Comorbidity is the coexistence of health-related disorders in conjunction with an index disease of primary interest.[12] While this concept seems relatively simple, comorbidity is complex, with little consensus regarding practical aspects of its measurement and classification.[13,14] Despite these issues, comorbidity amongst breast cancer populations appears to be common, with a prevalence at least that of the general age-matched population.[15-17] Given projections of an aging population,[18] the absolute number of breast cancer patients with concurrent comorbidities is likely to increase over the coming decades.[19] In addition to its interaction with age, comorbidity and breast cancer are linked by shared risk factors[2,20] and biological pathways predisposing to carcinogenesis.[21-25]

Comorbidity has several impacts upon the cancer journey. It may influence the detection of breast cancer and the stage at which it is diagnosed in a number of conflicting ways.[26] In general, patients with breast cancer and comorbidity receive less guideline-concordant cancer treatment, which is of variable quality and reduced tolerability.[27] There is also ample evidence that breast cancer patients with comorbidity have poorer prognosis, both disease-specific and overall.[28,29] While the direct impact of comorbidity on non-cancer mortality is relatively straightforward, several mechanisms may contribute to reduced breast cancer-specific survival, not least of which is a reduction in the receipt of potentially curative cancer treatment.[29]

Although reasons for the underuse of definitive cancer treatment are multifaceted, uncertainty about the efficacy and toxicity of therapies amongst patients with comorbidity is a particular concern, with a paucity of evidence from randomised trials.[30,31] The lack of randomised data on this issue has meant a reliance on observational study designs using conventional regression methods for control of confounding. Comorbidity has complex interrelationships with other drivers of cancer inequities; including advanced age, minority ethnicity, and socioeconomic deprivation.

Failure to adequately account for these factors will confound any attempt to untangle the causal pathways between comorbidity, effective cancer treatment, and survival.

This thesis will focus on the relationship between comorbidity and the index disease of primary breast cancer. A novel measure of comorbidity, the Cancer, Care, and Comorbidity (C3) Index will be used to define comorbidity, which was developed in a New Zealand cohort of cancer patients using national administrative data sources.[32] The overarching goal is to determine the impacts of comorbidity on breast cancer care and outcomes from the disease. The influence of comorbidity on breast cancer diagnosis and standards of treatment will be examined, followed by an evaluation of treatment efficacy in relation to comorbidity burden, employing propensity score methods to control for confounding by indication.

1.1. Objectives

The main research objectives of this thesis are:

1. To review evidence relating to the impacts of comorbidity on breast cancer care and outcomes.
2. To describe the burden of comorbidity in a diverse population of New Zealand women with primary breast cancer and sociodemographic factors associated with its presence.
3. To determine the impacts of comorbidity on breast cancer diagnosis and standards of treatment.
4. To determine the effects of breast cancer treatments on survival in relation to comorbidity.

1.2. Thesis Outline

This thesis is divided into 8 chapters, as follows:

Chapter 1. Introduction: This first chapter is introductory, clarifying the focus of the thesis and defining the specific research objectives.

Chapter 2. Background: The second chapter presents background contextual information regarding comorbidity, breast cancer, and the New Zealand setting for this thesis.

Chapter 3. Literature review: Chapter 3 addresses the first research objective, with a literature review summarising the current evidence with respect to the impacts of comorbidity on breast cancer diagnosis, treatment, and disease outcomes. The interlinking relationships between comorbidity and additional drivers of cancer inequities are explored. From this, a conceptual framework is developed, depicting the pathways connecting comorbidity with breast cancer survival.

Chapter 4. Methods: This chapter details the general methods used in the studies of this thesis, providing an overview of the study population, data sources, variables, and statistical analyses.

Chapter 5. Study 1 - *The burden of comorbidity amongst patients with breast cancer:* Study 1 addresses the second research objective, with an examination of comorbidity in the study population. The chapter begins with a description of the baseline characteristics of the study cohort, including the prevalence and distribution of comorbidity. The survival impacts of comorbidity are then investigated, followed by a nested cross-sectional study exploring sociodemographic factors associated with the presence and severity of comorbidity within the cohort.

Chapter 6. Study 2 - *The impacts of comorbidity on breast cancer diagnosis and standards of treatment:* Chapter 6 presents the second study on this thesis, which focuses on the third research objective, providing an investigation into the effects of comorbidity on breast cancer diagnosis and the standards of treatment received. The first section comprises a series of analyses evaluating comorbidity burden in relation to breast cancer diagnosis, modelling screen-detection status, missing cancer stage, and stage at diagnosis. Subsequent sections address the impact of comorbidity in relation to guideline-non-concordant cancer treatment; with models examining indicators of treatment receipt, quality, and timeliness.

Chapter 7. Study 3 - *The effects of breast cancer treatment on survival in relation to comorbidity:* Study 3 is presented in Chapter 7 and concentrates on the fourth research objective, with an examination of the survival impacts of breast cancer treatments in the context of comorbidity.

Chapter 8: Discussion: The final chapter provides an interpretation of the results and a discussion of their accuracy. The thesis concludes with a discussion of the implications of this work and recommendations for clinical practice and future research.

Chapter 2. Background

Comorbidity, Breast Cancer, and the New Zealand Setting

2.1. Introduction

Chapter 2 provides the context for this thesis, presenting background information on comorbidity, breast cancer, and the New Zealand setting.

The concept of comorbidity is introduced and its related constructs described, specifically: multimorbidity, functional status, frailty, morbidity burden, and complexity. Methodological issues pertaining to the measurement of comorbidity are outlined, using examples of approaches previously applied to breast cancer populations. A rationale for the selection of the C3 Index as the most appropriate measure for this thesis to examine is presented.

The second section of this chapter deals with breast cancer, providing a synopsis of its epidemiology, histopathological characteristics, diagnostic, and management considerations.

Finally the New Zealand setting for this thesis is described with respect to the burden of chronic disease and its unequal distribution within New Zealand society. An overview of the national healthcare system as it pertains to cancer services is also provided.

2.2. Nosology of Comorbidity

In 1970 Feinstein introduced the term comorbidity, proposing a definition of: "…any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study."[12(p456-7)] He noted that although patients with more than 1 medical diagnosis were common, "…the inter-relationships and effects of multiple diseases have not received suitable taxonomic attention..."[12(p455)] This foremost paper discussed issues arising from failure to consider comorbidity in medical statistics, and outlined the potential impacts of pre-existing comorbidity on the diagnosis, treatment, and outcomes of an index disease.

Since Feinstein's seminal definition, the concept of comorbidity has evolved, with multiple different interpretations in existence. In 2003, the National Institute on Aging Geriatrics and Clinical Gerontology Program convened an interdisciplinary taskforce in order to: "…explore conceptual and methodological complexities of comorbidity and its assessment."[33(p275)] The general consensus was that: "Given the complexity and heterogeneity involved in comorbidity,…no single definition or measure would serve all research and clinical purposes."[33(p276)] Rather, this may vary depending upon the research objectives, setting/

population, and outcomes of interest. A conclusion was reached that further research was required in order to advance the theoretical aspects of comorbidity, but without losing sight of the practical issues involved with its measurement.

In their 2009 narrative review on the definition of comorbidity, Valderas et al[34] identified 4 important distinctions. These were: (1) a requirement to clarify the nature of co-occurring conditions; (2) their relative importance, and which should be designated the index disease; (3) the time span and chronology of conditions; and (4) *expanded conceptualisations* relating to comorbidity, such as multimorbidity, morbidity burden, frailty, and patient complexity. The interrelationships between comorbidity and these expanded notions will be further discussed in the following subsection.

2.2.1. Related Constructs

While the core definition of comorbidity assumes the occurrence of conditions additional to an index disease, several related constructs have also been described. Although significant overlap exists, these concepts are distinct clinical entities, with different methods of assessment, strategies for management, and impacts on patient outcome.[35,36] **Figure 1** is a model adapted from Valderas et al[34] showing the integration of these constructs.

2.2.1.1. Multimorbidity

Whilst this term is often used synonymously with comorbidity, multimorbidity is a distinct phenomenon, with van den Akker et al[37] providing principle clarification as: "...the co-occurrence of multiple chronic or acute diseases and medical conditions within one person."[37(p69)] In contrast with comorbidity, which focuses on co-occurring conditions in relation to a primary disease, multimorbidity is an aggregate measure, with emphasis on the cause and effect of multiple combined conditions. While comorbidity is particularly relevant to the single disease paradigm of specialty services, multimorbidity is a useful construct in primary care, where focus is on the patient as a whole without privileging any one disease.[34] Like comorbidity, multimorbidity is predictive of mortality, health service use, disability, and health-related quality of life.[38,39]

2.2.1.2. Functional Status and Disability

Functional or performance status, dis/ability, capacity, activities of daily living, and health-related quality of life are terms which have been used interchangeably with little coherence.[40] Early functional models, such as Nagi's schema from 1965,[41] describe a linear progression from disease leading to impairments, functional limitations, and finally, disability. Over time, these concepts have evolved, with realisation of the complexity of their interrelationships, and appreciation of the influence of environmental factors over the process.[42,43]

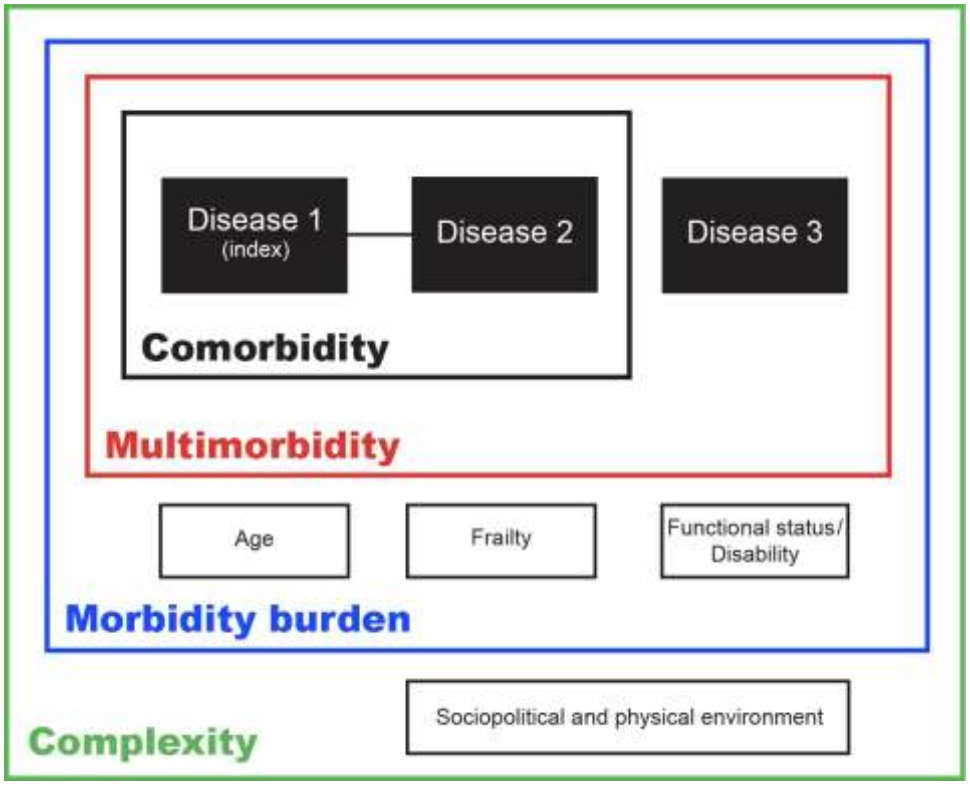


Figure 1. Comorbidity Constructs

Adapted from Valderas et al with permission.[ⓘ]

Functional status and disability are often assessed by standardised instruments which use self-reported difficulty in tasks, such as the Katz[44] and Lawton-Brody[45] scales which were developed in geriatric populations. The Eastern Cooperative Oncology Group (ECOG)[46] and Karnofsky[47] systems are additional widely used methods of assessing performance status, particularly within oncology. However, as established by Extermann et al,[35] these geriatric and oncology functional scores have only moderate correlation, and should not be used interchangeably. There was also very poor correlation between these functional measures and comorbidity. Thus, for elderly cancer patients, comorbidity and functional status (using both geriatric and oncology scoring systems) should be assessed independently. In breast cancer populations, functional status has been found to predict treatment delivery and survival independent of comorbidity and age.[48-51]

2.2.1.3. Frailty

There has also been much confusion regarding the construct of frailty, due to a significant degree of overlap and co-occurrence with comorbidity, disability, and advanced age.[36,52] Frailty has been defined as: "…a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems…causing vulnerability to adverse

outcomes."[52(pM146)] Fried et al[52] operationalised frailty as a syndrome meeting 3 or more of 5 criteria: unintentional weight loss, self-reported exhaustion, weak grip, slow walking speed, and low physical activity. Evaluating these criteria in the Cardiovascular Health Study, they noted that while there was some overlap with disability and comorbidity, frailty could exist as a distinct entity and was independently predictive of disability, hospitalisation, and death. In women undergoing treatment for breast cancer, frailty has been associated with postoperative complications, prolonged hospital stay,[53] non-initiation of endocrine therapy,[54] and increased mortality.[55]

2.2.1.4. Morbidity Burden

Morbidity burden is an expansion of multimorbidity to include functional status in addition to the number and severity of chronic conditions.[49] While there is no gold standard measure of morbidity burden,[49] tools such as the Index of Co-existent Disease (ICED)[56] and Total Illness Burden Index (TIBI)[57] have been used in an attempt to summarise these 3 domains. The ICED (or its immediate precursor[6]) and a subset of the TIBI (the cardiopulmonary index[8]) have been used in breast cancer populations for assessment of morbidity burden in relation to cancer treatment[6,8,49,58,59] and mortality.[59] The American Society of Anesthesiologists' (ASA) class[60] is a further commonly used measure of overall health status, particularly in prediction of perioperative adverse events. The ASA class has been used as part of a multiple informants approach to measuring comorbidity, in the prediction of breast cancer treatments.[61]

2.2.1.5. Complexity

Complexity is the broadest construct related to comorbidity; considering the interactions between all determinants of health at an individual level.[62] In their scoping review on the classification of patient complexity, Schaink et al[63] proposed a conceptual framework to enhance the understanding of complex patients within their sociopolitical and physical environment (**Figure 2**). Five health dimensions were included in this complexity framework: health and social experiences, demographics, mental health, social capital, and medical/physical health.

Measurement of patient complexity within populations is difficult, as the contribution to complexity from each health determinant may vary between individuals.[62] At an individual level, the Comprehensive Geriatric Assessment (CGA) is a commonly utilised clinical tool for the assessment of complexity in the elderly. The CGA is a multidisciplinary diagnostic and treatment process which identifies medical, psychosocial, and functional issues, with the aim of developing an integrated plan to maximise overall health.[64] While the individual components of CGA may vary, the domains of comorbidity, functional status, social status/support, cognition, mental health status, nutrition, fatigue, and presence of geriatric syndromes are generally included.[65] Several consensus guidelines now recommend its routine use in geriatric oncology.[65,66] The utility of the CGA amongst breast cancer patients has been shown in the prediction of operative treatment,[67] chemotherapy-associated toxicity,[68] and survival.[51]

The Older Americans Resources and Services (OARS) Questionnaire[69] is another tool used to measure complexity. The OARS methodology was designed to assess an individual's functioning across 5 dimensions (social and economic resources, mental and physical health, and activities of daily living). The OARS subscales have been applied to the prediction of chemotherapy receipt[70] and toxicity,[30] as well as relapse and survival outcomes in patients with breast cancer.

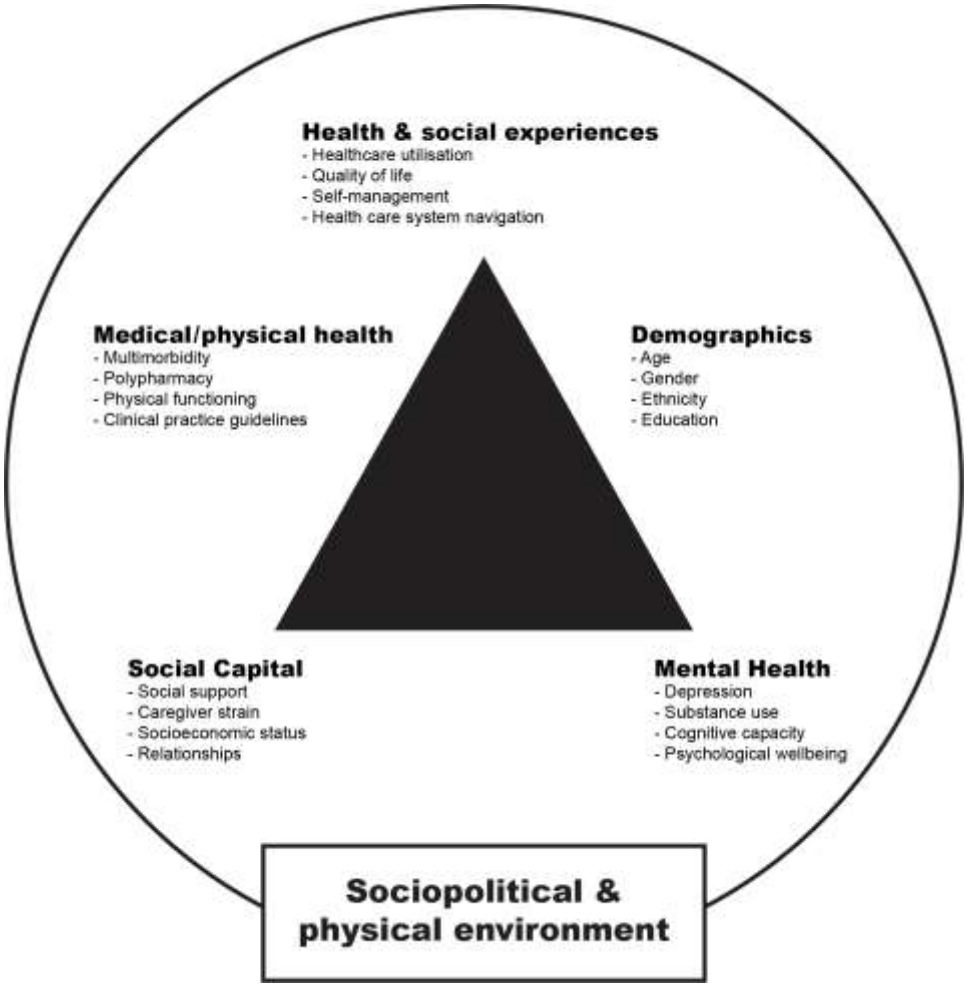


Figure 2. The Complexity Framework Showing 5 Health Dimensions

Adapted from Schaink et al,[63] Swiss Medical Press GmBH.

Why does this thesis focus on comorbidity?

The focus of this thesis is comorbidity in the context of a population of women with a primary diagnosis of breast cancer. Thus, with an index disease of interest, comorbidity is a more appropriate construct than multimorbidity. Whilst the expanded conceptualisations of comorbidity are useful considerations in individuals, particularly within the settings of primary care and geriatric medicine, they are difficult to measure in a large cohort using administrative data sources. Validated measures of functional status and frailty are not currently available within routinely-collected patient data in New Zealand. It is therefore unfeasible to measure combination constructs such as morbidity burden and complexity at a population level.

2.2.2. Measurement of Comorbidity

Even if its related constructs are set aside, classification of comorbidity is difficult. Whilst comorbidity has been studied in a variety of settings and population groups, with several authors discussing and comparing the use of various methods,[13,14,71-78] there remains little consensus regarding how best to approach its measurement.[13,14] Appropriate measurement of comorbidity is contextual and requires a number of conceptual decisions.[13,33,79] Differences in the methods employed can give a different picture of an individual's level of comorbidity, both quantitatively and qualitatively.[71] Methodological issues in the measurement of comorbidity may arise from a number of factors; to be discussed in this subsection. A narrative summary of some of the previous approaches used to measure comorbidity amongst breast cancer populations is given in **Table 1**.

2.2.2.1. Designation of the Index Condition

Different conditions are likely to have a varying impact on outcome depending on the primary disease of interest.[13,72] For example the impact of chronic obstructive pulmonary disease (COPD) on breast cancer outcomes is likely to be different to its impact on outcomes from congestive heart failure (CHF). For this reason, some authors propose that disease-specific indices be used in preference to generic ones.[13,78,80] Such approaches tend to be modifications of existing indices however, though without their established reliability,[77] and with a reduction in comparability across other research settings.[13,81]

2.2.2.2. Selection of Coexisting Conditions

The set of conditions stipulated for inclusion in the operationalisation of comorbidity is decisive for the amount of comorbidity measured.[35,76,79] Because there is no standard list of diseases to be considered, prevalence estimates of comorbidity are thus related to the number of conditions to summed, making cross-study comparisons difficult. A systematic account of every possible diagnosis gives a good appreciation of the overall burden of disease, but may yield an unmanageable amount of potentially irrelevant information and create a spurious measure of comorbidity.[72,76] Parsimonious decisions to concentrate on a single or few highly prevalent or influential conditions have practical and statistical advantages, but may result in a less representative view of the distribution of comorbidity, and do not permit an estimation of the impact of overall comorbidity burden on outcomes.[74,79] Numerous restrictions on selection may be considered, such as limiting the definition of comorbidity to conditions which may be: chronic (vs acute), active (vs inactive), cogent (vs non-cogent),[82] symptomatic (vs asymptomatic), or somatic (vs psychiatric). The index disease, as well as any potential complications of such, is not usually included in the comorbidity score (eg, liver metastases due to breast cancer).[14,71,77]

Table 1. Approaches to Measuring Comorbidity and Related Constructs in Breast Cancer Populations

Name[a]	Author (Year)	Development Population	Data Sources	Items	Scoring Method	Modifications	Application to Breast Cancer
ACE-27	Piccirillo et al[83] (2003)	11 906 patients with cancer	Clinical notes	27 conditions	Sum of conditions with each weighted according to severity	Fleming et al[84] (2011)	Overall survival[85]
ASA class	Saklad[60] (1941)	Surgical patients	Clinical notes		Score given to 1 of 6 degrees of physical state		Treatment receipt[61]
C3 index	Sarfati et al[32] (2014)	14 096 New Zealand patients with breast, colorectal, gynaecological, upper gastrointestinal or urological cancers. Validated in an additional 11 014 patients.	Administrative (*ICD-10* codes from the National Minimum Dataset)	42 conditions	Sum of weights based on impact on hazard ratio of 1-year non-cancer mortality		Treatment receipt[86,87]
CCI	Charlson et al[88] (1987)	608 hospitalised general medical patients. Validated in 685 women with breast cancer.	Clinical notes	17 conditions in 19 categories	Sum of weights based on relative risk of 1-year overall mortality	Charlson-Deyo[89] (1992) Romano et al[90] (1993) D'Hoore modification[91] (1996) Katz et al[92] (1996) Hypertension-augmented CCI[93] (2009)	Treatment receipt, quality & toxicity; breast cancer-specific, non-breast cancer & overall mortality[b]
CGA			Patient self-report & clinical notes	Usually 8 domains including comorbidity			Treatment receipt[67] & toxicity[68]; overall survival[51,68]
CPI	Fleming et al[94] (1999)	848 patients with breast cancer	Administrative data (*ICD-9* codes from Medicare database)	34 categories	Multiplicative based on 1-year overall survival		Breast cancer-specific & overall mortality[94]
ICED	Greenfield et al[56] (1993)	356 patients undergoing hip joint replacement	Clinical notes	14 organ systems & 10 functional systems	Combined highest scores from comorbidity & functional systems		Treatment receipt[49,58]
KFI	Kaplan & Feinstein[82] (1974)	188 men with diabetes	Clinical notes	12 body systems	Highest score from component severity scores		Overall mortality [95]
MACSS	Holman et al[96] (2005)	1 118 989 hospitalised patients. Validated in an additional 14 231 patients including 615 with breast cancer.	Administrative data (*ICD-9* codes from Western Australia health database)	102 conditions	Individual conditions based on relative risk of 1-year overall mortality, 30-day readmission, or average length of stay		30 day readmission, length of stay, 1-year overall mortality[96]

Table 1 continued. Approaches to Measuring Comorbidity and Related Constructs in Breast Cancer Populations

Name[a]	Author (Year)	Development Population	Data Sources	Items	Scoring Method	Modifications	Application to Breast Cancer
NCI index	Klabunde et al[97] (2000)	14 429 prostate & 7472 breast cancer patients. Validated in an additional 14 439 prostate & 7471 breast cancer patients.	Administrative (*ICD-9* codes from SEER-Medicare database)	12 conditions in 13 categories	Sum of weights based on 2-year non-cancer mortality		Treatment receipt, quality & toxicity; breast cancer-specific & overall mortality[b]
OARS questionnaire	Duke University[69]	83 community residents (physical health section)	Patient self- report	5 dimensions including physical health (16 conditions)	Summary rating for each of 5 dimensions		Treatment receipt[70] & quality; breast cancer relapse, overall survival[30]
Satariano	Satariano & Ragland[98] (1994)	936 women with breast cancer	Clinical notes	7 conditions	Count of unweighted conditions based on breast cancer-specific, non-breast cancer, & overall mortality	Newschaffer et al[95] (1997)	Treatment receipt[59]; non-breast cancer[98] & overall mortality[59,95,98]
Tammemagi	Tammemagi et al (2003[99] & 2005[100])	1155 lung & 906 breast cancer patients	Clinical notes	19 conditions for lung & 77 conditions for breast cancer	Count of unweighted conditions based on overall survival		Breast cancer recurrence/ progression; breast cancer-specific & overall mortality[100]
TIBI	Greenfield et al[57] (1995)	1738 general patients	Patient report of symptoms	15 disease categories	Sum of weighted disease categories based on functional outcomes	Cardiopulmonary index[8] (1997)	Treatment receipt, [8,49,59] overall mortality [59]

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; CCI, Charlson Comorbidity Index; CPI, Comprehensive Prognostic Index*; ICD, International Statistical Classification of Diseases & Related Health Problems*; KFI, Kaplan-Feinstein Index; MACSS, Multipurpose Australian Comorbidity Scoring System; NCI, National Cancer Institute; SEER, Surveillance, Epidemiology, and End Results.

[a] Only related constructs incorporating a comorbidity component are included.

[b] Multiple instances of use; summary of examples pertaining to chemotherapy given in Edwards et al.[27]

2.2.2.3. Definition of Coexisting Conditions

Categorisation of the conditions to be included in an assessment of comorbidity may be inconsistent and depend on the diagnostic criteria applied.[72] Classification systems such as the *International Statistical Classification of Diseases and Related Health Problems (ICD)*[101] are often used, but may not be useful for all diseases, particularly those which are not easily dichotomised and exist within a spectrum.[34] Conditions may be counted as separate entities or aggregated as a concordant group of related conditions with similar pathogenesis and management (eg, hypertension and myocardial infarction (MI) may be combined as an overarching term, cardiovascular disease).[102] Ideally, conditions will be mutually exclusive, however it is possible to double count cause-and-effect diseases such as CHF secondary to valvular heart disease.[77] Diseases may also be pooled by organ system, as exemplified by the Cumulative Illness Rating Scale (CIRS)[103] and its variants.[104,105]

2.2.2.4. Accounting for the Severity of Conditions

The prognostic impact of a condition may differ depending upon its severity.[72] For example, Sarfati et al[32] found that breast cancer patients with uncomplicated diabetes experienced a slight survival advantage (hazard ratio [HR] of non-cancer mortality 0.8), while those with complicated diabetes had an increased risk of death (HR 2.8). Several indices incorporate an assessment of physiological severity, such as the Kaplan-Feinstein Index (KFI),[82] CIRS,[103] ICED,[56] TIBI,[57] ASA class,[60] and Adult Comorbidity Evaluation-27 (ACE-27).[83] Accounting for severity however can considerably increase the complexity of an index, making it less practical to implement.

2.2.2.5. Accounting for the Relative Importance of Coexisting Conditions

The treatment and survival impact of a number of individual comorbid conditions has been assessed in breast cancer populations, including; diabetes,[100,106-119] cardiovascular disease,[93,100,107-109,112,113,115-117,119-127] renal disease,[107,109,112,116,119,123,128,129] cerebrovascular disease and dementia,[109,112,120,123,130] pulmonary disease,[107,109,112,116,120,123] previous malignancy,[109,112,113,116,120,123,131] liver disease,[109,123] and gastrointestinal conditions.[109,112,116,120] The prognostic impact of diabetes has been particularly well studied, imparting a generally negative influence on survival.[100,106,107,110-113,116,118] The Multipurpose Australian Comorbidity Scoring System is another approach previously applied to patients with breast cancer, which comprises a list of 102 conditions to be evaluated individually.[96]

Summation of the total number of comorbid conditions from a candidate list into an ordinal score (a *comorbidity count*) provides a simple measure of comorbidity. This has been used in a number of breast cancer studies, and has been found to be predictive of stage at diagnosis,[132] treatment patterns,[129,133-135] and survival.[98,100,107] Some authors have used an explicit process to define the conditions to be totalled, such as the Tammemagi[99] and Satariano[98] approaches, both of which

were developed in breast cancer populations. The implicit assumption is that all conditions contribute equally to outcome, with the overall impact driven by the number of conditions present. Amongst patients with breast cancer, some diseases, such as CHF or dementia, have a greater deleterious effect on prognosis than do other, more minor conditions such as dyslipidaemia.[107,112,113,116,120] Thus schemes have been developed which weight the individual contributions of conditions according to their specific impact on outcome. Again, however, if weightings are overly customised, the index will be less useful when applied to other settings.[81]

A number of different weighted approaches have been used in studying breast cancer populations, including the Charlson,[88] (and its modifications[89,91-93,136]) National Cancer Institute (NCI),[97] and C3 indices.[32] Of these, the Charlson Comorbidity Index (CCI) is the most extensively cited. Developed in the US in 1987 by Charlson et al[88] using medical records to predict 1-year overall mortality amongst 608 hospitalised patients, the index was subsequently validated in a cohort of 658 women with breast cancer. Reflecting its intent to predict short term mortality, the 16 contributing conditions are severe; and as such tends to under-classify prevalence when applied to breast cancer cohorts.[29] Common minor conditions are excluded, such as obesity and hypertension; both of which have been shown to exert independent influence over breast cancer survival.[93,100,122,127,137]

2.2.2.6. Accounting for the Combined Effects of Multiple Conditions

How comorbidities cumulate to determine outcome is complex. Conditions may be additive, multiplicative, or the incremental weight may decrease with an increasing number of diseases.[71,138] An index is a summary of a collection of factors with a common consequence; no assumption is made of correlation between items.[139] Most comorbidity indices assume an additive relationship and ignore interactions that may differ from their simple or weighted sum. For example, the interaction between COPD and CHF might exceed their simple sum; while conversely, hypertension related to diabetes might be over-weighted in an index that tallies both individually. Individual diseases with common pathophysiologic mechanisms may cluster, with the impact of this cluster greater or lesser than their total.[81] Whilst considerably unwieldy, some authors have attempted to account for such interdependencies through the incorporation of interaction terms, although differences in model fit were insubstantial.[140,141]

2.2.2.7. Accounting for Time Span and Chronology of Conditions

The recency and length of time a comorbid condition has been present may be important to the aetiology, treatment, and prognosis of an index disease.[34] For example, the prognosis for patients with a distant history of MI who receive a new breast cancer diagnosis may be different to those with a more recent MI event. Merging historical and recent diagnoses may result in an antagonistic combination, weakening their independent effects.[142] Repeated events may also be important, with the mortality risk following a second MI event likely to be greater than the first.

Consideration may also be given to disease-specific complications of comorbidity, with the existence of one disease a prerequisite for the occurrence of another (such as diabetes and diabetic neuropathy).[37] The time point at which comorbidity is ascertained and the *lookback period* has important implications for its measurement. While the ascertainment of comorbidity at index admission or during short lookback periods is convenient and more likely to identify currently active problems, longer lookback periods identify more important conditions per patient, thereby assigning comorbidity to a greater proportion of a cohort.[142-144]

2.2.2.8. Designation of the Outcome of Interest

While the ideal comorbidity index would predict a variety of relevant outcomes, the impact of comorbidity is inconstant, with the assigned weighting dependent on the outcome it has been specifically modelled to predict.[38] Moreover, while weights derived in a development population may be a good fit to that data, optimal fit in a different cohort is not guaranteed.[14,75] In aggregate however, adverse outcomes are positively correlated.[75] Thus, for exploratory purposes, a comorbidity score developed in one setting may be applied to another, with the CCI in particular showing good predictive ability in a number of contexts.[13,89]

2.2.2.9. Data Source

The presence of comorbidity may be established from medical records, patient self-report, clinical judgement, or administrative databases. Many indices rely on information obtained from retrospective note review.[56,82,83,88,98,99,103] This gives excellent comorbidity ascertainment and exemplifies the information available to treating clinicians, reflecting the target purpose to assess impact on clinical decision-making and disease prognosis.[81] Detailed information is available, enabling an evaluation of disease chronology and severity. However, clinical note abstraction can be enormously costly/resource intensive and is not guaranteed to be entirely complete, standardised, nor error-free.[95,145] Patient consent is usually required, and records must be available over a sufficient time period. Some indices have been developed to collect information directly from patients (eg, the TIBI[57]), or adapted for patient interview/self-report (such as the Katz-modification of the CCI[92]). Self-reported comorbidity correlates moderately well with medical record review, particularly for more serious and well-defined entities,[92,146,147] and has good predictive validity for health resource utilisation.[92,148] In retrospective studies however, recall accuracy may be affected by cognitive impairment,[81] and patients may have died or be uncontactable. Collection of an overall health status rating from a clinician, using tools such as the ASA class[60] is simple and efficient, but may mask the true complexity of comorbidity.[81]

Administrative databases, such as hospital discharge data and insurance claims databases have also been widely used to quantify comorbidity. Such data sources are relatively easy to obtain and cost-effective, making this a practical way to measure comorbidity in a large cohort. However the data is not collected for research purposes, and may be incomplete, inaccurately coded, or

lacking in detail.[75,78,145,149] While studies have generally shown higher ascertainment of comorbidity from medical note review than from administrative data sources, the extent of this difference is variable, depending on the index/conditions considered, the outcome of interest, the look-back period, and the quality of the data source itself.[144,145,150] Despite correlation between these sources being moderate at best, where comorbidity has been included as a covariate in multivariate risk adjustment models, both medical record and administrative data improve model fit to a similar degree, with both sources combined better than either alone.[95,151,152] Lash et al[61] recommend a multiple informants approach, finding that the simultaneous combination of the interview-based CCI, medical record-derived ICED, ASA class, and a clinicians subjective assessment into a single estimate of comorbidity was superior to models which included each component individually, in an evaluation of the impact of comorbidity on receipt of treatment in a breast cancer cohort.

Which approach to choose?

Measurement of comorbidity is subject to context, and the approach should be a function of the individual study aim, population, and setting. A basic framework considers the completeness and relevance of content (content validity), the extent to which the index makes sense (face validity), correlation between the index and other measures (concurrent validity), the ability to predict future outcomes of relevance (predictive validity), feasibility, reliability, and generalisability.[13,77]

This thesis will examine the impact of comorbidity on breast cancer care and outcomes in a population of New Zealand women. Given this index condition, a comorbidity measure developed in a breast cancer population, or at least a population with cancer in general would provide optimal content and face validity. Selection (and weighting) of conditions in relation to their impact on mortality outcomes would further enhance content/face validity, as well as optimise predictive validity. As national administrative data was to be used for comorbidity ascertainment, clinical records based indices were deemed unfeasible. Following consideration of these factors, the C3 index was ultimately selected for use in this thesis.

2.3. Breast Cancer

2.3.1. Epidemiology

Breast cancer is the most frequently diagnosed cancer amongst women worldwide.[1] While genetic factors account for 5-10% of cases, the major drivers of international and interethnic variations in incidence are nonhereditary; related to differences in screening, reporting, and risk factors. Elevated incidence rates in developed countries are attributed to greater prevalence of risk factors related to reproduction and lifestyle.[1-3] Advancing age is also a significant risk factor,[2,3] with a median age at diagnosis of 62 and median age at death of 68.[153]

In New Zealand, breast cancer is the most commonly diagnosed cancer and second most common cause of cancer death (after lung) amongst women, with more than 3000 cases diagnosed and more than 600 dying from the disease annually.[154] While overall incidence is similar to other developed countries, with an age-standardised rate of 85.0 per 100 000,[155] Māori have the highest known incidence of any population group in the world (particularly young Māori [156]), with an age-standardised rate of 117.9 per 100 000.[157] This incidence gap is also widening, with static rates for non-Māori and rising incidence for Māori.[154,158] Whilst this disparity is largely unexplained, higher rates of obesity and alcohol intake may contribute.[159]

2.3.2. Histopathology

Breast cancer is a biologically heterogeneous disease. Many axes of classification have been used as a means to stratify patients by prognostic risk and predict response to treatment; including tumour stage, grade, histological type, biomarker status, and molecular subtype.

2.3.2.1. Stage

Cancer is staged according to the anatomical extent of the primary tumour and any regional or distant spread. While several staging systems exist, the accepted standard is the tumour-node-metastasis (TNM) classification, published by the American Joint Committee on Cancer (AJCC).[160] This system categorises breast cancer according to the extent of disease at the primary site (tumour-T), regional lymph nodes (nodes-N), and spread to distant sites (metastasis-M). Categories are then aggregated to describe 5 stages: 0 (in situ), I, II, III, and IV (distant metastasis). Clinical classification is based on evidence acquired before treatment from physical examination and imaging; while pathological stage is derived from histological examination of the surgical specimen/s. Where multifocality or multicentricity is present, the diameter of the largest lesion is used to assign T stage.[160] The current TNM system does not assign an independent value to these features,[160] as their prognostic impact remains controversial.[161,162]

2.3.2.2. Grade and Markers of Proliferation

Histologic grade provides a qualitative assessment of tumour differentiation, and is a powerful prognostic factor.[163,164] The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson system[163]) evaluates 3 features: tubule formation, nuclear pleomorphism, and mitotic count. A score is given to each component and an overall grade is assigned from 1 (favourable) to 3 (unfavourable). Tumour proliferation may also be evaluated by immunohistochemistry (IHC), using monoclonal antibodies to the nuclear antigen Ki-67.[165] While the independent prognostic value of Ki-67 is robust,[166,167] its use in clinical practice remains controversial, due to issues regarding inter-laboratory reproducibility and the optimal thresholds to distinguish low and high values.[168,169]

2.3.2.3. Histopathologic Type

Cancers arising from the terminal ductal lobular unit may be characterised as originating from either the lining epithelium of ducts (ductal), or the milk-producing lobules (lobular). Invasive disease is distinguished from in situ by the penetration of neoplastic cells beyond the ductal-lobular system into stroma. The most common category is invasive carcinoma of no special type (NST), which display no particular features to merit classification as a special type.[3] Special subtypes comprise the remainder, and are classified on the basis of cell morphology, growth, architectural patterns, and biomarker expression. Histopathological classification has prognostic value; for instance, lobular carcinomas have a different pattern of relapse which is later than invasive carcinoma NST, and generally improved survival. Lymphomas can also occur, as may cancers originating from stromal components, such as phylloides tumours and sarcomas.

2.3.2.4. Lymphovascular Invasion

The invasion of a lymphatic or blood vessel by tumour cells is a critical step in the process of metastasis and is often associated with other adverse tumour features.[170] While lymphovascular invasion (LVI) appears to be a poor prognostic indicator, its independent value remains unclear in the setting of otherwise low risk histopathology[170] and adjuvant endocrine therapy.[171]

2.3.2.5. Tissue Biomarkers and Molecular Subtypes

Estrogens play a major role in promoting proliferation of breast epithelium and can drive carcinogenesis via a number of mechanisms.[172] Breast cancer cell estrogen receptor (ER) expression is an important marker of prognosis and response to endocrine therapy.[173] Although linked with increased survival,[174-178] ER expression is also associated with higher recurrence beyond 5 years.[179] Progesterone receptors (PRs), while correlated with ER expression,[180] (being induced by ER[181]) provide independent prognostic information.[182-184] Despite obtaining the same proportional benefits from endocrine therapy as those with ER/PR-positive tumours,[180] for patients with ER-positive/PR-negative disease, survival is worse.[177,178,184] Human epidermal growth factor receptor-2 (HER2) is a tyrosine kinase encoded by the oncogene *ERBB2*.[185] Without treatment, HER2-positive tumours have unfavourable prognosis.[186-188] The clinical utility of HER2 status relates to prediction of response to anti-HER2 therapy and other treatments.[186-188]

The introduction of gene-expression profiling using microarrays has revealed that breast cancer is a group of molecularly distinct neoplasms.[189] Four main *intrinsic subtypes* have been distinguished: luminal (A and B), HER2-enriched, basal, and normal-like,[190] which differ markedly in their risk factors, natural histories, and responsiveness to therapy.[191] A number of gene-expression assays have been developed and validated for clinical use, such as the 21-gene recurrence score (OncotypeDX®).[192] For the purposes of prognostication and treatment decisions, clinicopathological surrogate definitions have also been proposed, based on routine IHC.[193]

2.3.3. Diagnosis and Staging

Breast cancer may be diagnosed following a symptomatic presentation or by screening. In New Zealand, screening is provided by Breast Screen Aotearoa (BSA), which offers funded biennial mammograms to women aged 45-69 years.[194] The principle of screening is to advance diagnosis so that prognosis may be improved by earlier intervention. Meta-analyses of screening trials demonstrate a breast cancer mortality risk reduction of 20-30%.[195,196] Cohort and case-control analyses in New Zealand women of screening age show that screened women have more favourable tumour biology and a third lower risk of breast cancer death than unscreened.[196]

Evaluation of a potential breast cancer follows a sequence formalised as the triple assessment; involving examination, imaging, and tissue biopsy. Standard imaging includes mammography and ultrasound, with magnetic resonance imaging (MRI) reserved for situations where doubt remains about the extent of disease.[3,197] Pathological diagnosis is usually by core needle biopsy, followed by open biopsy where diagnostic uncertainty remains. Axillary ultrasound is performed with fine needle aspiration (FNA) of any abnormal appearing lymph nodes. Bone scintigraphy and computed tomography may be considered for patients with suspicion of metastatic disease.[197,198]

2.3.4. Management

The treatment of breast cancer is multidisciplinary, depending on the particular features of the disease. In general terms, early breast cancers (stage I and II) are treated with surgery, followed by adjuvant therapy (radiotherapy, chemotherapy, HER2-directed therapy, and/or endocrine therapy) as necessary. More advanced cancers (stage III, and increasingly some earlier stage disease) may be treated with neoadjuvant therapy prior to surgery. Metastatic cancers (stage IV) are incurable and surgery is not usually performed (other than for local control).

The following section synthesises the evolving evidence-base for each of the 5 therapeutic options: surgery, radiotherapy, chemotherapy, HER2-directed therapy, and endocrine therapy.

2.3.4.1. Surgery

The principal treatment for non-metastatic breast cancer is surgical, with removal of the tumour and any locoregional extension. The goals of surgery include complete resection of disease in order to reduce the risk of local recurrence and provide pathologic staging of the tumour and axillary nodes; affording prognostic information and guiding adjuvant (postsurgical) treatment. Over the past 50 years, surgical strategies have become increasingly conservative, aiming to minimise morbidity and optimise cosmesis, whilst maintaining oncological efficiency.[199]

The oncological equivalency of breast conserving therapy (breast conserving surgery [BCS] followed by whole breast irradiation [WBI]) and mastectomy in stage I-II breast cancer has been

demonstrated, with long-term results from 6 seminal studies in the 1970s/1980s[200-205] (and subsequent meta-analyses[206-208]) showing no difference in overall survival. Selection of procedure is based upon a range of factors, including: the ability to achieve an acceptable cosmetic result, contraindication to radiotherapy, fitness for surgery, and patient preference.[197,199,209] The success of BCS is contingent on the ability to excise the tumour with a concentric margin of normal tissue. A positive margin (ie, the presence of invasive cells or ductal carcinoma in situ [DCIS] at the inked resection margin) results in higher rates of local recurrence.[210,211] If margins are inadequate, further surgery involving re-excision or completion mastectomy is required. Although the definition of margin adequacy remains an issue of controversy,[212-216] the minimum acceptability of *no tumour on ink* for invasive disease is endorsed by current guidelines.[211,217-220]

The extent of axillary nodal involvement is the most powerful predictor of recurrence and survival in early breast cancer.[221-223] Although axillary lymph node dissection (ALND) with levels I-II lymphadenectomy was the traditional standard of care,[199,224] for those 70-80%[223] with negative nodes ALND provided no therapeutic benefit, whilst potentially imposing significant morbidity.[222,223] The desire to avoid unnecessary ALND without losing knowledge of pathological nodal status led to the introduction of sentinel lymph node biopsy (SLNB), which is now the standard initial approach to patients with clinically negative nodes.[224] Based on the principle of sequential dissemination of tumour cells from the primary tumour to regional lymph nodes with entrapment by the first draining (*sentinel*) node/s; the metastatic status of these nodes is reflective of the remainder of the nodal basin.[223] Management of the axilla following a positive SLNB result has also become increasingly minimalist. Although historically, patients with any sentinel node metastasis underwent completion ALND,[222] only half exhibited subsequent axillary disease.[223] This practice has been challenged by attempts to identify cohorts with involved sentinel nodes, but at low enough risk for non-sentinel involvement that ALND may be avoided.[225-227]

2.3.4.2. Radiotherapy

While all clinically detectable cancer within the breast and axillary nodes may be removed surgically, microscopic deposits of neoplastic disease could remain. Locoregional recurrence may occur in the conserved breast following BCS, the chest wall post-mastectomy or regional nodal basins; including the axillary, supraclavicular, and internal mammary regions. Adjuvant radiotherapy aims to treat these deposits, reducing the risk of locoregional failure and improving survival by eliminating the reservoir from which distant metastases may seed.[208] The overall benefits of adjuvant radiotherapy are clear, with the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses demonstrating a two-thirds reduction in local recurrence,[228,229] and an overall survival benefit at 15 years.[208] Due to disease diversity however, not all patients have the same risk of harbouring residual neoplasia following surgery and systemic treatment. The identification of patient subpopulations most likely to benefit from radiation treatment has therefore been a key subject of research.

Radiotherapy is indicated for most women following BCS, with the 2011 EBCTCG Overview showing a 15% proportional reduction in the 15-year risk of breast cancer death.[230] Conventionally fractionated-WBI has been the standard of care, involving delivery of external beam radiation to the breast in 25-30 fractions to a total dose of 45-50 Gray (Gy).[231] However, in another example of treatment de-escalation over time; hypofractionated regimes, which deliver more radiation per dose over fewer days (40-42.5 Gy over 15-16 fractions) have been developed, which are oncologically equivalent[232] and now preferred for the majority of patients.[219,233]

The benefits of radiotherapy following mastectomy are also well-established, although the absolute magnitude of gain depends on baseline risk of recurrence.[208] Data from the 2005 EBCTCG Overview suggests that postmastectomy radiotherapy is beneficial for women who remain at 20% or higher 10-year risk of locoregional recurrence despite adequate surgery and adjuvant systemic therapy.[208] For patients with this degree of risk, radiotherapy reduces recurrence by two-thirds, and in doing so, improves survival. The role of radiotherapy in patients at intermediate risk (particularly those with 1-3 axillary metastases) remains less clear,[234] with contemporary data awaited.[235] Hypofractionated schedules have also come into use after mastectomy, based on extrapolated evidence from trials of hypofractionated-WBI.[236,237]

The optimal timing of adjuvant radiotherapy is yet to be determined. Observational studies demonstrate that treatment delays greater than 6-12 weeks are associated with increased risk of recurrence and reduced survival.[238,239] New Zealand guidelines recommend that radiotherapy commence within 6 weeks of surgery, once the surgical site has healed. If adjuvant systemic therapy is also required, radiotherapy is typically given after the conclusion of chemotherapy, although trastuzumab and endocrine therapy may be given concurrently.[217,240]

2.3.4.3. Chemotherapy

Contrary to surgery and radiotherapy, chemotherapy is a systemic treatment. When given in the adjuvant setting, chemotherapy can reduce the risk of distant recurrence by eradicating micrometastatic disease not clinically evident at the time of initial staging. A series of formative trials and subsequent EBCTCG meta-analyses have shown adjuvant chemotherapy substantially reduces the risk of recurrence and improves survival when added to local therapy.[241-248]

Unlike the increasingly minimalist approach to local therapy, the indications for adjuvant chemotherapy have expanded. While its role was initially established in premenopausal women with high risk node-positive disease,[249] subsequent trials have revealed benefit in postmenopausal women,[250] and those with node-negative or ER-positive disease.[251,252] The decision to treat uses a risk-stratification approach based on projected absolute benefit taking into account cancer biology. Genomic analysis and web-based risk-benefit calculators such as Adjuvant! Online[253] may be employed to determine the most appropriate candidates for therapy,

particularly in the setting of node-negative or ER-positive disease.[188,219] Chemotherapy is also used in the neoadjuvant setting, with the aim of downstaging tumours in an attempt to permit less extensive surgery. In addition to affording equivalent survival outcomes to adjuvant treatment,[254] neoadjuvant therapy permits an early evaluation of treatment efficacy, with its surrogate endpoint, complete pathologic response, a strong predictor of clinical benefit.[255]

Chemotherapy regimens have been refined over time, with more effective (but also more toxic) schedules coming to light. Adjuvant! Online classifies regimes as first, second, or third generation; projecting proportional risk reduction with and without therapy based on estimates of therapeutic efficacy from the 1998 EBCTCG Overview.[245,253] First generation chemotherapy consists of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) -like regimes, or 4 cycles of doxorubicin and cyclophosphamide (AC).[248] Broadly speaking, second generation regimes contain higher doses of anthracyclines, conferring a 22% greater reduction in breast cancer mortality compared with first generation schedules (based on the 2012 Overview).[248] Third generation regimes consist of taxanes in addition to anthracyclines and bestow an additional 14% benefit over second generation.[248]

The optimal timing for the initiation of adjuvant chemotherapy also remains uncertain. While it is generally agreed that wait times over 12 weeks result in worse disease outcomes,[256,257] poorer outcomes have also been shown with shorter intervals.[258] New Zealand guidelines recommend that treatment commence within 6 weeks of surgery, as stipulated by many of the original trials.[198]

2.3.3.4. HER2-directed Therapy

The discovery of the *HER2* oncogene and development of targeted anti-HER2 therapy has dramatically improved outcomes for patients with HER2-positive disease. The first of these agents was trastuzumab, a monoclonal antibody which binds the HER2 protein, inhibiting cell growth. Initially regulated for the treatment of HER2-positive stage IV disease, the benefit of trastuzumab in early breast cancer is now well-established.[259] The publication of 5 landmark trials in the mid-2000s[260-264] led to its use in the neo/adjuvant setting, in combination with taxane-containing chemotherapy. Trastuzumab (Herceptin®) has been publically funded in New Zealand for non-metastatic disease since July 2007.[265] Initially, this was limited to a 9 week adjuvant course (the Finland Herceptin® regime[263]), however political pressure[266] and a change of government prompted the approval of 12 months treatment from November 2008, funded directly through the Ministry of Health.[267] Chemotherapy and dual HER2-blockade with additional agents such as lapatinib and pertuzumab have also been investigated in the neo/adjuvant setting,[268-271] but remain unfunded in New Zealand at the present time.[272] These, and other Medsafe approved but non-funded systemic agents for early breast cancer (such as PD-L1 inhibitors) may be accessed through self-funding or clinical trials, which are mostly run through the Australasian group Breast Cancer Trials.

2.3.4.5. Endocrine Therapy

The concept that changing the hormonal balance of a patient with breast cancer could lead to regression of disease was recognised over a century ago.[273] The initial trials of ovarian ablation as a single intervention demonstrated less recurrence and prolonged survival amongst women younger than 50 years.[246,274] The first and most extensively tested systemic endocrine agent, tamoxifen, has a clear impact on survival[180,241,243,244,246,275] which is irrespective of age, but limited to those with ER-positive disease.[180,246,275] Numerous endocrine agents have since been developed, which may be broadly grouped as selective estrogen receptor modulators (SERMs); aromatase inhibitors, which block peripheral conversion of androgens to estrogen; and ovarian suppressors, which inhibit ovarian estrogen production.[273] Unlike tamoxifen, aromatase inhibitors may only be used in postmenopausal women.[180,246,275] Given for 5 years, or in sequence with tamoxifen, aromatase inhibitors produce greater reductions in recurrence and breast cancer mortality than tamoxifen alone.[276] In premenopausal women, ovarian function may also be ablated (by surgical oophorectomy or pelvic irradiation) or suppressed using luteinising hormone-releasing hormone (LHRH) analogues. Ovarian suppression/ablation in conjunction with adjuvant systemic endocrine therapy and chemotherapy may be indicated in premenopausal women with higher risk disease.[218,219,277]

Adjuvant endocrine therapy has become the standard of care for all women with hormone receptor-positive disease, now defined as ≥1% staining for ER and/or PR.[173] A minimum of 5 years treatment is recommended,[180,246] with evidence of additional benefit by extending therapy to 10 years, particularly in higher risk disease.[278] Endocrine therapy may also be given to postmenopausal women in the neoadjuvant setting,[279] or as primary treatment in elderly patients who are unfit or unwilling to undergo surgery.[280-282]

2.3.5. Prognosis

While breast cancer is a diverse disease, its overall prognosis is reasonable, with near 90% 5-year overall relative survival.[153] The most important prognostic factor is stage,[3] with 5-year relative survival estimates ranging from 99% with localised disease and 85% with regional disease down to 27% for cases with distant spread.[153] Fortunately, the majority of cases present early, with 92% localised to the breast or regional nodes at diagnosis.

Overall, New Zealand ranks 14th amongst OECD countries for breast cancer mortality, with an age-standardised mortality rate of 27.0 per 100 000 in 2015.[155] Ethnic disparities in mortality have also been observed. Survival trends show that although mortality rates amongst non-Māori, non-Pacific women have been gradually reducing over time, they have been increasing amongst Māori and Pasifika.[283,284] The latest Ministry of Health statistics from 2013 showed a 90% greater breast cancer mortality rate for Māori compared with non-Māori, with an age-standardised mortality rate of 30.9 vs 16.3 per 100 000.[154]

2.4. The New Zealand Setting

2.4.1. The Country and its People

Aotearoa New Zealand is a country of almost 4.9 million people[285] spread over 2 main islands in the southwest Pacific, covering a land area of 268 021km^2.[286] Māori are the indigenous people of Aotearoa, settling from Polynesia in the 13th century.[287] Subsequent immigration, initially by British colonisation in the 1800s followed by people from the Pacific Islands and Asia, has created the multicultural society of today. According to the 2013 population census, the majority of the population identify as European (74.0%), with Māori (14.9%), Asian (11.8%), and Pacific peoples (7.4%) forming the 3 other main ethnic groups.[288] Te Tiriti o Waitangi is the founding document of New Zealand, signed by Māori rangatira (chiefs) and the British Crown in 1840.[287]

2.4.1.1. Auckland and Waikato Regions

This study is set in the adjacent Auckland and Waikato regions of New Zealand, situated in the upper/central part of the North Island. The Auckland region includes 3 District Health Boards (DHBs): Waitemata, Auckland, and Counties Manukau; while Waikato has the Waikato DHB (**Figure 3**). Together they account for just under half (43.6% in 2018[285]) of the total population.

There are clear demographic differences between the 2 regions. The predominantly urban Auckland comprises 35% of the national population[285] and is ethnically diverse.[289] From the 2013 census, 65% of New Zealand's Pacific and Asian population live in the Auckland region, along with one-quarter of Māori. Compared with the rest of the country, the Auckland region has a relatively younger age structure; although this is highly variable by ethnicity. There are also large within-region differences by socioeconomic deprivation, also related to ethnicity. By contrast, the Waikato DHB serves a population of around 400 000[285] and has a large rural community, with 60% of the population living outside the main centre of Hamilton.[290] Waikato has an age structure similar to the national average, though it has a higher proportion of people living in deprivation, and an ethnic mix which includes more Māori and fewer Pacific Islanders.[291]

2.4.2. Healthcare Services in New Zealand

New Zealand's contemporary healthcare system has its roots in the Social Security Act of 1938, which aimed to create a national health service providing free universal healthcare.[292] Despite several structural changes, core elements of this original scheme remain, with subsidised primary care and access to publically funded hospital-based services.[293] Currently, public health care is delivered by 20 geographically defined DHBs, which are responsible for funding and provision of services at a local level.[294] Primary care is provided in community clinics by independent general practitioners and allied health professionals who are remunerated through a mixture of patient co-payments and government subsidies administered by Primary Health Organisations.

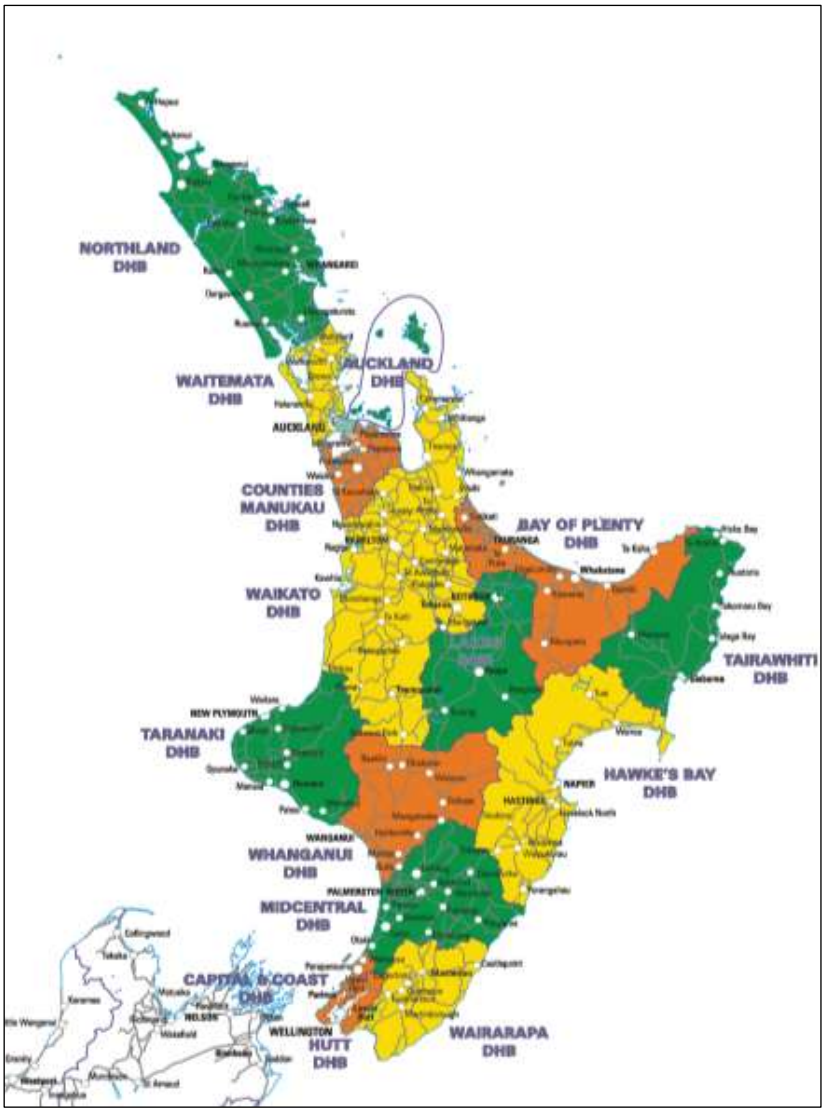


Figure 3. Map of the North Island Showing District Health Board Catchment Areas

Reproduced with permission from the Ministry of Health.[295]

Although the majority of secondary and tertiary healthcare is delivered through the public system, a strong private sector remains, offering specialist elective services.[293] Approximately 40% of breast cancer patients in the Auckland and Waikato regions access private care.[296] All oncoplastic breast surgical procedures may be performed in the private sector. Although private outpatient oncology care is accessible, private radiation therapy (including intraoperative radiotherapy) and parenteral chemotherapy facilities are only available in a few major centres.

While the majority of healthcare expenditure is shouldered by the government (generated through general taxation), accounting for around 80% of total health spending, approximately one-third of the population holds private health insurance.[294] In 2017, New Zealand spent 9.0% of its gross domestic product on health care, similar to Australia (9.1%) and the United Kingdom (9.6%), but nearly half that of the United States (17.2%).[297] The Pharmaceutical Management Agency of New

Zealand (PHARMAC) is a government agency which makes decisions around public funding of pharmaceuticals based on criteria including drug efficacy and relative cost-effectiveness, with costs contained by mechanisms such as reference pricing and tendering.[294]

New Zealand has a Cancer Control Strategy with dual goals of reducing the incidence and impact of cancer, and reducing inequalities.[298] A number of initiatives have been developed under the umbrella of the National Cancer Programme. In 2013, provisional national tumour standards were published for 10 cancers, including breast.[299] Known as the Standards of Service Provision; they describe the level of service that a person with cancer should expect in New Zealand. Developed by clinical working groups and informed by national and international evidence-based guidelines, the standards cover a range of quality indicators, including timely access to services, diagnosis, and multidisciplinary care. The Faster Cancer Treatment (FCT) programme was introduced in 2012 to improve access to treatment and reduce waiting times.[300] Four regional cancer networks facilitate and coordinate cancer services across DHBs. Multidisciplinary care is provided through these networks, with teams comprised of surgeons, radiologists, pathologists, oncologists, and cancer nurses. An effective multidisciplinary approach results in more streamlined treatment, improved interdisciplinary communication, increased patient satisfaction, and improved cancer outcomes.[197] All patients with a confirmed breast cancer in New Zealand should have their treatment plan discussed at least once at a multidisciplinary team meeting.[197,198]

2.4.3. The Burden of Chronic Disease in New Zealand

Similar to other developed nations, the burden of illness in New Zealand is largely due to long-term conditions, with 1 in 4 adults affected by multimorbidity.[301] Although both improving, health expectancy (the number of years a person can expect to live in good health without functional limitation) has not kept pace with life expectancy, with rates of disability increasing in all age groups.[302] The Global Burden of Disease Study showed that chronic conditions cause 81.8% of health loss in New Zealand, with almost 60% caused by 8 conditions: cardiovascular and respiratory diseases, diabetes, cancers, mental health disorders, musculoskeletal disorders, and dementia.[303] Modifiable health behaviours account for one-third of health loss, with obesity, unhealthy diet, smoking, alcohol, and drug use acting as the leading modifiable risk factors.[302]

Patterns of disease and mortality are changing in the New Zealand. With population aging, cancers have overcome cardiovascular disease to become the leading cause of mortality,[302] accounting for around one-third of deaths.[304] In 2015, breast, colorectal, prostate, melanoma, and lung malignancies together accounted for over 60% of cancer registrations.[305] Obesity is also a critical health challenge for New Zealand, with one of the highest rates in the developed world,[297] affecting over one-third of adults in 2017/18.[306] Consistent with this, diabetes is also increasing across the population, with an 80% increase from 2005 to 2017, according to the New Zealand Virtual Diabetes Register.[307]

The burden of disease is not evenly distributed within the population. Chronic diseases predominantly affect people of older age, with half of New Zealanders aged over 65 possessing 2 or more long-term conditions.[301] While there are significant differences by ethnicity, the overall population structure of New Zealand is aging, similar to other developed countries.[288] This, along with the adoption of increasingly unhealthy lifestyles has led to a rise in incidence of long-term conditions, such that the WHO has called chronic conditions: "The health care challenge of the 21st century."[308(p11)]

As seen in other countries, chronic disease is socially patterned in New Zealand, with the indigenous population and more socially deprived experiencing greater disparities. Despite provisions in the Treaty of Waitangi and government efforts to support equitable care, Māori continue to experience inequities in disease incidence and outcomes.[309] There is increasing recognition that these disparities are a consequence of the differential distribution of social, political, economic, and environmental determinants of health, as well as inequities in the timing and quality of healthcare.[159] Māori are disproportionately affected by chronic conditions, experiencing higher rates of cancer, cardiovascular and respiratory diseases, diabetes, and mental illness.[309,310] There are also marked disparities with respect to health risk factors, with Māori more likely to smoke, be obese, and drink hazardously than non-Māori.[310] Although life expectancy has increased across the board, with larger increases for Māori than non-Māori, inequities remain,[302] with Māori experiencing lower life expectancy (77.1 years for females, 73.0 years for males) than the general population (83.2 years for females, 79.5 years for males).

2.5. Conclusions: The Context for this Thesis

Comorbidity is the presence of health-related conditions that coexist with a primary disease of interest. Despite this simple definition, comorbidity is complex, with many related and overlapping constructs. Measurement of comorbidity is not straightforward, and the most appropriate approach should be a function of local context. With this in mind, the C3 index was selected for application in this thesis, where non-metastatic breast cancer acted as the primary disease of interest. Breast cancer is a significant cause of morbidity and mortality amongst women worldwide. Evolving understanding of its biological heterogeneity means prognosis is variable, and treatment is increasingly tailored to the individual characteristics of both patient and tumour.

This study of comorbidity and breast cancer was conducted in New Zealand, a country with many similarities to other Western nations; with a relatively wealthy population of predominantly European descent and a centrally organised healthcare system. Like many developed countries, the burden of chronic conditions in New Zealand is on the rise, with disproportionate impact on the indigenous population, the elderly, and the socially deprived. The interwoven relationships between comorbidity, breast cancer, and these other drivers of health inequities will be the focus of the next chapter.

Chapter 3. Literature Review

Breast Cancer in the Context of Comorbidity

3.1. Introduction

This chapter reviews current knowledge with respect to breast cancer in the context of comorbidity. Five areas of the literature are explored in depth. It begins with a discussion of the co-occurrence of breast cancer and comorbidity, examining the prevalence of comorbidity amongst patients with breast cancer, along with potential reasons for their coexistence.

Secondly, the influence of comorbidity over the diagnosis of breast cancer is explored, with a discussion of potential explanatory hypotheses for the links between comorbidity and the stage at which cancer is diagnosed. The impacts of comorbidity on the uptake of mammographic screening and staging investigations for cancer are also addressed.

The third section provides an overview of the potential impacts of comorbidity on the treatment of breast cancer, including the quality of treatment delivered and its tolerability. Potential explanations for these trends are identified and discussed. Chemotherapy is examined in additional detail, with reference to a systematic review/meta-analysis conducted as part of this work. While the full methods and results of this study are not included in the main body of this thesis, they may be accessed from the following publication:

> Edwards MJ, Campbell ID, Lawrenson RA, Kuper-Hommel MJ. The influence of comorbidity on chemotherapy use for early breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat. 2017;165(1):17-39. https://doi.org/10.1007/s10549-017-4295-4

A summary of the evidence relating to the deleterious influence of comorbidity on outcomes from breast cancer is provided in Section 4; including cancer recurrence and survival, quality of life, and economic impacts.

Section 5 discusses other drivers of breast cancer inequities and attempts to disentangle their complex interrelationships with comorbidity.

The chapter concludes with a discussion of the potential causal pathways leading from comorbidity to survival outcomes from breast cancer. A conceptual framework is developed, which seeks to understand the key factors contributing to disparities in survival for patients with coexistent comorbidity.

3.2. Co-occurrence of Comorbidity and Breast Cancer

3.2.1. Prevalence amongst Patients with Breast Cancer

Whilst there is general agreement that comorbidity is relatively common amongst patients with breast cancer, prevalence estimates can vary widely, depending on the study population and methods used to measure comorbidity. Studies using a broader interpretation of comorbidity identify greater prevalence than those employing a more restrictive approach. For example, Tammemagi et al,[100] using 77 conditions identified from medical records, found 71.7% of their breast cancer cohort had at least 1 comorbidity. Studies which use more limited criteria identify less comorbidity, though even if the definition is limited to a single index, estimates may differ.[27]

Table 2 shows a range of prevalence estimates for C3 conditions amongst breast cancer populations (selected studies). Significant variations in prevalence are evident within individual conditions. For example, prevalence estimates of hypertension range between 5.8-69.1%, while COPD/asthma can be seen to range between 0.1-52%. Overall estimates of comorbidity are variable as well, ranging between 12.7-86.9%. Some general trends can be seen however; with hypertension, diabetes, pulmonary disease, and joint disorders consistently amongst the most common conditions, regardless of the study population or data source.

Despite these inconsistencies, some patterns may be noted. Patients with breast cancer tend to have less comorbidity than patients with other types of cancer. This is particularly notable for cancers strongly associated with risk factors for the development of chronic disease (eg, smoking and lung cancer). Studies evaluating comorbidity prevalence by cancer site show 1.5 to 3-fold higher rates amongst patients with lung and colorectal cancer than patients with cancers of the breast or prostate.[15-17,116] Secondly, at least in older patients with breast cancer, comorbidity prevalence is likely to be similar to that of the general age-matched population. In their Annual Report on the Status of Cancer, Edwards et al[15] noted that patients with breast cancer had similar levels of comorbidity to the general US population aged ≥65 years (32%). Conversely, in a Danish case-control study, comorbidity was more frequent amongst breast cancer cases than controls, with a particularly strong association between breast cancer and renal disease.[17]

3.2.2. Why Might Breast Cancer and Comorbidity Coexist?

3.2.2.1. Shared Risk Factors

Breast cancer and long-term conditions share many common risk factors. With similar incidence,[15-17] the primary drivers of comorbidity amongst patients with breast cancer are likely to be the same as those that drive morbidity in the overall population. Advancing age confers a higher cumulative risk of developing (and dying from) breast cancer, as well as a number of chronic conditions.[2,3] Precise mechanisms underpinning the interaction between age and cancer

Table 2. Prevalence Estimates (%) of C3 Conditions amongst Breast Cancer Patients

Study:	**Chia**[109]	**Edwards**[15]	**Harlan**[311]	**Fleming (1999)**[94]	**Fleming (2005)**[26]	**Klabunde (2000)**[97]	**Klabunde (2007)**[312]	**Patnaik**[112]	**Piccirillo**[313]	**Sarfati**[116]	**Satariano**[98]	**Siegelmann-Danieli**[107]
Data Source:	MR	Admin	MR	Admin	Admin	Admin	Admin	Admin	MR	Admin	MR	Admin
Age Range:	22-93	≥65	All	>67	≥67	≥66	≥66	≥65	All	All	40-84	≥70
Alcohol abuse										0.4		
Anaemia	2.5									1.3		
Angina			1.0	7.7					4.2	2.1		
Anxiety										1.0		
Arrhythmia				19.8						3.8		1.1
Cerebrovascular disease	0.7	4.6	1.4	16.2	11.1	1.6	3.6	4.3	2.8	2.0	3.2	1.0
Coagulopathy				20.0	23.2					2.5		
CHF	0.7	6.9	1.2	25.0		2.7	5.7	6.7		2.3		1.3
Connective tissue disease	1.6				5.2					0.5		
COPD/asthma	6.5	9.5	10.4	52.0	36.2	3.9	7.2	8.8	8.2	2.9	8.2	0.1
Dementia	0.0	1.4	0.0	4.4		0.6	1.1	1.4		0.7		0.4
Diabetes (complications)	4.7			10.0		0.5	1.0			2.3		
Diabetes (no complications)	14.2	14.5[a]	8.3[a]	21.5	18.2[a]	7.5	10.2	13.0[a]	10.4[a]	2.9	11.9[a]	1.8[a]
Endocrine	6.3[b]		9.1[b]	13.9[b]	29.2					0.9	13.6[b]	1.0[b]
Epilepsy										0.3		
Eye problem										1.5	8.5	
Gastrointestinal disease	0.2	1.0	0.4		31.8	0.4	0.5	1.1	2.4	0.7	9.2	
Hepatitis		0.3								0.3		
Hypertension	28.8		27.8	69.1	67.6				34.5	8.0	43.8	5.8
Inflammatory bowel disease				38.8						2.2		
Inner ear disorder										0.9	3.6	
Intestinal disorder			0.9	8.5						1.8		
Joint disorder	7.2	2.2	13.7	65.8	46.3	1.2	1.5	2.0		0.9	21.0	1.1
Liver disease	0.4	0.1	2.5	2.2			0.0	0.3		0.4	1.1	
Malnutrition										0.4		
Metabolic disorder										3.8		
MI	0.6	1.8	1.4	25.7		0.4	1.4	1.7	3.1	2.0	3.6	2.1
Neurological condition				19.2	21.6					0.9		
Obesity				0.0	2.8				3.9	1.8		2.9
Osteoporosis			0.0		5.2					0.7	9.1	1.2
Other cardiac					59.0[d]					2.6	26.5[d]	
Other cancer	0.4			8.5	8.8			16.3	12.4	1.5	6.0	2.0
Paralysis		0.5	0.1	2.1		0.1	0.4	0.6		1.1		
Peripheral nerve/muscular disorder										0.4		

Table 2 continued. Prevalence Estimates (%) of C3 Conditions amongst Breast Cancer Patients

Study:	Chia[109]	Edwards[15]	Harlan[311]	Fleming (1999)[94]	Fleming (2005)[26]	Klabunde (2000)[97]	Klabunde (2007)[312]	Patnaik[112]	Piccirillo[313]	Sarfati[116]	Satariano[98]	Siegelmann - Danieli[107]
Psychiatric			4.1	14.9					5.8	1.0		0.4
Peripheral nerve/muscular disorder										0.4		
Psychiatric			4.1	14.9					5.8	1.0		0.4
PVD	0.6	2.7	0.3	15.3	14.4	1.5	2.1	2.6		1.0	6.6[e]	0.2
Pulmonary embolism			0.0							0.4		0.3
Renal disease	1.8	1.2	0.3	3.5	6.3	0.4	0.7	0.9		1.4	2.5	0.4
Sleep disorder										0.2		
Valve disease				6.5						1.1		0.5
Urinary tract disorder				39.9	9.7					0.3	8.2	
Venous insufficiency										0.2		
Overall:	NR	32.2	NR	63.4	NR	25.0	NR	41.7	NR	12.7	48.4	86.9

Abbreviations: Admin, administrative data; MR, medical record; NR, not recorded; PVD, peripheral vascular disease.
[a] Diabetes with and without complications combined.
[b] Thyroid disease.
[c] Upper and lower gastrointestinal disease combined.
[d] Cardiovascular disease not further specified.
[e] Arterial and venous disease combined.

have been debated, and include oxidative damage, immune system modification, and impaired cellular repair mechanisms.[314] Postmenopausal obesity, alcohol, and physical inactivity have also been identified as risk exposures for the development of breast cancer; as well as predisposing to a number of chronic conditions, including cardiovascular disease, diabetes, and liver disease.[2,20]

3.2.2.2. Chronic Conditions may predispose to Breast Cancer

A number of chronic conditions have been causally linked with an elevated risk of breast cancer. While these associations predominantly relate to common risk factors, there is also evidence for the existence of biological pathways which directly link certain conditions with breast cancer. The relationship between diabetes and breast cancer has been the focus of particular attention. A 2007 meta-analysis of 20 case-control and cohort studies demonstrated a 20% increase in breast cancer risk amongst women with diabetes.[21] Metabolic syndrome, which comprises a cluster of risk factors for diabetes and cardiovascular disease has also been linked with the development of postmenopausal breast cancer, with a 2013 meta-analysis of 9 studies showing a 52% increase in risk.[22] Hypertension as a single component was found to impose a 13% increase in risk, an association supported by others.[315-317] Aberrations in lipid profile have also been associated with increased risk of breast cancer.[316,318] The mechanisms postulated to underlie these associations relate to alterations in circulating concentrations of insulin, insulin-like growth factors, and endogenous sex hormones, with consequent mitogenic effects on breast tissue.[21] In common with type II diabetes, obesity causes an alteration in the production of adipocytokines, which promote breast carcinogenesis.[23,24] Obesity also imposes a subclinical inflammatory state, with increased adipose tissue infiltration of inflammatory mediators such as interleukin-6, C-reactive protein, and tumour necrosis factor-α, which are also implicated in the pathogenesis of breast cancer.[25]

Diseases of the immune system have also been linked with breast cancer, through unexplained, likely multifactorial mechanisms.[314] Systemic lupus erythematosus[319] and rheumatoid arthritis[320] have both been linked with an increased incidence of breast cancer. Inconsistent results have been reported with respect to the relationship between breast cancer and thyroid disease, with some studies noting an increased risk of breast cancer with (treated) hyperthyroidism,[321] and a protective effect of hypothyroidism,[322,323] while others have found no difference in the prevalence of either.[324-326] Although not typically associated with chronic infection, elevated breast cancer incidence has been noted amongst patients with HIV, presumably due to immune deficiency.[327]

3.2.2.3. Treatment for Chronic Conditions may Influence Breast Cancer Risk

Breast cancer risk may also be related to treatment received for previous conditions. Exposure to ionising radiation is a well-established cause of breast cancer, particularly among women aged less than 40 at the time of exposure.[328] An increased risk of breast cancer has been consistently reported following radiation treatment for a number of conditions, including paediatric malignancies, Hodgkin's lymphoma, and tuberculosis.[2,328]

On the other hand, breast cancer risk may be commuted by some of the drugs used to treat chronic disease. Increasing understanding of the role of the hyperinsulinaemic state in carcinogenesis has led to interest in the protective effect of antidiabetic drugs such as metformin.[329] Evidence of such an effect has been inconsistent however, and subject to confounding and time-related biases. A 2014 meta-analysis which attempted to account for these methodological issues showed a trend towards a reduction in breast cancer risk with metformin, which reached borderline significance following adjustment for body mass index [BMI].[329] The potential protective effect of nonsteroidal anti-inflammatories has also been investigated, with 2 meta-analyses[330,331] and a subsequent prospective cohort study[332] reporting modest reductions in breast cancer risk. There is also some evidence to suggest that angiotensin-converting enzyme and angiotensin receptor blockers, used for the treatment of hypertension, are protective against breast cancer recurrence.[333] Statins, a class of lipid lowering drugs used for the prevention of cardiovascular disease have also received attention. While a meta-analysis of randomised trials suggested that statins as a group are not associated with breast cancer risk,[334] a subsequent prospective study provided evidence that the hydrophobic class of statins in particular are associated with a reduction in incidence.[335]

3.2.2.4. Comorbidity may be a Consequence of Breast Cancer Treatment

Breast cancer may also cause or exacerbate comorbidity. Complications from breast cancer treatments can result in a variety of comorbid outcomes, particularly amongst those with the highest risk of developing such conditions from the outset.[336] General anaesthesia in the elderly has been implicated in the development of neurocognitive dysfunction, including Alzheimer's disease and related forms of dementia.[337] Radiotherapy may result in long-term toxicities such as pneumonitis, cardiac morbidity, and secondary cancers; including leukaemia, sarcomas, lung, oesophageal, and contralateral breast.[208,338-340] Numerous toxicities are associated with chemotherapy, with anthracyclines in particular linked to long-term cardiotoxicity and rarely, secondary malignancies.[341] Trastuzumab is also linked with cardiotoxicity, particularly when given in combination with anthracyclines.[342,343] Taxanes are specifically associated with the development of neurotoxicity, pneumonitis, and hepatotoxicity.[341] While endocrine therapy is generally well tolerated, it too may result in comorbid complications, with tamoxifen implicated in the development of endometrial cancer and thromboembolic events;[180] while aromatase inhibitors lead to an increased risk of osteoporosis and bone fracture.[278]

Longitudinal data regarding the effect of breast cancer and its treatment on the development of new comorbidities is relatively limited. Following a cohort of early breast cancer patients over time, Harlan et al[311] found that women who received chemotherapy alone, chemotherapy in combination with radiotherapy, or radiotherapy in addition to tamoxifen were significantly more likely (than patients not receiving such treatments) to develop at least 1 new comorbid condition by 30 months post-diagnosis; with arthritis, osteoporosis, and hypertension among the most

frequently reported. Similarly, in a pair of Australian retrospective cohort studies, women with hormone receptor-positive breast cancer treated with endocrine therapy had higher risk of developing a number of new conditions than age-matched women without a history of cancer,[344] with different comorbidity profiles for those on tamoxifen as opposed to aromatase inhibitors.[344,345] Conversely, Jordan et al,[346] who matched older 5-year breast cancer survivors with population-based breast cancer-free controls; found no significant difference in the acquisition of incident Charlson comorbidities 10 years following breast cancer diagnosis. However breast cancer continued to constitute a mortality risk 6-10 years post-diagnosis, with slightly higher all-cause mortality than controls, potentially suggesting a role for the development of comorbidities not measured by the CCI.

Pre-existing chronic conditions may also be exacerbated by the distracting influence of breast cancer and its treatment, which may result in reduced adherence to medications used to treat comorbidity. For example, in a study of prevalent statin users with breast cancer, adherence to statins fell by 15% during the breast cancer treatment period, and remained low in subsequent years.[347] Similarly, a study examining adherence to oral type II diabetes medications during breast cancer treatment found that adherence declined from 75% prior to breast cancer diagnosis to 25% during breast cancer treatment, rising again to only 32% 3 years post-treatment.[348] Another study found that, 2 years following breast cancer diagnosis, 37% of previous users were non-adherent to antihypertensives, 75% were non-adherent to diabetes medications, and 39% were non-adherent to statins.[349] Nonadherence was related to certain breast cancer treatments; with radiotherapy and endocrine therapy associated with nonadherence to antihypertensives, while chemotherapy was linked with nonadherence to diabetes medications.

3.3. Impacts of Comorbidity on Breast Cancer Diagnosis

3.3.1. Stage at Presentation and Screen-detection

Stage at diagnosis is the single most important prognostic factor for breast carcinomas.[3] The presence of pre-existing comorbidity may affect the detection of breast cancer and the stage at which it is diagnosed in contrasting ways, with the magnitude and direction of this effect dependent upon healthcare system and other individual level factors.[336,350] Studies in different populations have reported that patients with comorbidity may have their breast cancer diagnosed at an earlier,[26,132,351-353] similar,[122,123,354,355] or later stage[26,130,352,356-362] than those without comorbidity. Fleming et al[26] propose 4 separate hypotheses to explain the links between comorbidity and cancer stage at diagnosis: (1) the *surveillance hypothesis*; (2) the *physiological hypothesis;* (3) the *competing demands hypothesis*; and (4) the *death from other causes hypothesis*. These hypothesises have been summarised into a conceptual framework incorporating physician-patient interaction, comorbidity, cancer screening, and stage at diagnosis,[336] as shown in **Figure 4**.

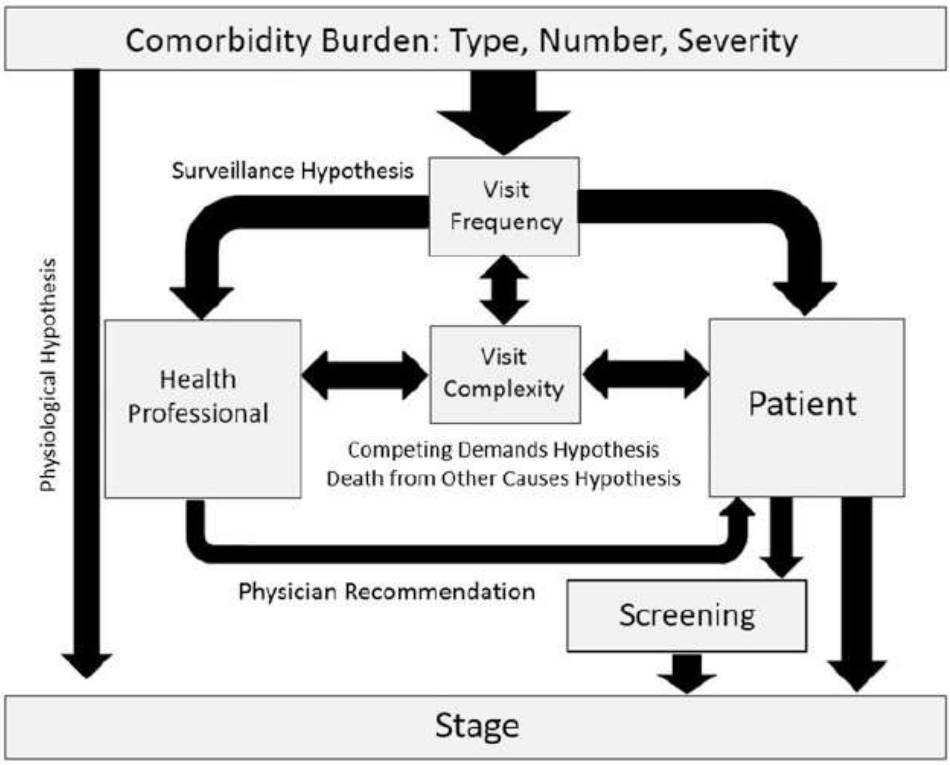


Figure 4. Framework Linking Comorbidity Burden with Cancer Stage at Diagnosis

Reproduced from Fleming et al[336] with permission.[②]

3.3.1.1. Surveillance Hypothesis

According to a surveillance hypothesis, patients with coexisting chronic conditions are more likely to have frequent contact with health services, with greater opportunity for early cancer diagnosis through the early detection and investigation of symptoms, or by the offer of screening.[12,26,132,363] Evidence of a surveillance effect has been more obvious for cancers with effective screening programmes, such as breast and colorectal, supporting the contention that more frequent health visits may relate to higher rates of screening.[357,364] Consistent with this, Burg et al[365] found that undergoing annual check-ups with a physician was a strong predictor of recent mammography. Fisher et al[366] found that breast cancer patients who had attended their primary care provider twice or more during the 2 years preceding their cancer diagnosis had lower odds of a late stage diagnosis (and reduced mortality) than women who only attended once or not at all; a finding that was only partially explained by a greater use of screening mammography. A surveillance effect is particularly notable in healthcare systems where screening coverage is related to funding incentives. For instance, within the US Veterans Administration health system where colorectal cancer screening is a quality performance measure, patients with comorbidity display similar rates of screening[364,367,368] and earlier stage at cancer diagnosis[369] than those without comorbidity.

[②] **Figure 4** is reprinted by permission from Springer Nature: Springer Science Business Media Singapore. Impact of Comorbidity on Cancer Screening and Diagnosis by Fleming S, Sarfati D, Kimmick G, Schoenberg N & Cunningham R, © 2016. https://link.springer.com/book/10.1007/978-981-10-1844-2

There is also evidence to support the earlier detection of breast cancer amongst patients with comorbidity. West et al[351] found that patients with higher levels of comorbidity were more likely to be diagnosed with local stage disease than regional, although the study was limited by a lack of multivariate analysis. Similarly, in a study by Vaeth et al,[132] women with 2 or more functionally limiting comorbid conditions were half as likely to receive a diagnosis of advanced stage breast cancer. This pattern was also noted by Moritz et al,[353] who showed that patients possessing at least 3 comorbid conditions were half as likely to present with an advanced breast malignancy.

Others have found that the relationship between comorbidity and cancer stage depends on the type and severity of the concurrent conditions. Yasmeen et al[352] classified comorbidities as stable or unstable, noting that the presence and number of stable conditions was associated with greater mammography and earlier stage at diagnosis, with the inverse true of unstable conditions. Fleming et al[26] found that after controlling for mammography and physician visitation, some conditions (diabetes, endocrine, psychiatric, and haematological disorders) increased the odds of presenting with an advanced stage diagnosis, while others (cardiovascular disease, musculoskeletal disorders, and gastrointestinal disease) were associated with lower odds.

3.3.1.2. Competing Demands Hypothesis

A contrasting hypothesis is that of competing demands, which contends that the management of chronic conditions may constitute a contesting pressure, distracting both patients and health providers from early cancer symptoms or the delivery of screening.[26,132,370] Cancer prevention activities may be neglected in a primary care model which focuses on "…disease-centred care in an encounter-based system."[363(p1195)] This is supported by studies which show an increase in the likelihood of late stage cancer amongst patients with comorbidity. In a study by Gonzalez et al[356] using the CCI, comorbidity increased the odds of a late stage breast cancer diagnosis in a dose dependent manner. A similar finding was reported in New Zealand using the C3 index, with patients possessing the highest comorbidity burden experiencing nearly 4-times greater odds of metastatic disease at diagnosis than those with no comorbidity.[357] Breaking this down into its component conditions, nearly all comorbidities were associated with greater odds of regional and distant disease (vs local), following adjustment for age, ethnicity, and socioeconomic deprivation. The influence of cerebrovascular disease and CHF was especially great, with more than 5 times the odds of distant disease at diagnosis.

3.3.1.3. Death from Other Causes Hypothesis

Related to competing demands, the death from other causes hypothesis posits that patients with comorbidity are less likely to be offered cancer screening due to an explicit decision (by healthcare provider or patient) that such investigation is inappropriate given their elevated risk of death from other causes.[26] Consistent with this, many authors have reported a reduction in

screening amongst patients with comorbidity,[361,363,371-378] although not all, with others finding no difference,[379,380] or even higher[352,381,382] rates of mammography with concurrent comorbidity.

The survival benefits of mammographic screening are not immediate, with little reduction in mortality within the first 5 years following commencement.[195,383] Therefore, individuals with a life expectancy of less than 5 years (due to age and/or comorbidity) would not be expected to derive benefit. This is supported by observational and simulation studies which show that older women with moderate to severe comorbidities experience no survival benefit from having their cancer detected by screening, compared with a symptomatic presentation.[384,385] Hence, women who derive no benefit from screening should be spared its potential adverse effects; which include discomfort and psychological distress, false positive results, and harm from the identification and treatment of nonlife-threatening lesions.[383]

The optimal age range for national breast cancer screening programmes has been the subject of debate, with international variations in practice. The impact of screening outside the age range 50-69 is uncertain, with few women beyond this included in the original trials of mammography.[195] While in New Zealand screening is provided through the publically funded organisation BSA for women aged 45-69,[194] a recent study using Auckland and Waikato breast cancer registry data showed that 15% of breast cancers amongst women older than 70 were diagnosed via screening.[86] In the US, no explicit guidelines for older women exist, although consideration of comorbidity and life expectancy is expected.[386-389] Despite this, there is evidence to suggest that ongoing screening in the context of poor life expectancy is common, with a study by Schonberg et al[380] finding that around 40% of women with a life expectancy of less than 5 years due to comorbidity still receive screening mammography.

Studies in US cohorts have shown that physician recommendation is a strong predictor of breast cancer screening.[390,391] Vignette studies, which ask physicians to consider clinical decisions based on summarised information about hypothetical patients, demonstrate that inappropriate screening amongst patients with comorbidity is likely to be common, with one study reporting that 47.7% of primary care physicians would recommend mammography to an 80 year old woman with terminal lung cancer,[392] while another found that 37.7% of physicians would offer mammography to a frail 90 year old.[393]

3.3.1.4. Physiological Hypothesis

The physiological hypothesis proposes a biological interaction between comorbidity and cancer at a cellular level, which increases the aggressiveness of cancer such that patients present at a later stage of disease.[26,350] This was investigated in a study by Newschaffer et al, who uncovered evidence of a comorbidity-stage mortality interaction for regional stage breast cancer, which the authors contend may be "….attributable to biologic coaction..."[394(pM377)]

Similar mechanisms to those which lead to an increased risk of breast cancer may affect the aggressiveness of disease. An increase in the levels of pro-angiogenic growth factors in some chronic diseases (such as cardiovascular disease), which encourage tumour progression has been suggested, leading to the contention that medical optimisation of comorbidities may improve cancer survival.[395] Similarly, in the case of type II diabetes and metabolic syndrome, insulin resistance, hyperinsulinaemia, activation of the insulin-like growth factor pathway, and impaired regulation of sex hormones may promote breast cancer growth.[21] Diabetes has been associated with unfavourable tumour characteristics, such as hormone receptor-negative and higher stage disease.[362] Several authors have reported an increased risk of presenting with advanced stage disease amongst patients with pre-existing diabetes,[26,357,361,362] which may indicate potentiation of tumour growth by the diabetic state. This effect is even stronger amongst patients with more severe or longer-standing diabetes.[26,114,357] While this may relate to a reduction in screening participation by diabetic women,[361,363,373-376,378] evidence of an association persists in studies that control for recent mammography.[26,361]

Opposing the physiological hypothesis is evidence that the treatment of some comorbidities may actually reduce the growth of breast cancer,[26] for example the use of metformin for the treatment of diabetes,[329] nonsteroidal anti-inflammatories for arthritis,[330-332] and statins for dyslipidaemia.[335]

3.3.2. Staging Investigations

Despite the importance of staging to prognostication and the guidance of treatment decisions, missing data on stage is a feature of many population-based cancer registries. While this may be related to issues of data quality or patient characteristics associated with poorer access to health services, poor life expectancy (due to advanced age or comorbidity) is a major explanatory factor.[396] In this setting, staging investigations may not be performed as clinicians assume that such patients are either imminently dying or unlikely to benefit from cancer treatment. This pattern is most pronounced for cancers where staging is relatively straightforward, compared with malignancies which are more complex, or require resectional surgery to stage (such as upper gastrointestinal or liver cancers).[396] While definitive surgery of the breast and axilla is required to obtain pathological staging for breast cancer, clinical stage may be established reasonably easily through a combination of physical examination and imaging. The proportion of breast cancer patients with missing stage information on cancer registries is therefore comparatively low.[396,397]

Nonetheless, strong associations between comorbidity and missing stage have been observed in breast cancer cohorts. In a Danish study, nearly 18% of patients with severe comorbidity (CCI ≥3) had unstaged disease, compared to 8.1% of those without comorbidity.[398] In a study which used New Zealand Cancer Registry (NZCR) data, the odds ratio (OR) of unstaged breast cancer in patients with similarly high CCI scores was 2.83.[396] A further study by the same authors noted a gradient by comorbidity, with the highest category (C3 >2) experiencing nearly 3 times the odds of

unstaged disease.[357] Subgroup analysis by individual conditions revealed a particularly strong association for dementia, with 49 times the odds of unstaged disease. Seneviratne et al[399] investigated factors associated with unstaged breast cancer in the NZCR, finding once more that higher levels of comorbidity were associated with unknown stage. Missing stage was associated with greater risk of overall mortality, with a HR of 1.59 compared to staged disease.

3.4. Impacts of Comorbidity on Breast Cancer Treatment

3.4.1. Receipt of Treatment

There is consistent evidence that pre-existing comorbidity reduces the likelihood of receiving guideline-concordant treatment for breast cancer. In general terms, the likelihood of treatment reduces with increasing levels of comorbidity. Comorbidity severity also interacts with stage of disease in this respect, with a study by Greenfield et al[6] finding that higher levels of comorbidity were associated with less vigorous treatment for more advanced disease.

Comorbidity has a significant impact on the likelihood of receiving locoregional treatment, with multiple studies reporting a reduction in the receipt of any surgical treatment,[86,130,400] definitive primary therapy (BCS or mastectomy with axillary surgery plus radiotherapy as indicated),[49,59,61,114,400-402] ALND,[50,120,123,401,403] and postmastectomy reconstructions[87] for patients with comorbidity. Adjuvant radiotherapy is also less likely to be administered in patients with comorbidity following BCS[9,120,404] and mastectomy,[405] as well as overall.[86,122,130,400-403,406] The impact of comorbidity on the receipt of endocrine therapy is less clear. Consistent with evidence that endocrine therapy may constitute a reasonable solo treatment in the elderly,[280-282] some authors have reported an increase in the likelihood of endocrine treatment amongst patients with comorbidity,[120,403,406] while others have found no difference.[61,114,122,401]

Perhaps the most substantial treatment impact of comorbidity is its influence over the receipt of chemotherapy and HER2-directed therapy. While chemotherapy can provide significant survival benefits for those with higher risk disease, it is also associated with a range of serious toxicities which may impact upon the decision to treat patients with comorbidity. For this reason, the impact of comorbidity on the use of chemotherapy for non-metastatic breast cancer was examined in detail. As referenced in the introductory section of this chapter, a systematic review and meta-analysis was performed; assessing the receipt, quality, and toxicity of chemotherapy in relation to comorbidity.[27] Of the 33 studies which examined receipt of chemotherapy by comorbidity, 19 (58%) reported a reduction in treatment for patients with comorbidity (with the odds of treatment declining with increasing levels of comorbidity severity), while the others reported no difference. Ten studies were included in a meta-analysis examining chemotherapy receipt; returning ORs of 0.88 (95% CI 0.80-0.96) and 0.63 (95% CI 0.49-0.80) for receipt of chemotherapy by patients with comorbidity scores of 1 and ≥2 respectively, compared with no comorbidity (**Figure 5**).

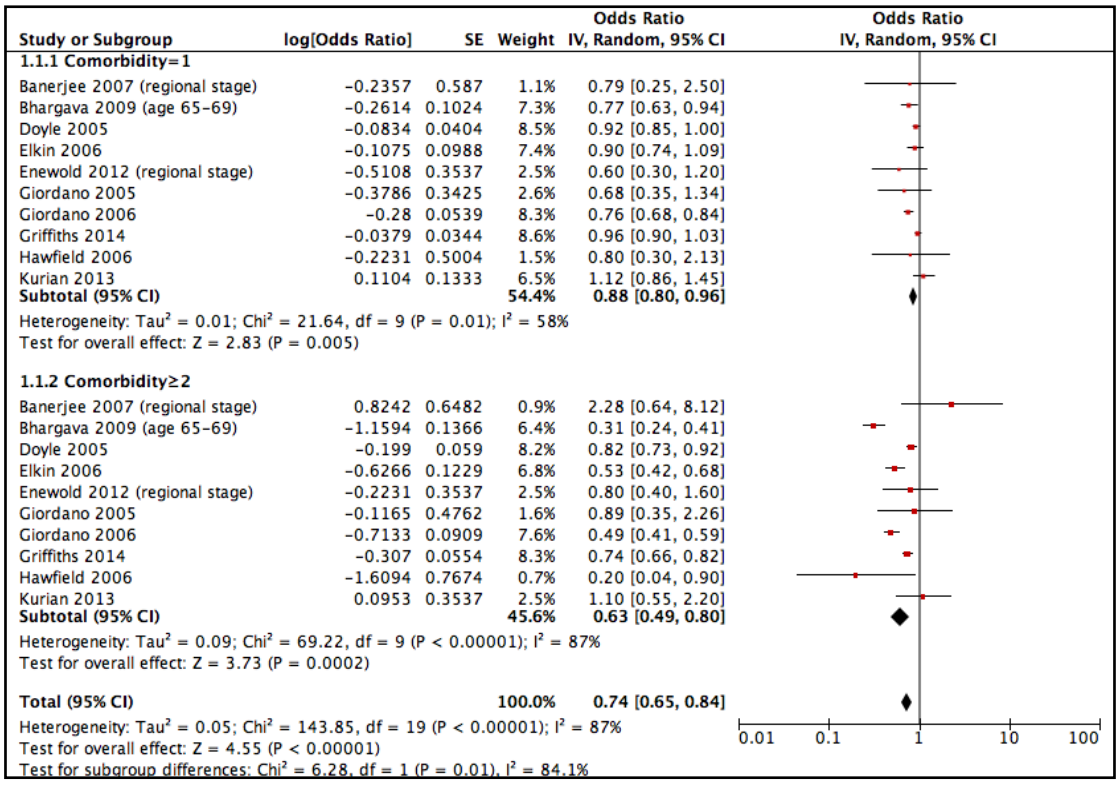


Figure 5. Forest Plot of Receipt of Chemotherapy: Comorbidity versus no Comorbidity

Abbreviation: IV, inverse variance. The software package RevMan version 5.3[407] was used to pool results from eligible studies using a generic inverse variance method and random effects analysis. Subgroups are patients with a comorbidity count or index score of 1 and patients with a count/score of ≥2. Comparison group is patients with a comorbidity count/score of 0. Reproduced from Edwards et al with permission.[③]

3.4.2. Quality and Timeliness of Treatment

For comorbid patients who do receive treatment for breast cancer, the quality and timeliness of that treatment is often worse. Treatment quality may be measured in various ways, with unplanned alterations often related to toxicities experienced during the course of therapy.

In order to achieve maximal survival benefits from chemotherapy, it is important to maintain planned dose intensity.[408,409] From the systematic review,[27] while some studies reported an increase in unplanned treatment modifications during chemotherapy,[30,121,410] the majority found no differences in dose proportion (ratio of actual to expected doses)[411,412] nor relative dose intensity[121,129,134,411,413] by comorbidity. Comorbid patients do however experience more first cycle[412,414] and planned dose reductions,[129] which signifies intentional prescribing rather than a response to toxicity. This may be appropriate, depending on the comorbid condition. For example, patients with renal insufficiency require dose adjustments for antineoplastic agents with higher renal clearance.[415] In an ancillary study of Cancer and Leukaemia Group B (CALGB) 49907

③ **Figure 5** is reprinted with permission from Springer Nature: Springer Science Business Media New York. Breast Cancer Research and Treatment. Influence of Comorbidity on Chemotherapy Use for Early Breast Cancer: Systematic Review and Meta-analysis. Edwards MJ, Campbell ID, Lawrenson RA & Kuper-Hommel MJ. © 2017. https://doi.org/10.1007/s10549-017-4295-4

analysing the impact of renal function on breast cancer outcomes in older patients receiving renal dose-adapted chemotherapy, pre-treatment renal function was not predictive of dose modifications, per protocol completion, haematological toxicity, relapse-free or overall survival.[416]

Choice of regime is a further important consideration for patients with comorbidity, due to the toxicity profiles of particular drugs. For instance, anthracyclines, with their associated risk of cardiotoxicity, are less likely to be used in patients with comorbidity, particularly by patients with cardiac disease.[115,126,417-420] Preference may be given to regimes containing taxanes,[117,119,417] unless patients are diabetic,[115] due to their increased risk of peripheral neuropathy.[410] Comorbid patients are also more likely to be treated with CMF[115,128,419] despite lesser benefit compared to second and third generation regimes,[248] likely due to the perception that CMF is less toxic. Third generation regimes, whilst being the most efficacious, are also potentially the most toxic, and are consequently used less frequently by patients with comorbidity.[115,117,119] Patients with comorbidity (particularly cardiac disease) are also less likely to receive trastuzumab.[117,119,400] The type of endocrine therapy prescribed may also be affected by comorbidity, with Berglund et al[400] reporting increased use of aromatase inhibitors in preference to tamoxifen with increasing comorbidity, although this is likely to be explained by the uncontrolled confounding influence of age.

Some differences by comorbidity have been reported with respect to surgical procedure.[9,130,406,421] Although BCS is usually a less morbid operation, mastectomy may be preferred in comorbid patients due to a desire to avoid neoadjuvant therapy, further surgery for an involved margin, or radiotherapy; particularly for those with relative contraindications such as collagen vascular disorders, significant cardiac or pulmonary disease, pacemakers, or previous radiotherapy to the site.[197] A study by van de Poll-Franse et al[406] found that older women with diabetes were more likely to undergo mastectomy than BCS, while Gorin et al[130] noted the opposite amongst women with Alzheimer's. Others who have assessed surgery in relation to comorbidity have reported an increase in receipt of mastectomy relative to BCS,[421,422] the inverse,[9] or no relationship.[50,122,401,423]

The adverse survival impact of delayed treatment is well known.[424,425] Delays to the receipt of breast cancer surgery have been noted for patients with comorbidity in the US[422] and Canada.[426] A local study by Seneviratne et al[427] showed that a CCI score of ≥1 was associated with twice the odds of experiencing a delay greater than 31 days from diagnosis to surgery. Delays to the receipt of adjuvant treatment also have a deleterious effect on breast cancer recurrence and survival.[238,239,256-258] In a study by Hershman et al,[428] women with an NCI index score ≥2 had twice the odds of experiencing a delay more than 3 months between BCS and the initiation of radiotherapy. This finding however has not been replicated by others,[429,430] with one study even noting a reduction in delay to radiotherapy (>12 weeks) amongst comorbid patients who had received initial adjuvant chemotherapy.[430] Inconsistent results have also been noted with respect to chemotherapy, with a study by Fedewa et al[431] reporting increasing risk of delay (>90 days) to chemotherapy with rising comorbidity burden, while others have found no difference.[257,432]

3.4.3. Tolerability of Treatment

Treatment-related complications can potentially impair quality of life and shorten remaining life expectancy, thereby cancelling any gains obtained by therapy. Comorbid patients may suffer a greater burden of toxicity due to a reduction in their physiological reserve. Polypharmacy is also an issue, with high level drug interactions significantly increasing the risk of severe toxicity from systemic therapy.[433]

The extent to which comorbidity affects the tolerability of cancer treatments relates to the type and severity of the comorbidity, as well as to the treatment modality itself. Houterman et al[423] examined the overall prevalence of treatment complications during the first year following breast cancer diagnosis, finding no significant differences by level of comorbidity severity nor age, although complications were not subdivided by treatment modality. Outcomes after breast cancer surgery were examined by Dehal et al,[434] who found that comorbidity burden was associated with an increased risk of postoperative complications, prolonged hospital stay, non-routine disposition, and inpatient death.

The landmark study CALGB 49907, which investigated the impact of self-reported comorbidities amongst women aged 65 years and older receiving standard intravenous polychemotherapy (AC or CMF) or oral capecitabine for breast cancer, found that while comorbidity was associated with shorter overall survival (with a threshold of ≥4 conditions), it was not associated with toxicity nor time to relapse.[30] Patients who received AC or CMF experienced superior disease-free and overall survival compared to those who received capecitabine, reinforcing the importance of using standard regimes in older patients.[435]

Overall, evidence regarding chemotherapy-related toxicity in relation to comorbidity appears to be mixed. While major non-haematological toxicity has been associated with comorbidity,[436,437] most authors have found no differences with respect to haematological or overall toxicity.[30,437,438] The association between comorbidity and febrile neutropenia has also been inconsistent, with some studies noting an increased risk of neutropenia with the presence of comorbidity (particularly diabetes, CHF, cerebrovascular disease, previous cancer, thyroid disorders, and osteoarthritis),[109,124,412,420] but not all.[134,413,439] The link between comorbidity and anthracycline-associated cardiotoxicity is more established, with a meta-analysis identifying severe comorbidity, diabetes, hypertension, and extremes of body weight as risk factors.[440] Subset analyses from the seminal clinical trials of trastuzumab implicated left ventricular dysfunction,[342,441] antihypertensive use,[442,443] and elevated BMI[342] in the development of trastuzumab-related cardiotoxicity. A small retrospective study of 45 elderly patients receiving trastuzumab identified prior cardiac disease and diabetes as additional risk factors for the development of cardiotoxicity.[444] Diabetes is also a known risk factor for chemotherapy-induced neurotoxicity, with a Spanish study reporting significantly more dose reductions and treatment delays due to paclitaxel-induced peripheral neuropathy.[410]

Three studies were included in a meta-analysis which evaluated hospital admission for chemotherapy-associated toxicity (**Figure 6**). The results showed that admission was increased amongst patients with comorbidity; returning ORs of 1.42 (95% CI 1.20-1.67) for patients with a comorbidity score of 1, and 2.23 (95% CI 1.46-3.39) for patients with a score ≥2. The systematic review also uncovered evidence that comorbid patients undergoing chemotherapy are more likely to be admitted to hospital for any reason during the course of their treatment,[134,420,445] possibly due to the exacerbation of pre-existing conditions or even a lower threshold for admission in such patients.

Non-completion of planned treatment may represent a response to toxicity. There is some evidence of reduced chemotherapy completion rates amongst patients with comorbidity,[446,447] although other authors have noted no difference.[121,411,438,448,449] The literature surrounding adherence to endocrine therapy is also conflicting. In a study by Hershman et al,[450] comorbidity burden was associated with early discontinuation and reduced adherence to endocrine therapy. Sedjo et al[451] showed a reduction in adherence to aromatase inhibitors with comorbidity, particularly with heart disease, other malignancy, and depression. Contrary to this however are the findings of Hadji et al[452] and Partridge et al,[453] who report reductions in the risk of noncompliance with comorbidity. Lash et al[454] found an inverse relationship between tamoxifen discontinuation and increasing number of baseline prescription medications, despite there being no association with comorbidity count.

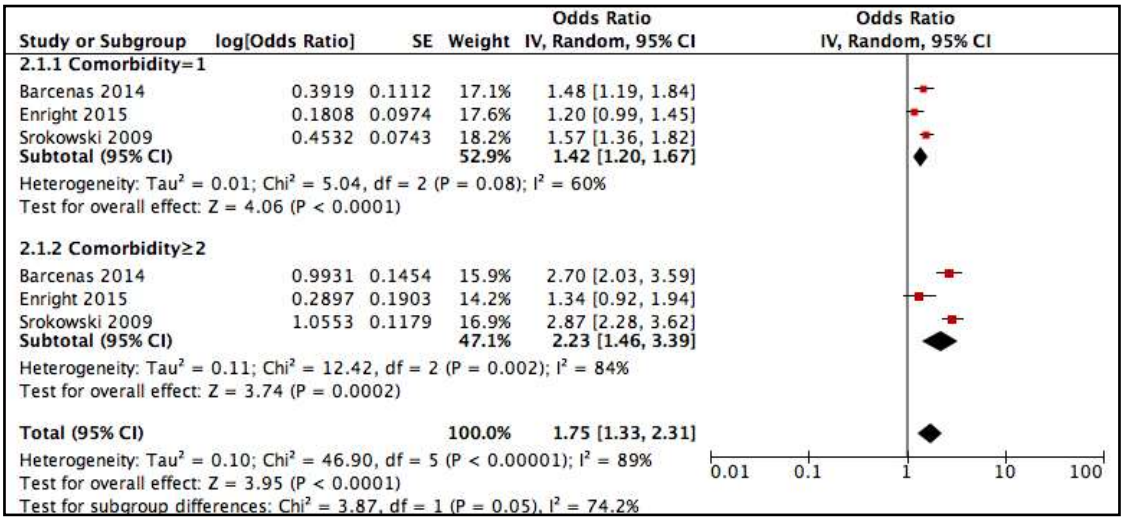


Figure 6. Forest Plot of Hospital Admission due to Chemotherapy-associated Toxicity: Comorbidity versus no Comorbidity

See **Figure 5** caption for figure details. Reproduced from Edwards et al with permission.[④]

[④] **Figure 6** is reprinted with permission from Springer Nature: Springer Science Business Media New York. Breast Cancer Research and Treatment. Influence of Comorbidity on Chemotherapy Use for Early Breast Cancer: Systematic Review and Meta-analysis. Edwards MJ, Campbell ID, Lawrenson RA & Kuper-Hommel MJ. © 2017. https://doi.org/10.1007/s10549-017-4295-4

3.4.4. Reasons for the Underuse of Cancer Treatments

Consistent with the literature that comorbid patients are less likely to receive potentially curative cancer treatments is the finding from hypothetical vignette-based studies that clinicians are less likely to recommend such treatment for breast cancer patients with comorbidity.[31,455-457] Reasons for the underutilisation of cancer treatments in individuals with comorbidity are likely to be multifaceted and relate to both patient and physician factors.

Uncertainty about the efficiency and tolerability of breast cancer treatments in patients with comorbidity is a commonly cited concern, with a paucity of evidence from randomised trials.[30,31] For trial designers, there is tension between providing evidence that can be directly generalised to the whole patient population, and optimising internal validity by including only those for whom the benefit to harm ratio is most favourable.[458] Recruitment of frail older patients is also difficult, with low inclusion rates attributed to a variety of factors including: feeling overburdened by their condition and the additional required healthcare visits, poor family support, transportation problems, cognitive deficits, communication issues in obtaining consent, insufficient staff awareness of eligibility criteria, and the additional time (and financial resources) required for such patients to participate.[459] As a result, trials tend to exclude patients older than 65 years, as well as those with comorbidity and/or reduced performance status.[460-462] This has been particularly apparent in trials evaluating adjuvant systemic therapies. Amongst 4 CALGB trials of adjuvant chemotherapy for node-positive breast cancer, only 8% of participants were 65 years or older (with only 2% >70 years).[463] The 2005 EBCTCG Overview was unable to provide reliable data on the net survival benefit of chemotherapy in older women due the inclusion of too few women aged over 70 years.[246] Older patients are also substantially underrepresented in US Food and Drug Administration registration trials of chemotherapy (but not endocrine therapies).[464,465] Those that are included are generally healthier than the broader elderly population due to restrictions placed on comorbidity and performance status, hampering the external validity of such trials.[466,467] Extrapolation of results to real-world patients may be therefore inappropriate, with the benefit of treatment likely to be less pronounced. With the results of such trials informing the development of treatment guidelines, only a simplified, inadequate approach can be offered. For example, the St Gallen Consensus do not set an upper age limit on the use of therapies, but rather issue a broad statement that treatment decisions should be individualised, taking into account comorbid conditions and life expectancy.[168]

Inadequate life expectancy due to competing risks of mortality may also be used to justify the omission of cancer treatments in patients with comorbidity. While life expectancy can be estimated from life tables based on chronological age,[468] this may be influenced by comorbidity. Indeed, substantial heterogeneity by comorbidity status has been demonstrated for similarly aged individuals without cancer, with the production of comorbidity-adjusted life tables.[469] A number of prognostic indices have been developed which incorporate additional predictors of survival.[470] A widely used example is ePrognosis, which estimates 10-year all-cause mortality based on a

number of factors including age, sex, comorbidity, functional status, and health-risk behaviours.[471] While such tools can be useful adjuncts when making decisions about cancer treatment, they are not disease-specific and therefore do not permit an estimation of cancer-specific survival.

Risk of relapse and cancer-specific mortality are additional factors to consider when evaluating the potential benefits of adjuvant therapy. Absolute and relative treatment benefits must be distinguished, with increasing risk of competing mortality incurring smaller absolute benefits.[472] Extermann et al[473] conducted a Markov analysis at various levels of age and comorbidity, assessing the threshold 10-year relapse-risk at which adjuvant chemotherapy and/or tamoxifen provided an absolute 1% reduction in relapse or mortality. While older and comorbid patients could expect a relapse reduction similar to that obtained by younger and healthier patients, there was a marked divergence with respect to mortality. Due to increasing risk of competing cause mortality in older and sicker patients, maximum mortality benefits were reached after 5 years rather than 10. However, although the absolute magnitude of benefit obtainable by treating older and sicker patients may be small (1-3% reduction in mortality with chemotherapy amongst elderly patients), this is in line with the range of effectiveness of common secondary prevention interventions (such as beta-blockers or antiplatelet therapy after MI[474,475]), and translates to a significant impact from a population perspective, given the prevalence of such patients.[473]

The time dynamic of relapse is also relevant, with recurrence risk for an ER-positive tumour remaining elevated beyond 10 years, compared with ER-negative disease where recurrence is most likely by 5 years.[179] Various decision aids which estimate survival and risk of relapse in the context of tumour characteristics and various treatment options have been developed, but have not been sufficiently validated in older women, nor do they incorporate an objective assessment of comorbidity.[476] The closest is Adjuvant! Online which predicts expected benefits from adjuvant treatments based on 6 clinical factors, one of which is a subjective 6-level classification of general health.[253] While there should be no issue in mistaking *major problems (+30)* or *(+20)* from *perfect health*; distinguishing *minor problems*, *average for age* and *major problems (+10)* may not be straightforward. Validation studies have used the default option of minor problems,[477-479] however the algorithm is extremely sensitive to comorbidity input. A deterministic sensitivity analysis by Ozanne et al[480] found that comorbidity was by far the most influential variable, underscoring the importance of accurate classification. Adjuvant! was also developed in a relatively young population; 35-59 years, with validation studies demonstrating suboptimal accuracy amongst women aged outside of the range 40-75 years.[476] A Dutch study found that Adjuvant! performed poorly in older patients and was sensitive to comorbidity modelling, significantly under- or overestimating overall survival and recurrence depending on the comorbidity option selected.[472]

Patient preference plays a large role in the threshold risk of relapse required to justify adjuvant treatment. Vignette studies show that patients with cancer are much more likely to opt for radical treatment with minimal chance of benefit than healthy controls or medical professionals.[481] Age

does not seem to influence willingness to accept treatment, although older patients do have a somewhat higher threshold in terms of the survival benefit required to accept more toxic treatment options.[482] Interviews with elderly breast cancer patients have identified concerns about the potential for toxicity as a major reason for declining cancer treatment;[483] with it reasonable to assume a similar trend amongst those with comorbidity. Physician recommendation also has a major influence over patient treatment decisions,[483,484] and it is difficult to ascertain how differences in the way treatment risk: benefit profiles are communicated to the elderly/comorbid contribute to their expressed preferences about treatment. Several risk predictive scores for chemotherapy-associated toxicity have been developed, which can aid in such discussions.[485-487]

The way in which patients and physicians view the relative importance of factors contributing to treatment decisions is likely to differ. In a study of patients with colon cancer, physicians were more likely to rank comorbid conditions and the medical literature as important factors when deciding upon adjuvant chemotherapy; while patients were more likely to rank physician opinion, family preference, and family burden.[484] While it is clear that physicians view comorbidity as an important variable,[31,455-457,484,488] there is significant variation in their ability to accurately assess comorbidity and subsequent recommendations.[456,488] For example, in a study evaluating recommendations for chemotherapy amongst patients with colon cancer, of those for whom treatment was not recommended due to comorbidity, 35% had an actual CCI score of 0, while 19% of patients who received a recommendation for chemotherapy had a CCI score of ≥2.[488]

3.5. Impacts of Comorbidity on Breast Cancer Outcomes

3.5.1. Survival

There is ample evidence that breast cancer patients with pre-existing comorbidities have poorer overall prognosis, with increased risk of breast cancer death, as well as death due to other causes. A 2012 systematic review found that breast cancer patients with at least 1 comorbidity were at substantially increased risk of non-cancer and all-cause death; and modestly increased risk of breast cancer-specific death.[28] The general trend was of greater risk with increasing levels of comorbidity, with ratio measures of association ranging between 1-3 per category increase for all-cause mortality, and 0.1-1 for breast cancer mortality. Similarly, a 2015 summary of 17 cohort studies reported that comorbidity increases the risk of breast cancer mortality by 20-50%, and competing cause mortality up to 6-fold.[29] The comparatively greater impact of comorbidity on competing cause mortality indicates that comorbid patients with breast cancer are more likely to die from conditions other than breast cancer, contributing to large disparities in all-cause mortality.

While comorbidity amongst survivors of early stage breast cancer contributes to higher mortality than similar patients without comorbidity, these women are no more likely to die from their other conditions than the general population.[16] On the contrary, Cho et al[489] showed that women with

DCIS or stage I breast cancer had slightly lower mortality than non-cancer controls. This could reflect the fact that women with early breast cancer may be more likely to engage in health preventative behaviours, be of higher socioeconomic status, and have greater access to health services than the general population, masking the true impact of comorbidity.[16,490]

The relative impact of comorbidity on survival tends to be greater for cancers with better prognosis. Patients with more biologically aggressive cancers (such as pancreatic and lung adenocarcinomas) are likely to die from their malignancy regardless of their comorbidities.[85,491,492] Thus, the mortality influence of comorbidity is most important in situations where the prognostic impact of the tumour is small. While breast cancer is a variable disease, overall, prognosis is favourable.[153] The role of comorbidity in determining breast cancer survival may therefore be substantial, potentially more so than stage. This was illustrated in a study by Patnaik et al,[112] where older patients with 1 of 13 comorbid conditions and stage I breast cancer had similar or poorer overall survival than patients who had no comorbid conditions but stage II tumours.

Similarly, comorbidity exerts a greater influence over breast cancer survival in early rather than late stage disease,[15,98,122,491] since the likelihood of cure is higher and more dependent on treatment decisions. Satariano et al[98] for instance, noted an interaction between comorbidity and breast cancer stage at diagnosis, where increasing stage had little additional effect on all-cause survival amongst patients with at least 3 comorbidities. The type of comorbidity is also likely to be important, with a study by Siegelmann-Danieli et al[107] showing that survival from early stage disease was adversely affected by a number of comorbid conditions, while advanced stage survival was only influenced by the presence of dementia or major functional debility.

Comorbidity may impact survival though several mechanisms. While the direct independent impact of comorbidity on non-cancer (and consequently all-cause) mortality is relatively straightforward; it can be difficult to disentangle the effects of comorbidity on breast cancer-specific death. Comorbidity may play a direct role in accelerating cancer progression, although evidence of this is conflicting.[350] Consistent with this hypothesis, Piccirillo et al[85] reported that in a cohort of cancer patients (including breast), the likelihood of cancer recurrence increased with increasing degree of comorbidity severity. Conversely however, Kiderlen et al[493] found that among patients with non-metastatic breast cancer, relapse-free progression was superior for patients with diabetes (irrespective of the presence of other comorbidity) compared to those without diabetes, which was speculated to reflect a potential therapeutic effect of metformin.

A second mechanism may relate to increased toxicity of cancer treatments amongst patients with comorbidity, leading to higher treatment-related cancer mortality. However, as discussed in the previous section, evidence with respect to this amongst comorbid patients with breast cancer appears to be mixed. It is also possible that the deleterious association between comorbidity and breast cancer-survival is artefactual; due to differential misclassification of cause of death towards

cancer-specific mortality.[494] The likelihood of this occurring will be specific to individual countries, populations, and cancer sites. In a study by Kendal et al,[492] cancer site had a 30-fold stronger association with cancer-specific survival than age at diagnosis, while age displayed a 5-fold stronger association with comorbid death than cancer site. It is unlikely; therefore, that for patients with breast cancer (a relatively good prognosis cancer with increasing age-related cumulative risk), misclassification in the direction of cancer-specific death plays much of a role.

A further mechanism, and probably the most important, is reduced receipt of definitive cancer treatment by patients with comorbidity, thereby increasing the risks of recurrence and cancer mortality.[29] This is made evident by the findings of studies which show that the overall improvements in breast cancer survival rates witnessed over the past few decades (attributed primarily to advances in adjuvant treatment and earlier diagnosis through the introduction of mammographic screening[495]) have been experienced primarily by patients without comorbidity.[496,497] The extent to which this mechanism may act to reduce cancer survival in patients with comorbidity is an important distinction, since treatment decisions are potentially amenable to intervention. Some authors have attempted to determine whether treatment retains a beneficial effect on cancer outcomes amongst patients with comorbidity despite their increased risk of competing cause mortality (and potentially, toxicity-related mortality), using propensity score methods to control for confounding by indication. In a study of patients with stage III colorectal cancer, while patients with CHF, COPD, or diabetes were less likely to receive adjuvant chemotherapy, those who did had a clear survival advantage over similar patients who did not.[498] Likewise, Bradley et al[499] found that amongst men with intermediate to high risk prostate cancer, those who received some form of cancer-directed treatment had substantially superior survival compared with those who did not, irrespective of comorbidity status. Conversely however, treatment offered no survival benefit for comorbid men with low risk disease. Such findings suggest that some comorbid patients may have potentially curative treatment unnecessarily withheld, to the detriment of their survival.

3.5.2. Quality of Life

The presence of coexistent comorbid conditions has been associated with poorer quality of life across a range of cancer types.[500] A prospective study conducted before and 1 year after breast cancer surgery found that the number of self-reported and medical record-verified CCI comorbidities had a negative correlation with multiple quality of life domains, including physical functioning, bodily pain, social functioning, and vitality, as well as overall quality of life scores.[501] In addition, certain individual comorbidities (hypertension, arthritis, and diabetes) were negatively associated with multiple domains. Similarly, in a study by Deshpande et al,[502] greater Katz-CCI burden was associated with lower physical and social functioning 1 year post-diagnosis. Comorbidity has also been shown to exert negative impacts on quality of life amongst breast cancer patients during the course of radiotherapy[503] and chemotherapy[504] treatment.

3.5.3. Economic Impact

The economic impact of chronic conditions is substantial, extending far beyond the obvious treatment-related expenses born by patients and healthcare organisations.[308] Patients (and their families) assume expenses associated with lost employment, as well as the immeasurable costs of disability, shortened life span, and poorer quality of life. Loss of workers from industry due to morbidity and death also mean that employers, governments, and societies suffer the costs of lost productivity. According to the WHO, the challenge of chronic conditions to the efficiency and effectiveness of current healthcare systems "…engender increasingly serious economic and social consequences…(such that they)…threaten healthcare resources in every country." [308(p11)]

Comorbidity is likely to add to the cost of healthcare for patients with cancer, although few studies have investigated this directly. A systematic review of 12 studies examining the economic burden of comorbidity among cancer survivors found that total medical and out-of-pocket costs rose with increasing comorbidity burden, irrespective of the condition studied.[505] Taplin et al[506] investigated the costs of breast cancer care, finding that while total initial and terminal care costs were unaffected by comorbidity, total continuing care costs were higher with increasing levels of comorbidity. However, when cases were matched with similar non-cancer controls, the net cost of continuing care reduced with increasing comorbidity, indicating that the addition of a breast cancer diagnosis results in lower incremental costs among patients with higher levels of comorbidity.

3.6. Comorbidity and Other Drivers of Cancer Inequities

Disparities in health care and outcomes may occur across many axes. The same population groups which are disproportionately affected by chronic disease face a range of inequities across the cancer control continuum; experiencing disparities in incidence, stage at diagnosis, treatment, and mortality. The following section attempts to disentangle some of the complex interrelationships between comorbidity and other potential drivers of breast cancer inequities, including age, ethnicity, socioeconomic position, and geographic location.

3.6.1. Age

While the cumulative risk of breast cancer increases with age,[2,3] breast cancer is still the most frequently diagnosed cancer amongst young women in New Zealand, with approximately 12% of cases occurring between the ages of 25-44 years.[154] A relatively younger population are affected than many other cancers; including prostate, colorectal, and lung (which have a median age of onset closer to 70 years).[153] Comorbidity exerts a relatively greater influence on younger patients with cancer. This was illustrated by Braithwaite et al,[122] who noted an interaction between comorbidity and age; whereby comorbidity had a greater impact on all-cause survival amongst younger women.

The biological characteristics of breast cancer vary by age. Breast cancer in young women is typically more aggressive, with higher proportions of HER2-enriched, triple negative, and luminal B tumours, as well as incident stage IV disease.[507] Conversely, several favourable changes in histology occur with advancing age, with an increase in the proportion of tumours which are low grade, hormone receptor-positive, and HER2-negative.[508] Despite this, elderly women with breast cancer have worse survival.[509] The link between age and comorbidity means that elderly women are more likely to die from causes other than breast cancer, particularly in early stage disease.[5,510]

Older women with breast cancer face similar treatment challenges to those with comorbidity. While the therapeutic options for breast cancer are the same across the aging spectrum, current approaches are often empiric. Underrepresentation in clinical trials[460-462] has resulted in a scant evidence-base upon which to base treatment recommendations for the elderly.[31] In a review by Bouchardy et al,[511] reduced life expectancy due to age and comorbidities was cited as the main reason for the omission of treatment amongst women with breast or gynaecological cancer. Comorbidity only explains part of the under-treatment however, with several studies showing a persistent impact of age after adjustment for comorbidity (and functional status),[5-11] suggesting that physicians react more to chronological than physiological age.

3.6.2. Ethnicity

Ethnic disparities in breast cancer are well documented, with indigenous and ethnic minority populations experiencing worse survival rates in many countries.[159,512-514] In New Zealand, a number of authors have explored survival inequities between Maori and non-Māori, finding 60-70% higher age-standardised breast cancer mortality overall.[283,309,515] Reasons for this disparity are likely to be multifactorial, with proposed explanations including: more advanced cancer stage at diagnosis, more aggressive tumour biology, inferior treatment, and higher rates of comorbidity.

Māori and Pasifika present with more advanced stage disease than non-Māori, non-Pacific.[309,515-520] A likely contributing factor is reduced screening, with Māori and Pacific women of screening age less likely to present with screen-detected cancer.[518,520] Aggressive biology may also contribute, with more high grade,[520-522] hormone receptor-negative,[518,520,522] HER2-positive,[518,522] and ductal tumours[523] detected amongst Māori and Pacific women. Disparities in access and treatment have been examined in a series of papers by Seneviratne et al, who showed that Māori are more likely to undergo mastectomy for small cancers,[421] less likely to receive reconstructions[421] and radiotherapy,[524] and less likely to adhere to endocrine therapy than non-Maori.[525] Māori also experienced more delays to surgery[427] and adjuvant treatment.[429] In a model attempting to explain the variation in breast cancer mortality between Māori and Europeans, the greatest contribution to disparity was stage at diagnosis (40%), with screening differences contributing 15%, biological characteristics 7%, healthcare access factors 2-3%, treatment 15%, and the remaining 15% explained by patient factors; comorbidity, smoking, and BMI.[519]

Internationally, comorbidity is an important factor explaining breast cancer survival disparities amongst Indigenous women. In a study of Canadian women with stage I breast cancer, comorbidity was the most important factor explaining the 3-times poorer survival among First Nations women.[526] Similarly, in the US, comorbidity (particularly diabetes and hypertension) explained 49% of the all-cause and 77% of the competing cause survival disparity between African American and White women with breast cancer.[100]

3.6.3. Socioeconomic Position

Many countries display a social gradient in health, where those in more disadvantaged positions experience worse health and greater mortality.[527] In New Zealand, there is good evidence that socioeconomic position impacts upon breast cancer survival, and that this is correlated with ethnicity.[309] Trend studies evaluating breast cancer mortality by socioeconomic status show that the deprivation gap in New Zealand has remained essentially unchanged over time.[283,528] In a study by McKenzie et al,[529] patients with breast cancer in the 2 most deprived groups experienced 50% greater excess mortality than the least deprived group. The relationship between socioeconomic position and mortality remained after adjusting for tumour factors, and was only partially explained by ethnicity, signalling an independent prognostic impact. Similar disparities in breast cancer survival by socioeconomic position have been shown in countries with different healthcare and social welfare systems; including the US, United Kingdom, Canada, and Australia.[530]

The majority of studies examining socioeconomic position in relation to health outcomes use an ecologic measure of deprivation to categorise patients, rather than direct measures of individual wealth.[530] Some have also used health insurance status as a surrogate measure. In the US, it has been shown that uninsured or publically insured patients with breast cancer present with more advanced stage disease[531,532] and have worse survival than those with private insurance.[532,533] In New Zealand, data from the Auckland and Waikato registers suggests that patients who access private treatment have a 14% improvement in breast cancer-specific survival.[296]

In a review of socioeconomic inequalities in breast cancer survival, there was evidence that deprivation influenced outcomes through a number of mechanisms, including: lower screening uptake, presentation with more advanced disease, more aggressive tumour biology, greater comorbidity, higher rates of smoking and alcohol consumption, poorer nutrition and more obesity, less social support and more psychological distress, differential access to healthcare services, and poorer treatment.[530] More advanced stage at diagnosis was the factor most commonly cited, though this was not the sole explanatory mechanism. This was examined in a New Zealand breast cancer cohort by Jeffreys et al[534] who reported an 8% deprivation gap in 5-year relative survival between the least and most deprived cases, with 34% of this gap explained by differences in disease stage.

Comorbidity is more common in deprived populations, with a social gradient evident from the results of the 2016/2017 New Zealand Health Survey.[310] In a population-based study of breast cancer from the Netherlands, a similar gradient was observed, with the prevalence of comorbid conditions increasing with progressive degree of deprivation.[535] Modifiable health risk behaviours are also more common in people living in deprived circumstances, with the 2016/2017 New Zealand Health Survey revealing higher rates of smoking, hazardous drinking, and obesity in the most deprived quintile.[310] Such behaviours lead to poorer health status which, while not necessarily evident in quantifiable comorbidity scores, do impact upon cancer survival.[530]

3.6.4. Geographic Location

The prevalence of health conditions (and health outcomes) varies by geographic location, and is related to local social, economic, and physical context.[536] Inequalities are often examined using an urban/rural distinction; with common themes relating to inequity in health service provision due to greater distance from specialist services and a relative lack of primary care.[537,538] Distinct national and regional differences by urbanisation have been recognised however, reinforcing the importance of understanding patterns within local physical and cultural context.[537,539] For instance, while the 2002/2003 New Zealand Health Survey found that rural residents were significantly more likely to be physically active and eat more vegetables than their urban counterparts,[540] the US 2001 Urban and Rural Health Chartbook found that rural residents are more likely to be obese, smoke more, exercise less, and have less nutritious diets.[539]

Disparities in breast cancer mortality by rurality have been demonstrated in Australia,[541,542] Scotland,[543] Germany,[544] and the USA[545]; findings speculated to reflect inequalities in access to screening[546] (leading to more advanced stage at diagnosis[547]) and treatment. A systematic review of urban/rural differences in treatment for breast cancer found that, compared with their urban counterparts, rural patients were less likely to undergo BCS, postmastectomy reconstruction and radiotherapy.[548] The review suggested that anticipation of the social and financial costs of travel to receive treatment plays a role in determining the types of therapy received.

In New Zealand, an urban/rural health differential has been less evident.[549] Using data from the NZCR and 3 classifications of rurality, Bennett et al[550] found no differences with respect to breast cancer stage at diagnosis nor all-cause survival. Similarly, a study using Auckland and Waikato breast cancer registry data found that rurality had no overall impact on survival.[290] There was, however, effect modification with respect to ethnicity, with rural Māori experiencing inferior breast cancer survival compared to urban Māori. The seeming lack of rural inequities may relate to several factors; including issues with the definition of rurality,[549] with few New Zealanders actually living in highly rural/remote locations,[551] equitable screening through the nationally coordinated BSA,[194] and specialist cancer services being configured in a way that attempts to balance local access with cost-efficient centralisation.

3.7. Conceptual Framework: Pathways from Comorbidity to Breast Cancer Survival

Despite the body of literature examining the associations between comorbidity and cancer survival, there has been limited exploration of the underlying mechanisms at work. The discussion up to this point has raised a number of potential explanations for the inequities in breast cancer outcomes for patients with coexistent comorbidity. Drawing from the literature, a conceptual framework was developed (**Figure 7**), depicting the possible causal pathways linking comorbidity with survival outcomes from breast cancer, as well as potential interrelationships with other drivers of cancer inequities. Factors along these pathways have been categorised at the broad levels of individual patient, health service access, cancer biology, and treatment considerations, acknowledging their considerable overlap and mutual interactions.

The remainder of this thesis will attempt to draw together evidence in support of this framework, in order to provide an explanation for the previously described disparities in breast cancer survival for patients with comorbidity. The pathways to be investigated are shown in bold.

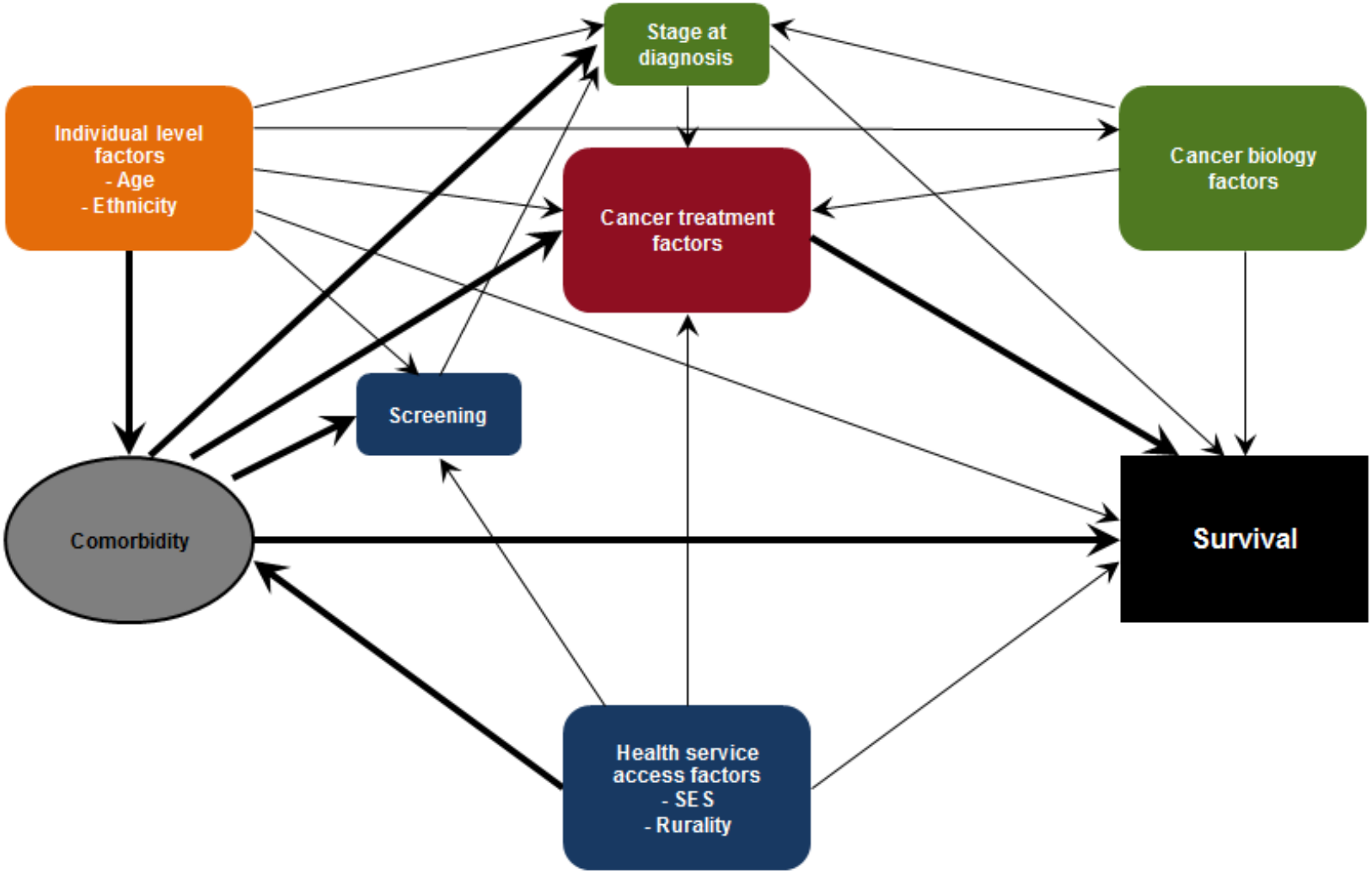


Figure 7: Conceptual Framework Depicting Pathways Linking Comorbidity with Breast Cancer Survival

Chapter 4. Methods

4.1. Introduction

An overview of the general methods used in this work is presented in Chapter 4, with methodological details specific to the analyses of Studies 1-3 given in Chapters 5-7. Chapter 4 is divided into 11 sections, with the current section introductory.

Section 2 details the existing ethical approvals for the main data sources utilised in this work; the Auckland and Waikato breast cancer registers, as well as the approvals obtained specific to the methods and analyses of this thesis.

Section 3 outlines the specific eligibility criteria for the overall inclusion of subjects in the study population.

Section 4 describes the data sources used, including the Auckland and Waikato breast cancer registers and supplemental sources of data; the National Minimum Dataset (NMDS), New Zealand Pharmaceutical Claims Data Mart (Pharms DM), and New Zealand Health Information Service Mortality Collection database.

Section 5 summarises the procedures involved in data collection, linkage with additional data sources, and data integration.

Sections 6-9 provide a description of the variables used in the studies of this thesis, which were applied in a variety of ways depending on the specific analysis. Factors may therefore act as primary exposure variables, covariates (ie, confounders), mediating variables, modifying variables, or outcome variables in different analyses. For simplification, these sections categorise and describe variables as they pertain to the main analyses of this thesis in Study 3. Additional uses of variables in Studies 1 and 2 are described in the relevant methods sections of Chapters 5-6.

Section 6 provides an explanation of the primary exposure variable: guideline-concordant treatment for breast cancer. The processes involved in the selection of relevant guidelines for application are described. Guideline-concordant and non-concordant treatment is defined under the categories of treatment receipt, quality, and timeliness. Eligibility criteria specific to each of the analyses carried out in Studies 2 and 3 are outlined.

Section 7 provides a description of the variables used as covariates. Covariates are categorised into individual level, healthcare access, cancer biology, and treatment factors.

Section 8 describes the comorbidity measures used. The development and validation of the C3 index, the main measure of comorbidity used in this thesis is described, as well as its application.

Section 9 details the primary and secondary outcome variables of interest: all-cause and breast cancer mortality.

Section 10 discusses the general statistical methods used in the data analyses of this thesis. This section is divided into a number of parts detailing the methods used for descriptive analysis, missing values analysis and multiple imputation, regression modelling, time to event analyses, and propensity score methods.

Section 11 outlines the assumptions and parameters used to estimate the required sample sizes for the treatment effects analyses of Study 3.

4.2. Ethical Approval

The Auckland and Waikato breast cancer registers function with ethical approval for the prospective collection of breast cancer-related information for research purposes (Auckland register: Northern A Health and Disability Ethics Committee, Ethics Reference. AKL/99/251; Waikato register: Waikato Ethics Committee, Ethics Reference. WAI/04/10/099). The requirement for individual patient consent was removed by amendments obtained in 2013 (Auckland register: Ethics Reference. AM03; Waikato register: Ethics Reference. AM02) with non-consented cases backdated to 2000. Ethical approval for the data linkages and analyses pertaining to this thesis was obtained from the Northern A Health and Disability Ethics Committee, Ethics Reference. 12/NTA/42/AM01.

Additional local approvals for this research were obtained from the research office at Waikato DHB and the Kaumatua Kaunihera research subcommittee of Te Puna Oranga (Māori Health Strategy Unit, Waikato DHB).

4.3. Study Population

The overall inclusion and exclusion criteria for the study were as follows:

Inclusion Criteria
• Women with incident, unilateral, non-metastatic invasive breast cancer (ICD-10 codes C50.0 - C50.9), diagnosed between 01/06/2000 and 01/06/2015. • Diagnosis of primary breast cancer made by FNA (in combination with clinical and/or radiological features of invasive breast cancer), core needle biopsy, or open biopsy. • Breast cancer treatment received at a facility located within the catchment area of the DHBs of the Auckland or Waikato regions. • Resident in New Zealand at the time of diagnosis. • Data inclusion on either the Auckland or Waikato breast cancer registers.
Exclusion Criteria
• Cancer originating from the stroma of the breast (such as sarcomas or phylloides tumours), lymphoma, or metastasis from extramammary malignancy. • Diagnosis of metastatic disease within 121 days of breast cancer diagnosis. • Death due to breast cancer within 121 days of breast cancer diagnosis. • Subsequent diagnosis of metachronous breast cancer up to the date of censoring: 01/01/2018.

4.4. Data Sources

This section describes the key data sources used in this thesis. Subjects were identified from the Auckland and Waikato breast cancer registers. Supplemental study data was obtained from the New Zealand Ministry of Health via a number of other data sources; including the NMDS, Pharms DM, and New Zealand Mortality Collection database. Data was linked between sources using National Health Index (NHI) numbers, which are assigned to all individuals who access health and disability support services in New Zealand.[552]

4.4.1. Auckland and Waikato Breast Cancer Registers

The Auckland and Waikato breast cancer registers are prospectively maintained databases containing information on all patients diagnosed with in situ and/or invasive breast cancers within these regions. To be eligible for inclusion, patients must have sought breast cancer treatment at, or been resident within the catchment areas of the Auckland or Waikato regional DHBs. Patients must also be resident in New Zealand at the time of diagnosis. The Waikato register was established in 2005 (with historical cases backdated to 1991), while the Auckland register was established in June 2000. Eligible women are identified from public and private hospitals within

the region (Waikato) or from the NZCR (Auckland); a population-based register of all primary malignancies diagnosed in New Zealand (excluding non-melanoma skin cancers).[553] Relevant demographic, diagnostic, treatment, and follow-up data are abstracted from clinical notes (inpatient/outpatient records and multidisciplinary team meeting discussions) and entered into a Microsoft Access database by trained data entry personnel. Patients are followed up annually and data on disease outcomes (local or distant recurrence and death) is recorded. Mortality data is supplemented by annual data linkage with the Mortality Collection. Patients who have migrated out of the region are traced and their records obtained from general practitioners.

4.4.2. National Minimum Dataset

Data from the NMDS was used to define comorbidity in the study cohort as well as to check and supplement data on ethnicity and domicile. The NMDS is a national collection of hospital discharge information from public and private hospital admissions and day patients.[554] It holds dates of admission/discharge, as well as coded clinical information regarding primary and secondary diagnoses and inpatient procedures. The NMDS in its current form was introduced in 1999, with back-loaded public hospital information available from 1988. Data coding is performed on site by trained coders and supplied to the Ministry of Health who maintain the database. The discharge summary (completed by a treating clinician) is the primary source of information; however this is checked against and supplemented by the entire medical record; including inpatient notes, operation notes, laboratory results, radiology reports, and clinical letters. Codes are assigned in accordance with the standards and conventions of the WHO's ICD, 10th revision, Australasian Modification (ICD-10-AM).[555]

4.4.3. Pharmaceutical Claims Data Mart

The Pharms DM is a data warehouse containing claim information from pharmacists for subsidised pharmaceutical dispensings that have been processed by the Sector Services General Transaction Processing System.[556] It is jointly owned by the Ministry of Health and PHARMAC. Data held includes: demographic information, chemical name and formulation, dates, and quantities of medicines dispensed. Each medicine is categorised according to their primary indication for use. While pharmaceutical data has been collected since 1992, NHI numbers have only been included since 2002 (with 2005 the first year that >80% of claims reported NHI (Chris Lewis, Information Analyst: Analytical Services, Ministry of Health; email communication, 14 August 2017). The quality of pharmaceutical data has improved over time, such that in 2010, NHI was provided for approximately 97% of dispensings.[557]

Data from the Pharms DM was used to supplement information recorded in the breast cancer registries regarding receipt of HER2-directed and endocrine therapies, as well as adherence to endocrine therapy. Prescription records for dispensings later than 01/01/2005 were obtained for

the following medications: tamoxifen citrate, anastrozole, exemestane, letrozole, goserelin, leuprorelin, triptorelin, and trastuzumab.

4.4.4. Mortality Collection

Date and cause of death was obtained from the Mortality Collection. Death records were requested up to the date of censoring: 01/01/2018. The Mortality Collection holds the date and cause of death for all deaths registered in New Zealand from 1988 onwards.[558] Cause of death is assigned by Ministry of Health registrars based on information obtained from Medical Certificates of Causes of Death and Coroner's reports, with additional sources such as the NMDS consulted as necessary. The WHO Rules and Guidelines for Mortality and Morbidity Coding[101] are followed. Data for deaths occurring later than 2000 is recorded using the ICD-10-AM coding system.[555]

4.5. Data Collection

Study data was obtained from the Microsoft Access databases of the Auckland and Waikato breast cancer registers. Data was exported into a Microsoft Excel spreadsheet, creating a dataset with a single observation for each study participant. Coding of categorical variables was performed. Data ranges were checked to ensure data was entered within prescribed limits. Where datum was outside the delineated parameters, original files were obtained and examined for accuracy, with data entry errors corrected where identified. Clinical files were also consulted for cases with missing data in order to maximise data availability.

Additional linkage of the study dataset with data from the NMDS, Pharms DM, and Mortality Collection was performed by crosslinking NHIs. Customised electronic data extracts from these sources were provided by Ministry of Health analytical services staff. These were then integrated with the study dataset in Excel. Once data cleaning, linkage, and integration was complete, the dataset was imported into Stata for Macintosh, Version 14.0[559] for analysis.

4.6. Exposure Variable: Guideline-concordant Treatment

Delineating what constitutes appropriate breast cancer treatment is not straightforward. A range of treatment modalities may be considered based on their projected benefits in the context of particular tumour characteristics. As there is no one size fits all treatment, a more detailed approach to defining the exposure variable was required. Given these difficulties, concordance with best practice treatment guidelines was considered a feasible and clinically relevant approach.

Treatment guidelines are produced by extrapolating results from clinical trials demonstrating the efficacy of therapies in particular patient subpopulations. Using information obtained from tumour staging and biological profiling, guidelines may be applied to individuals. Multiple breast cancer

guidelines exist internationally, which, whilst all inferred from the same available evidence base, may differ based on interpretation and local context. As appropriate cancer treatment must be considered within the context of the healthcare system in which it is delivered, national guidelines were regarded the most important source of reference in this study. As research advances, guidelines are updated to reflect emergent evidence. Retrospective judgement by current standards of care would result in earlier study participants being deemed non-concordant, despite receiving what would have been considered adequate treatment at the time. Changes to treatment standards over the time course of the study therefore also required consideration.

The first set of national guidelines was produced in 1997 by the Royal Australasian College of Surgeons Section of Breast Surgery in New Zealand.[560] A renewed set of guidelines was produced by the New Zealand Guidelines Group in 2009,[197] followed by national tumour standards from the Ministry of Health in 2013.[198] Although they remain provisional; as DHBs audit and improve their service delivery, the Standards of Service Provision represent the most current set of national guidelines at the time of this study. The FCT programme, introduced by the Ministry of Health in 2012 to improve timely access to cancer treatments also provide standardised targets for treatment waiting times.[300]

While New Zealand guidelines were the primary standards against which concordance was assigned; where detail was lacking, or there was a major change in clinical practice between publications, guidance from the St Gallen International Expert Consensus was sought. In addition to its international authority and credibility,[561] with particular influence over the development of the New Zealand guidelines and treating clinicians in New Zealand (Ian Campbell, Chair: National Breast Cancer Tumour Stream Work Group and Chairperson: New Zealand Guidelines Group; oral communication, 9 May 2016), the advantage of the St Gallen Consensus as a complementary guideline of reference to this study is its regular update.

The biennial St Gallen International Breast Cancer Conference on the Primary Therapy of Early Breast Cancer is one of the world's largest cancer congresses.[562] The most recent advances in breast cancer biology and multidisciplinary treatment are presented, and on the final day the panel, a selected group of breast cancer experts review the current evidence, voting on various issues to produce the St Gallen Consensus Statement.[563] This is then published for broad application, influencing international clinical practice over the ensuing 2 years. As the Consensus is produced by a panel that vote based on their own interpretation of the evidence, total agreement is not assured. The level of uncertainty attached to each recommendation, and the quality of the contributing evidence is reflected in the text. As such, only guidelines for which there was clear panel majority agreement were selected to define the minimum treatment standards applied in this study. Where Consensus Statements lacked required detail, reference was sought from the original trials upon which the recommendations were based, or from other major temporal guidelines.

Guideline-concordance was used and defined in a number of ways; depending on the treatment modality and year of diagnosis. Concordance was examined with respect to minimum standards for treatment receipt, quality, and timeliness. For each analysis, guideline literature was consulted and appropriate temporal standards selected. To enable time for recommendations to reasonably influence clinical practice, the guideline selected for application was that which was published within 1 calendar-year prior to the year of diagnosis. Unless a change was specified, guidelines were assumed unaltered in subsequent years. Treatment details for study participants were compared to the selected standards and assigned binary concordant/non-concordant status accordingly. Concordance was only evaluated with respect to under-treatment. Only treatment related to the management of primary breast cancer was considered. That is, treatment received after the diagnosis date of any locoregional or metastatic recurrence was classified as non-concordant. Recurrence was defined as the return of cancer at the site of the original primary, regional lymph nodes, or distant site after a disease-free interval following the receipt of (any) breast cancer treatment. Date of recurrence was defined as the date at which recurrence was identified; based on clinical examination, imaging, and/or histological confirmation.

Non-surgical treatment was defined in relation to the date of first (breast or axillary) surgery. Treatment received before surgery was termed neoadjuvant, and after as adjuvant. If no surgery was received, treatment was termed primary therapy. Endocrine treatment was classified as neoadjuvant if it was received ≥90 days prior to surgery, with preoperative therapy given for less time considered adjuvant. This was to identify endocrine treatment with true neoadjuvant intent, with 90 days the minimum duration in the majority of trials evaluating neoadjuvant endocrine therapy.[279] Pathological tumour size and nodal status were used to determine indication for adjuvant therapy where primary surgery was received. Clinical stage was used if no surgery was performed. In the setting of previous neoadjuvant therapy, indication for adjuvant therapy was based upon the maximum of baseline clinical and/or post-therapeutic pathological stage.[218,219]

Only treatment received within a reasonable time frame was termed concordant. This was to capture therapy relating to primary treatment, rather than that instituted in response to recurrence or new cancer. This acted to safeguard against imperfect data capture by the registers. Moreover, patients receiving treatment after extended delay may be expected to derive minimal benefit; with outcomes closer to those receiving no treatment at all. Commencement of treatment ≥365 days from diagnosis was considered non-concordant for neoadjuvant and primary therapy. For adjuvant therapy, treatment commenced ≥365 days after the last date of surgery was deemed non-concordant. Systemic endocrine therapy provided an exception, where treatment commenced within 5 years of diagnosis for primary or neoadjuvant treatment, or 5 years following the last date of surgery for adjuvant treatment was deemed concordant, due to evidence of benefit even after extended delay.[564,565] Systemic endocrine therapy commenced prior to diagnosis was also considered concordant, in order to account for the small number of clinical breast cancers managed with endocrine therapy alone prior to definitive pathological diagnosis.

Treatment details were obtained from the registers, with no treatment presumed if no record of such existed. In addition, for cases diagnosed later than 01/01/2005, detail on endocrine and HER2-directed therapy was supplemented by records from the Pharms DM. In cases of discrepancy, treatment was taken to have been received, due to the possibility of incomplete coverage by either source. Where the date of initiation differed between data sources, the earlier was taken as the date of commencement.

Sections 4.6.1-3 provide detail regarding the application of guidelines to the treatment analyses of Studies 2 and 3. The rationale for their selection and major changes to standards over the study period are described. Eligibility criteria for each treatment analysis are defined. A summary of treatment indications by modality and year of application is presented in **Table 3**.

4.6.1. Receipt of Treatment

4.6.1.1. Surgery: Breast

Exclusion Criteria
• Occult primary breast cancer (cT0).

Surgical excision of the primary breast tumour(s) is recommended for all non-metastatic breast cancers. A possible rare exception are patients with occult primary breast cancer; ie, breast cancer presenting as regional nodal metastases without clinical or radiological evidence of disease within the breast. In the absence of clear guidelines regarding the optimal management of such patients,[566] 4 patients with occult primaries were excluded from the analysis. Breast surgical treatment was defined as excision biopsy, wide local excision, or mastectomy.

4.6.1.2. Surgery: Axilla

Surgical staging and/or treatment of the axilla is recommended for all patients. Axillary surgical treatment was defined as SLNB, axillary sampling, or ALND (levels I-III).

4.6.1.3. Adjuvant Radiotherapy

Inclusion Criteria
• Receipt of breast surgical treatment for breast cancer. • Minimum indication for adjuvant radiotherapy as defined in **Table 3**.
Exclusion Criteria
• Breast surgery received ≥365 days after diagnosis. • Neoadjuvant radiotherapy. • Indication for radiotherapy unable to be determined due to missing data.

Table 3. Summary of Minimum Treatment Standards by Year of Diagnosis

Receipt of Treatment - Minimum Indications	
Surgery: Breast	
All years	All, unless cT0
Surgery: Axilla	
All years	All
Adjuvant Radiotherapy[a]	
2000 - 2007	Post BCS - All *Post-mastectomy* - ≥pN2, ≥pT3-4, or positive (invasive) margin
2008 - 2015	*Post BCS* - May be omitted if: >70 years, ≤pT1N0[b], ER$^+$, negative margins[c] & received endocrine therapy[d,e] Post-mastectomy - No change
Adjuvant Chemotherapy[a,f,g]	
2000 – 2001	Node$^+$ - All *Node*$^-$ - ≥1 of: pT size>20mm, ER/PR$^-$, G≥2, or age<35
2002 - 2005	ER/PR$^-$
2006 - 2007	*Node*$^+$ - ≥pN2; pN1 & HER2$^+$ *Node*$^-$ - ER/PR$^-$ or endocrine response uncertain[h] & ≥1 of: pT size>20mm, G≥2, LVI, HER2$^+$, or age<35
2008 – 2009	*HER2*$^+$ - ≥pN1; node$^-$ & ≥1 of: pT>20mm, G≥2, ER/PR$^-$, LVI, or age<35 *HER2*$^-$ - ≥pN2 or ER/PR$^-$
2010 - 2011	*HER2*$^+$ - ≥pN1; pN0 & pT size≥10mm or LVI *Triple negative* - ≥pN1; pN0 & pT size≥10mm (may be omitted if medullary, apocrine, or adenoid cystic carcinomas), G3, or LVI *HER2*$^-$*, ER/PR*$^+$ - ≥1 of: G3, pN2, or ≥pT size>50mm
2012 - 2013	Luminal B[i] (HER2$^+$) *HER2*$^+$ *(non-luminal)* - May be omitted if pT1a & node$^-$ Triple negative *ER/PR*$^-$ *special histological types* - Apocrine, medullary (unless node$^-$), adenoid cystic (unless node$^-$), or metaplastic carcinomas
2014 - 2015	*Luminal A*[j] - ≥pN2 or G3 Luminal B[k] HER2$^+$ (non-luminal) Triple negative *ER/PR*$^-$ *special histological types* - Apocrine, medullary, adenoid cystic (unless node$^-$), or metaplastic carcinomas
HER2-directed Therapy[a,g,l]	
2000 – 2006	NA
2007 - 2011	HER2$^+$ & either: ≥pN1; or pN0 & pT size≥10mm
2012 - 2015	HER2$^+$ & either: ≥pN1; or pN0 & ≥pT1b
Endocrine Therapy	
All years	ER &/or PR^{+t}
Quality of Treatment - Minimum Standard	
Surgery: Breast	
All years	Mastectomy or; BCS - requiring ≥2mm radial margin & no tumour on ink vertical margin
Surgery: Axilla	
2000 – 2003	Levels I & II ALND
2004 - 2009	Levels I & II ALND or; SLNB - unless: >cN0, >cT2,[a,m] or neoadjuvant therapy With completion ALND if ≥pN0(i$^+$)
2010 - 2012	Levels I & II ALND or; SLNB - unless: >cN0 or >cT2[m] With completion ALND if ≥pN0(i$^+$)
2012 - 2015	Levels I & II ALND or; SLNB unless: >cN0 or >cT2[m] With completion ALND if ≥pN1a, unless: ≤2 sentinel node macrometastases, BCS, WBI, & no neoadjuvant therapy[n]

Table 3 continued. Summary of Minimum Treatment Standards by Year of Diagnosis

Adjuvant Radiotherapy	
2000 - 2009	*Post-BCS*: Conventionally fractionated-WBI ≥45Gy in 25 fractions *Post-mastectomy*: Conventionally fractional chest wall irradiation ≥45Gy in 25 fractions
2010 - 2013	*Post BCS*: Conventionally fractionated-WBI ≥45Gy in 25 fractions or; Hypofractionated-WBI ≥40Gy in 15 fractions if: age ≥50, pT1-2N0 & negative margins[c,o] Post-mastectomy: No change
2014 - 2015	*Post BCS*: Conventional or hypofractionated-WBI ≥40Gy in 15 fractions Post-mastectomy: No change
Chemotherapy	
All years	Completion of expected number of cycles
Adjuvant Endocrine Therapy	
All years	MPR ≥80%
Timeliness of Treatment - Minimum Standard	
Breast Surgery	
All years	≤31 days (≤90 days sensitivity analysis)
Adjuvant Radiotherapy/Chemotherapy/HER2-directed Therapy	
All years	≤42 days (≤84 days sensitivity analysis)

Abbreviations: cN, clinical nodal stage; cT, clinical tumour stage; G, grade; i^+, isolated tumour cells; MPR, medication possession ratio; NA, not applicable; pN, pathological nodal stage; pT, pathological tumour stage.

[a] In the context of previous neoadjuvant therapy, indication for treatment taken from the most advanced of clinical or pathological stage.

[b] As per 2009 European Society for Medical Oncology guidelines.[567]

[c] Defined as no tumour on ink for invasive disease &/or DCIS.

[d] Defined as tamoxifen or an aromatase inhibitor received within 5 years of the last date of surgery.

[e] As per CALGB C9343 criteria.[568,569]

[f] Endocrine receptor positivity defined as ≥10% tumour nuclei staining for diagnosis dates between 2000-2005, and ≥1% staining for diagnosis dates in 2006 or later; or, in the absence of a documented staining proportion, where receptor status was reported as positive.

[g] May be omitted if age >75 years.

[h] Endocrine response uncertain defined as ER 1-10% or PR <1% staining.[240]

[i] Luminal B in 2011 defined as ER and/or PR^+ and tumour grade ≥2.

[j] Luminal A defined as: ER^+, PR≥20% staining, and tumour grade 1.

[k] Luminal B ($Her2^-$) in 2013 defined as: ER^+, $HER2^-$, & ≥1 of: PR staining <10% or G2. Luminal B ($HER2^+$) defined as: ER^+, $HER2^+$, any grade, and any level of PR staining.

[l] Clinical T size & N stage used if no surgery performed.

[m] Pathological T stage used if cT stage missing.

[n] As per Z00111 criteria.[225]

[o] As per Cancer Australia guidelines.[570,571]

As only adjuvant radiotherapy was evaluated, the analysis was limited to patients receiving surgical treatment of their breast primary. Fifty-four patients who received breast surgery ≥365 days after breast cancer diagnosis were excluded, along with 46 who received neoadjuvant radiotherapy, and 100 for whom an indication for radiotherapy was unable to be identified due to missing data on tumour characteristics and/or margin status. Radiotherapy was defined as the delivery of radiation (of any dose) to the conserved breast after BCS or chest wall following mastectomy, with or without regional nodal irradiation. Minimum indications for treatment differed by final surgical procedure as follows.

Following BCS: St Gallen advocated adjuvant radiotherapy for all patients until 2007, when the panel majority deemed it could be omitted in selected elderly patients who were to receive endocrine therapy.[572] This recommendation was influenced by the landmark study CALGB C9343[568,569] and subsequently reaffirmed by others.[573,574] Omission under trial criteria was also adopted by the New Zealand guidelines, although not until 2013.[198] Exploratory analyses revealed that, from 2008-2014, only 16 out of a possible 71 patients to whom such eligibility criteria could apply had radiotherapy omitted. Thus, for the final analysis, omission of radiotherapy in this subgroup was deemed acceptable from 2008 onward.[572] Rather than using clinical stage to define this subgroup as per the original trial,[568] pathological stage was used in accordance with European Society of Medical Oncology guidelines.[567] Endocrine therapy was defined as the receipt of tamoxifen or an aromatase inhibitor[218] within 5 years of the last date of surgery.

Following mastectomy: The St Gallen Consensus[575,576] and New Zealand guidelines[197,198] recommend postmastectomy radiotherapy for women at high risk of locoregional recurrence (≥20% at 10 years). Australasian practice guidelines define high risk as ≥4 axillary metastases, pathological T3-4 disease, or surgical margins positive for invasive tumour.[197,198,577,578]

4.6.1.4. Adjuvant Chemotherapy

Inclusion Criteria
• Receipt of breast surgical treatment for breast cancer. • Minimum indication for adjuvant chemotherapy as defined in **Table 3**.
Exclusion Criteria
• Breast surgery received ≥365 days after diagnosis. • Neoadjuvant chemotherapy. • Age >75 years. • Indication for chemotherapy unable to be determined due to missing data.

As only adjuvant treatment was considered; patients who received neoadjuvant chemotherapy (*n*=270) were excluded. Patients with missing data precluding the identification of indication for chemotherapy (*n*=64) or who received delayed breast surgery ≥365 days after diagnosis (*n*=54)

were also removed from the analysis. Concordance was defined as the receipt of chemotherapy of any regime and number of cycles. Indication for treatment was taken from relevant St Gallen guidelines. In 1998, St Gallen framed its threshold for systemic therapy in relation to 10-year mortality risk.[575] In 2005, risk categories were redefined and treatment was delineated in terms of endocrine responsiveness.[240] The introduction of trastuzumab and routine HER2 testing added another dimension in 2007, with further alteration to risk categories.[572] In 2011, in recognition of the importance of intrinsic biological subtype, treatment recommendations were made in relation to their surrogate definitions.[579]

In the 1998 Consensus report, the panel view was that chemotherapy could be omitted in elderly patients with hormone receptor-positive disease, irrespective of nodal status.[575] The following Consensus in 2001 removed this exemption, refuting the utility of age in isolation to treatment decisions.[576] However, as the omission of chemotherapy in the elderly was standard practice in New Zealand during the study period, an ongoing age threshold was imposed. As no further definition of *elderly* was provided by St Gallen, a semi-arbitrary cut-off of 75 years was applied, resulting in the exclusion of an additional 468 patients. This was based upon standard exclusion criteria of most of the adjuvant chemotherapy trials, with few patients older than 70 years included in the resulting EBCTCG overviews.[243,246] Exploratory analyses of the data revealed that only 25 out of 4419 (0.57%) patients who received neoadjuvant and/or adjuvant chemotherapy were in fact over the age of 75.

4.6.1.5. HER2-directed Therapy

Inclusion Criteria
• Diagnosis date 01/01/07 or later. • Tumour positive for HER2.[⑤] • Minimum indication for HER2-directed therapy as defined in **Table 3**.
Exclusion Criteria
• Age >75 years.

Publication of the first major studies of adjuvant trastuzumab in 2005-2006,[260-263] lead to an unprecedented interim update by St Gallen in 2006, advocating for its use in HER2-positive disease.[580] While originally only recommended for women at moderate to high risk of relapse (ie, node-positive disease, or node-negative with tumour size >1 cm), the indication for trastuzumab was extended in 2011 to node-negative tumours as small as 5 mm,[579] in recognition of the evidence that HER2-positivity confers poorer prognosis even in small tumours.[581-583]

The analysis was restricted to those diagnosed on or after 1 July 2007 (the date at which publically funded trastuzumab became available in New Zealand[265]), excluding 4822 patients.

[⑤] See Section 4.7.3.5 for definition of HER2-positivity.

Missing HER2 status in an additional 352 patients precluded an assessment of their potential eligibility. As with the chemotherapy analysis, patients over the age of 75 (*n*=71) were also excluded, as funding for trastuzumab is contingent on concurrent or sequential administration with chemotherapy.[272] Receipt of treatment was defined as the administration of at least 1 dose of HER2-directed therapy in a primary, neoadjuvant, or adjuvant setting. In addition to trastuzumab, lapatinib and pertuzumab were also accepted anti-HER2 therapy, with some patients receiving these agents through their participation in clinical trials.[270,271]

4.6.1.6. Endocrine Therapy

Inclusion Criteria
• Tumour positive for ER and/or PR; defined as ≥10% tumour nuclei staining for diagnosis dates between 2000-2005, and ≥1% staining for diagnosis dates in 2006 and beyond.[⑥]

Although it is well-established that endocrine therapy should be received by all patients with hormone receptor-positive breast cancer, the IHC cut-off to define receptor-positivity was uncertain during the early years of the study. While St Gallen initially advocated an empirical 10% threshold for treatment,[575,576,584] in 2005, 3 categories of endocrine responsiveness were defined, with the panel recommending endocrine therapy for patients with any detectable receptor level.[240] In accordance with New Zealand (2009, 2013),[197,198] Australian (2008),[585] and US (2010)[173] guidelines, a 1% cut point was therefore taken as the threshold from 2006.

Primary, neoadjuvant, and adjuvant endocrine therapy was examined. For 173 patients, missing ER and PR status precluded evaluation of eligibility. Concordance was defined as the receipt of any endocrine agent for the treatment of non-metastatic breast cancer listed on the New Zealand Pharmaceutical Schedule.[272]

- SERM: tamoxifen citrate.
- Aromatase inhibitors: anastrozole, exemestane, letrozole,
- LHRH analogues: goserelin, leuprorelin.

An additional, non-schedular LHRH analogue, triptorelin, was also regarded as concordant due to the participation by some patients in trials[586] evaluating this agent. Surgical or radiation ablation of the ovaries was also considered concordant under the following circumstances:

- Pre- or perimenopausal at breast cancer diagnosis.
- Date of ablation known.
- Ablation performed within 2 years of diagnosis.

[⑥] Or where receptor status was reported as positive in the absence of a documented staining proportion.

4.6.2. Quality of Treatment

4.6.2.1. Surgery: Breast

Inclusion Criteria
• Receipt of breast surgical treatment for breast cancer.
Exclusion Criteria
• Breast surgery received ≥365 days after diagnosis. • Final surgery BCS; with unknown circumferential or vertical margin width (or positive/negative status) for either invasive disease or DCIS. • Risk-reducing mastectomy ≥18 months after the date of first BCS.

Primary breast tumour/s may be surgically managed by either BCS with an adequate resection margin, or mastectomy. The minimum acceptable margin following BCS has de-escalated over time. The 1997 New Zealand guidelines regarded 5 mm as a reasonable aim.[560] In 2009, the New Zealand Guidelines Group recommended a circumferential margin of ≥2 mm,[197] which was unchanged by the 2013 Standards.[198] Internationally, practice has been less conservative. St Gallen's original endorsement of 10 mm[575] was relaxed by 2009, with a panel majority willing to accept no invasive tumour on ink.[587⑦] For DCIS, guidance has been inconsistent. Between 2013-2015 there was no differentiation between invasive and in situ disease,[168,588] however by 2017, the recommended margin for DCIS was raised to ≥2 mm.[219]

Concordance was defined as the receipt of mastectomy or BCS with an adequate surgical resection margin; assessed in relation to New Zealand guidelines which stipulate a circumferential margin of ≥2 mm, with no distinction between invasive tumour and DCIS.[197,198] The assumption of a complete anterior-posterior resection was made.[589⑧] As such, for vertical margin status, no tumour on ink for invasive disease and DCIS was considered concordant. If a re-excision was performed, the final margin status was used. Margin orientation and closest distance for invasive disease and DCIS was ascertained from the pathology report of the breast specimen/s. Where a margin was reported as clear without specifying a distance, the margin was taken to be concordant. Fourteen patients without a documented margin status following BCS were excluded. Fifty-four patients who received delayed breast surgery were also excluded, along with 3 patients who underwent subsequent risk-reducing mastectomy ≥18 months after the date of their first BCS. As only final surgical margins are recorded on the databases, any attempt to evaluate post-BCS margin status in these patients was not possible. Additional analysis was performed to assess the quality of post-BCS margins in isolation, excluding patients who underwent initial or eventual mastectomy.

⑦ Unlike the New Zealand guidelines, which reference circumferential margin status, St Gallen make no distinction based on the anatomical orientation of the closest margin.
⑧ The technique of wide local excision usually involves a subdermal to pectoral fascia resection of the tumour; skin and pectoral fascia/muscle are not usually removed unless there is obvious tumour invasion.

4.6.2.2. Surgery: Axilla

Inclusion Criteria
• Receipt of axillary surgical treatment for breast cancer.
Exclusion Criteria
• Axillary surgery received ≥365 days after diagnosis. • Type of axillary surgical procedure unknown.

According to St Gallen, levels I and II ALND remained the standard axillary management until 2003, when SLNB-based management was accepted for patients without clinical evidence of axillary nodal disease at diagnosis.[584] Based on the eligibility criteria of most of the original trials,[590-593] the New Zealand guidelines[197,198] also consider clinical T3-4 tumours as contraindications to the use of SLNB. Post-neoadjuvant SLNB was considered reliable by St Gallen from 2009.[587] The requirement for completion ALND following a positive SLNB result has become increasingly conservative over time, from isolated tumour cells[197,240,572,584,587] to isolated micrometastatic disease,[579] and even macrometastatic disease in the context of Z0111 trial selection criteria.[225,579]

Clinical stage was used to determine the indication for axillary procedure. Due to limited data on clinical nodal status amongst patients undergoing primary surgery, for the purposes of this analysis, patients were assumed to be clinically node negative unless otherwise stated. Where clinical T stage was missing, pathological T stage was used. Clinical stage at diagnosis was also used to determine the indication for procedure amongst patients who received neoadjuvant therapy, with clinically node positive and T3-4 tumours necessitating ALND regardless of any apparent tumour down-staging.[⑨] Type of axillary procedure was taken from operation reports, irrespective of the number of nodes retrieved. Nineteen patients with unknown axillary procedure were excluded, along with 35 who underwent axillary surgery ≥365 days after diagnosis. Concordant ALND was defined as a minimum level II dissection. Axillary sampling without SLNB was considered non-concordant.

4.6.2.3. Adjuvant Radiotherapy

Inclusion Criteria
• Receipt of adjuvant radiotherapy for breast cancer.
Exclusion Criteria
• Breast surgery received ≥365 days after diagnosis. • Radiation dose unknown.

[⑨] As it was not possible to determine the extent of any tumour downstaging following neoadjuvant therapy from the breast cancer registers, and evidence regarding the safety of SLNB in this setting was not available during the study period.

Quality of radiotherapy was assessed in terms of radiation dose received. Seventy-six patients with unknown radiation dose and 1 who received delayed breast surgery were excluded.

Following BCS, conventionally fractionated-WBI using a dose of at least 45 Gy in 25 fractions was standard until 2009, when both the New Zealand[197] and St Gallen Consensus[587] guidelines deemed hypofractionation to be an acceptable option in selected patients. In the absence of a clearly defined criteria for this subpopulation from either of these sources, the Cancer Australia guidelines from 2011 were applied.[570,571] In 2013, St Gallen widened its indication for hypofractionation, with the panel majority considering it an option for all patients following BCS.[588] Although a variety of hypofractionated regimes have been studied,[232] 40 Gy in 15 fractions was regarded as the minimum acceptable dose, in line with other major international guidelines.[197,218,233,237,570,594,595]

Partial or accelerated partial breast irradiation in general was not endorsed by the panel majority during the study period.[588] Hypofractionated irradiation of the chest wall following mastectomy was also considered to be non-standard. For simplification, indications for boost and/or regional nodal radiotherapy were not considered.

4.6.2.4. Chemotherapy

Inclusion Criteria
• Receipt of neoadjuvant and/or adjuvant chemotherapy for breast cancer.
Exclusion Criteria
• Breast surgery received ≥365 days after diagnosis and adjuvant chemotherapy delivered. • Chemotherapy regime and/or number of cycles received unknown. • Unconventional chemotherapy regime received.

Quality of chemotherapy was evaluated with respect to completion of the expected number of cycles for the chemotherapy regime commenced. Minimum expected number of cycles was defined according to standard chemotherapy prescribing protocols[218,596,597] (**Table 4)**. Neoadjuvant and/or adjuvant chemotherapy was assessed. If both neoadjuvant and adjuvant chemotherapy was received, patients were considered concordant if at least 1 of the 2 schedules was completed. For chemotherapy schedules containing trastuzumab, only completion of the non-trastuzumab component was evaluated for concordance. Seven patients without a recorded regimen or completed number of cycles were excluded from the analysis, as well as 2 who received an unconventional regime.[⑩] A further 3 patients who commenced adjuvant chemotherapy after receiving delayed breast surgery ≥365 days after diagnosis were also excluded.

[⑩] Unconventional regimes received: etoposide + cisplatin, cisplatin + doxorubicin.

Table 4. Minimum Expected Number of Cycles by Chemotherapy Regime

Chemotherapy Regime	Minimum Expected Number of Cycles
CMF	6
AC	4
FAC	6
FEC	6
AC - CMF	7 (AC x4 - CMF x3)
TC	4
TH[a,b]	4
TCH[a]	6
TAC	6
AC - T	8 (AC x4 - paclitaxel x4[b])
AC - docetaxel	8 (AC x4 - docetaxel x4)
FEC - docetaxel	6 (FEC x3 - docetaxel x3)
FEC - paclitaxel	7 (FEC x4 - paclitaxel x3[b])

Abbreviations: AC-T, sequential doxorubicin & cyclophosphamide followed by paclitaxel; FAC, 5-fluorouracil doxorubicin & cyclophosphamide; FEC, 5-fluorouracil epirubicin & cyclophosphamide; TAC, docetaxel doxorubicin & cyclophosphamide; TC, docetaxel & cyclophosphamide; TH, docetaxel (or paclitaxel) + trastuzumab; TCH, docetaxel carboplatin + trastuzumab.
[a] Only the non-trastuzumab component was evaluated.
[b] Weekly and 3-weekly paclitaxel regimes, with 3 weeks of weekly paclitaxel equivalent to 1 dose of dose-dense paclitaxel given every 3 weeks.

4.6.2.6. Adjuvant Endocrine Therapy

Inclusion Criteria

- Patients with ER and/or PR-positive breast cancer, as defined in **Section 4.6.1.6**.
- Diagnosis date 01/01/2005 or later.
- Receipt of breast surgical treatment for breast cancer.
- One or more dispensed prescriptions for tamoxifen or an aromatase inhibitor following the first date of breast surgery, recorded on the Pharms DM.

Exclusion Criteria

- Breast surgery received ≥365 days after diagnosis.
- First prescription dispensed ≥365 days after the last date of surgery.
- Neoadjuvant endocrine therapy.

Quality of endocrine therapy was defined in relation to adherence to treatment. For women with hormone receptor-positive breast cancer, tamoxifen and/or an aromatase inhibitor should be taken for a minimum of 5 years.[180,246] Ovarian suppression was not considered as the optimal duration of treatment is unclear.[598] Prescription records for tamoxifen and aromatase inhibitors obtained from the Pharms DM were used to ascertain adherence. As such, only patients with a diagnosis date on or later than 01/01/2005 were included in the analysis. Dispensing date and prescription refill interval (number of days covered by the prescription) were recorded for each prescription. Medication possession ratios (MPRs) were calculated for each woman by dividing the overall number of days covered by the prescription by the total number of days the medication was required; ie, 5 years, death, or the conclusion of study follow-up (01/01/2018). An MPR of <80% was regarded as non-concordant.[599]

4.6.3. Timeliness of Treatment

4.6.3.1. Primary Breast Surgery

Inclusion Criteria
• Receipt of breast surgical treatment for breast cancer
Exclusion Criteria
• Neoadjuvant therapy. • No preoperative pathological or cytological breast cancer diagnosis. • Date of first surgery unknown.

Delay to surgical treatment was assessed in relation to the time gap between breast cancer diagnosis and receipt of surgery to the breast primary. Exclusion criteria included unknown date of surgery (*n*=5), patients without a preoperative pathological or cytological diagnosis (*n*=357), and neoadjuvant therapy (*n*=363).

A 31 day threshold to define non-concordance was used, in keeping with the FCT Indicators[300] and Standards of Service Provision.[198] This indicator provides a target for all patients with a confirmed cancer diagnosis to receive their first cancer treatment within 31 days of *decision to treat.*[⑪] As date of decision to treat was not available in the breast cancer registers, date of diagnosis was used as a proxy, accepting that this would likely be earlier than the actual decision to treat. As such, sensitivity analysis was performed using a 90 day threshold, as it has been shown that delays greater than this can incur inferior survival.[424]

4.6.3.2. Adjuvant Therapy

Inclusion Criteria
• Receipt of radiotherapy, chemotherapy, and/or HER2-directed therapy following surgical excision of a primary breast cancer.
Exclusion Criteria
• Date of first adjuvant treatment unknown. • Definitive surgery performed after commencement of adjuvant therapy. • Intraoperative radiotherapy.

Timeliness of adjuvant therapy was evaluated in terms of the time gap between the date of definitive surgery (last date of breast or axillary surgery, including any subsequent completional surgery) and the date first adjuvant treatment (radiotherapy, chemotherapy, and/or HER2-directed therapy) was initiated. Adjuvant radiotherapy and systemic therapy (chemotherapy and/or HER2-directed therapy) were considered together and separately. Patients undergoing definitive surgery

[⑪] Date at which the treatment plan was agreed between the patient and responsible clinician.

after the commencement of adjuvant therapy were excluded (*n*=116). Further exclusion criteria were intraoperative radiotherapy (*n*=42) and unknown date of first adjuvant treatment (*n*=56).

Non-concordance was defined as the commencement of adjuvant treatment >6 weeks (42 days) after the date of definitive surgery, as per the Standards of Service Provision.[198] As a 12 week threshold has also been applied in studies examining delays to radiotherapy and chemotherapy,[238,258] sensitivity analysis was also performed using 12 weeks (84 days) as the cut-off for non-concordance.

4.7. Covariates

This section details the variables incorporated into the propensity score models for control of confounding in Study 3. Variables are categorised as individual, health service access, cancer, and treatment factors. A descriptive summary of these variables is given in **Table 5**.

4.7.1. Individual Factors

4.7.1.1. Age at Diagnosis

Patient age in years, at day of histological breast cancer diagnosis. Age was mostly treated as a continuous variable in regression analyses, although descriptive statistics are provided using continuous and categorical measures. Categorisation was into 4 groups containing roughly equivalent numbers: <50 years, 50-59 years, 60-69 years, and ≥70 years. The narrow age bands of the central 2 strata reflect the density of the distribution around middle age.

4.7.1.2. Menopausal Status

Menopausal status was categorised as pre-, peri- and postmenopausal. This was taken from patient clinical records based on patient age, menstrual history, history of bilateral oophorectomy, and/or biochemical results (follicle stimulating hormone, luteinising hormone, and estradiol levels).

4.7.1.3. Ethnicity

According to the official definition used by New Zealand Statistics: "Ethnicity is a measure of cultural affiliation, as opposed to race, ancestry, nationality or citizenship."[600(p1)] Key elements are that ethnicity must be self-identified, individuals can belong to more than 1 ethnic group, and ethnicity may change over time. New Zealand has a standardised process for the collection, recording, and output of ethnicity data, governed by Statistics New Zealand's Statistical Standard for Ethnicity, and the Ministry of Health Ethnicity Data Protocols for the Health and Disability Sector.[600,601] Statistics New Zealand's Ethnicity New Zealand Standard Classification 2005

Table 5. Descriptions of Covariates

Covariate	Values	Description
Individual factors		
Age at diagnosis	21 - 104 years	Years from date of birth to date of histopathological diagnosis of breast cancer.
Menopausal status	Premenopausal Perimenopausal Postmenopausal	Derived from clinical records based on age, menstrual history, history of bilateral oophorectomy, and/or biochemistry results.
Ethnicity	European Māori Pacific peoples Asian Other ethnic groups	Self-assigned ethnicity using level 2 Ethnicity Data Protocol codes identified from the breast cancer registers and linked national databases using prioritised output with an ever-Māori approach.
Health service access factors		
NZDep2013	1 - 5	Area level socioeconomic deprivation measured on an ordinal scale collapsed into quintiles, where 1 is least deprived and 5 is most deprived.
Treatment facility	Public Private	Institution at which primary surgical treatment (or consultation if no surgery performed) was received.
Residential status	Urban Rural	Based on Statistics New Zealand's 2004 Urban/Rural Profile classification categories.
Treatment region (register)	Auckland Waikato	Breast cancer register of record, depending on the DHB at which breast cancer treatment was received.
Mode of detection	Screen-detected Non-screen-detected	Screen-detected: Diagnosis by imaging in an asymptomatic (or unrelated symptomatic) women. Non-screen-detected: Diagnosis following symptoms directly related to the breast cancer.
Cancer factors		
Stage at diagnosis	I - III	Pathological (preferred) or clinical breast cancer stage at diagnosis, as per the AJCC TNM classification, 7th edition.
Grade	1 - 3	As per the Nottingham combined histologic grading system.
Histopathological type	Invasive carcinoma NST Lobular Other special subtype	In accordance with the WHO Classification of Tumours of the Breast.
Focality/centricity	Unifocal & unicentric Multifocal &/or multicentric	Unifocal & unicentric: not multifocal or multicentric. Multifocal: >1 tumour in the same quadrant of the breast. Multicentric: >1 tumour in separate quadrants of the breast.
ER status	Negative Positive	Based on the proportion of tumour cells showing nuclear staining for anti-ER antibody on IHC, where ≥1% was taken as positive.
PR status	Negative Positive	Based on the proportion of tumour cells showing nuclear staining for anti-PR antibody on IHC, where ≥1% was taken as positive.

Table 5 continued. Descriptions of Covariates

Covariate	Values	Description
HER2 status	Negative Positive	Based on membrane staining for the HER2 protein on IHC, where intense staining of >30% of tumour cells (3^+) was taken as positive; &/or HER2 gene amplification on FISH.
Treatment factors		
Breast surgery	Not received Received	Receipt or non-receipt of breast surgery (excision biopsy, wide local excision, or mastectomy) within 365 days of diagnosis, as recorded by the breast cancer registries.
Axillary surgery	Not received Received	Receipt or non-receipt of axillary surgery (SLNB, axillary lymph node sampling, or ALND) within 365 days of diagnosis, as recorded by the breast cancer registries.
Radiotherapy	Not received Received	Receipt or non-receipt of any dose of radiotherapy to the conserved breast, chest wall, &/or regional nodal basins within 365 days of diagnosis (for primary or neoadjuvant treatment) or 365 days of last date of surgery (for adjuvant treatment), as recorded by the breast cancer registries.
Chemotherapy	Not received Received	Receipt or non-receipt of at least 1 dose of systemic chemotherapy within 365 days of diagnosis (for primary or neoadjuvant treatment) or 365 days of last date of surgery (for adjuvant treatment), as recorded by the breast cancer registries.
HER2-directed therapy	Not received Received	Receipt or non-receipt of at least 1 dose of HER2-directed therapy within 365 days of diagnosis (for primary or neoadjuvant treatment) or 365 days of last date of surgery (for adjuvant treatment), as recorded by the breast cancer registries &/or Pharms DM.
Endocrine therapy	Not received Received	Receipt or non-receipt of at least 1 prescription for endocrine therapy (SERM, aromatase inhibitor, or LHRH analogue) within 5 years of diagnosis (for primary or neoadjuvant treatment) or 5 years of last date of surgery (for adjuvant treatment), as recorded by the breast cancer registries &/or Pharms DM; or, surgical or radiation ablation of the ovaries if pre/perimenopausal at diagnosis & performed within 2 years of diagnosis.
Year of diagnosis		
	2000 - 2015	Calendar year of date of histopathological diagnosis of breast cancer.

structure is used for coding ethnicity data in the health and disability sector. Four hierarchical levels are described, with individual ethnic groups differentiated into progressively broader categories according to "…geographic location or origin, or cultural similarities."[600(p3)]

Self-assigned ethnicity is recorded in the breast cancer registers using standard level 2 codes from the Ethnicity Data Protocols.[601] Prioritisation was used to assign a single ethnicity where more than 1 existed. The highest priority was given to Māori, followed by Pacific peoples, Asian, other ethnic groups, then European. Ethnicity was categorised for analysis using level 0 grouping as follows: European (Other European, European not further defined, and New Zealand European), Māori, Pacific peoples (Tokelauan, Fijian, Niuean, Tongan, Cook Island Māori, Samoan, Other Pacific Island, and Pacific Island not further defined), Asian (Southeast Asian, Indian, Chinese, Other Asian, and Asian not further defined), and *other* ethnic groups (Latin American/Hispanic, African, Middle Eastern, and other ethnicity) Ethnicity data was supplemented by information obtained from the NMDS, Pharms DM, and Mortality Collection. Where a discrepancy existed, an ***ever-Māori*** approach was used (and extended to all level 0 groupings), where the group with the highest prioritisation was taken as the final ethnicity.

4.7.2. Health Service Access Factors

4.7.2.1. Socioeconomic Deprivation

Socioeconomic deprivation status was determined using the New Zealand Index of Deprivation 2013 (NZDep2013), which combines 9 variables from the 2013 Census reflecting 8 dimensions of deprivation (communication, benefit and household income, employment, qualifications, home ownership, support, living space, and transport)[602] to assign a deprivation score to each meshblock.[603] The index is an ordinal scale which dividing the country into deciles; where a value of 1 represents the least deprived 10% while 10 characterises the most deprived 10%.[602]

Physical address at diagnosis was used to assign NZDep2013 scores to the cohort. Dwelling address is geocoded to domicile codes which are stored in the breast cancer registers. Missing data on domicile code was supplemented by information obtained from integration of the dataset with the NMDS, Pharms DM, and Mortality Collection. The domicile code table produced by the Ministry of Health was used to determine corresponding census area unit 2013 codes.[604] Population-weighted average NZDep2013 values were assigned at the level of area units (which are aggregations of meshblocks[605]) using New Zealand Atlas of Deprivation data tables.[606] Where a relevant area unit code was not included, a population-weighted average NZDep2013 score was derived using population counts from its component meshblocks.[602] To condense categories for analysis, NZDep2013 deciles were collapsed into quintiles, with quintile 1 denoting the least deprived 20% and quintile 5 the most deprived 20%.

4.7.2.2 Treatment Facility

Treatment facility was categorised as public or private based on the institution at which primary surgery was received. If surgery was not received, treatment facility was based on the outpatient setting at which consultation occurred.

4.7.2.3. Residential Status

Residential status was categorised in accordance with Statistics New Zealand's Urban/Rural Profile 2004 classification system, which depicts an urban/rural spectrum based upon the degree of urban influence.[607] Within this 7 level system, the usual residence and workplace addresses of the employed population within the area (from census data) are used as a proxy for proximity to, and dependence upon main urban areas. Main urban areas have a minimum population of 30 000 and are centred on a city or main urban centre. Satellite urban communities are urban areas where ≥20% of the usually resident employed population have an employment address within a main urban area, while independent urban communities are those where this is <20%. Rural areas are divided into categories with high, moderate, and low urban influence, with progressively increasing rural focus. Highly rural/remote areas have minimal dependence on urban areas in terms of employment, or a negligible employed population.

Domicile and census area unit 2001 codes were used to determine the corresponding Urban/Rural Profile Category,[608] which was categorised into 2 broad groups for analysis: urban (including main, satellite, and independent urban communities) and rural (including all rural and remote areas).

4.7.2.4. Geographic Region (Register)

The breast cancer registers include patients who received treatment at all public or private hospitals within their respective catchment areas. The Auckland region includes the Waitemata, Auckland and Counties Manukau DHBs (DHB codes: 021, 022, and 023), while the Waikato region includes Waikato DHB (code: 031). Treatment region was categorised as Auckland or Waikato, depending on the DHB at which treatment was received, and the subsequent register of record.

4.7.2.5. Mode of Detection

Mode of detection was classified as screen-detected or non-screen-detected, depending on whether the breast cancer was diagnosed by imaging (mammography, ultrasound, or MRI) in an asymptomatic woman (or a women with breast symptoms unrelated to the cancer), or following presentation with symptoms directly related to the breast cancer.

4.7.3. Cancer Factors

4.7.3.1. Stage at Diagnosis

Stage at diagnosis was categorised as I, II, or III in accordance with the AJCC TNM classification, 7th edition.[609] Pathological stage was used for the majority of patients (94.6% of those with observed stage information), with clinical stage used if an individual did not receive breast and/or axillary surgery (*n*=340), neoadjuvant therapy was given (*n*=349), or pathological stage was unknown (*n*=3). Clinical T stage was derived from radiological imaging or, if unavailable, from clinical examination. In cases of radiological discrepancy, the maximum dimension reported on MRI was used.[160] Where MRI was not performed; T stage was assigned according to the largest measurement from ultrasound or mammography. Missing clinical N stage was derived from a binary field *clinically suspicious nodes*, with cN0 (*n*=104) and cN1 (*n*=20)[⑫] assigned accordingly.

4.7.3.2. Grade

Cancers were categorised as grade 1, 2, or 3 as per the Nottingham combined histologic grading system.[163] Grade was determined from pathological examination of the surgical specimen/s or, where surgery was not performed, from core biopsy. The relevance of this 3 tiered grading system in the case of invasive lobular carcinomas has previously been a matter for debate,[3] leading to missing data for 13 patients during earlier years of the study. As it is now understood that the majority of classic invasive lobular carcinomas are grade 2, with pleomorphic lobular variants predominantly grade 3,[610] missing grade was assigned to these patients accordingly.

4.7.3.3. Histopathologic Type

Tumours were categorised as invasive carcinoma NST, lobular carcinoma, or *other* special subtype, as per the *WHO Classification of Tumours of the Breast*.[3] Carcinoma of mixed type, (comprising 10-49% nonspecialised pattern and another special type), microinvasive, and inflammatory carcinomas not otherwise specified were included with invasive carcinoma NST.[3] Lobular carcinoma encompassed classic and pleomorphic variants, signet ring lobular, tubulolobular, and mixed lobular/other carcinomas. Other special subtype included: adenoid cystic, cribriform, invasive micropapillary, medullary, metaplastic, mucinous, neuroendocrine, papillary, secretory, and tubular carcinomas, as well as adenomyoepithelioma with carcinoma, carcinoma with apocrine differentiation, and mixed other carcinoma not otherwise specified.

4.7.3.4. Focality/centricity

Tumours were classified as multifocal/multicentric or unifocal/unicentric based on histological examination of the surgical specimen/s, or, where surgery was not performed, from imaging.

[⑫] Accepting that some patients to be potentially under-staged with such an approach.

4.7.3.5. Biomarker Status

While the optimal method of molecular classification is by gene-expression profiling to distinguish intrinsic subtype, this was not possible in the current study, as very few of the cohort accessed such technology. It was also difficult to fully implement clinicopathological surrogate definitions,[579] as a lack of routine Ki-67 testing precluded differentiation of luminal A from luminal B disease. Biomarker status was therefore measured by 3 separate binary variables denoting ER, PR, and HER2 status. Testing was performed on tissue samples taken from the core biopsy or surgical specimen/s. In cases of discrepancy, status was taken as positive, due to the potential for false negative results owing to tumour heterogeneity or issues with tissue fixation.[173]

Hormone receptor status was derived from individual IHC assays of anti-ER and anti-PR antibodies. The lower cut-point for receptor positivity was taken as 1% positive staining of tumour nuclei.[173] For HER2 status, positivity was defined as intense membrane staining for the HER2 oncoprotein of >30% of invasive tumour cells (3^+) on IHC, and/or *ERBB2* gene amplification detected by fluorescence in situ hybridisation. Where a simplistic positive or negative result was reported in the absence of objective quantification, this was taken as the final status.

Missing biomarker status for 9 patients with mucinous carcinomas and 1 with tubular carcinoma was assigned ER/PR-positive and HER2-negative, as per the distinct expression features of these subtypes.[3] In accordance with PHARMAC criteria requiring HER2-positivity for the funding of trastuzumab[272]; 10 patients with missing HER2 status, and 8 apparently HER2-negative patients who received trastuzumab were reclassified as HER2-positive.

4.7.4. Treatment Factors

Six treatment modalities were evaluated: breast surgery, axillary surgery, radiotherapy, chemotherapy, HER2-directed therapy, and endocrine therapy. For each, treatment was dichotomised as received/not received, based on data obtained from the breast cancer registers and/or Pharms DM. Treatment given in primary, neoadjuvant, and adjuvant settings was included. Treatment was defined as per Section 4.6. Any treatment commenced after the diagnosis date of disease recurrence, or outside the reasonable time frames described was designated not received. Treatment was considered irrespective of a potentially inappropriate indication.[⑬]

4.7.5. Year of Diagnosis

Calendar year of the date histological diagnosis of breast cancer was made. Year of diagnosis was treated as a categorical variable (2000-2003, 2004-2007, 2008-2011, and 2012-2015) for descriptive analysis, and a continuous variable when included in propensity score models.

[⑬] For example, a documented record of endocrine therapy was classified as being received even if the tumour was hormone receptor-negative.

4.8. Treatment Effect Modifier: Comorbidity

A major aim of this thesis was to investigate how the survival impact of treatment may be altered by the presence of coexisting comorbidity. In this endeavour, comorbidity may be considered an effect-modifying (or moderating) variable. Comorbidity was measured by the C3 index, with its development and application discussed below.

4.8.1. Development and Validation of the C3 Index

Developed by Sarfati et al[32] in 2014, the C3 index is the only comorbidity index to have been developed and validated in New Zealand using national administrative data sources. Several steps were involved in the process of selecting relevant comorbid conditions for inclusion.[116] Initially, categories of conditions included in the most commonly used cancer-related comorbidity indices (the CCI,[88] ACE-27,[85] and Elixhauser[149] indices) were selected. Following expert review by cancer clinicians, additional relevant conditions considered influential to function or length of life in cancer patients were added. Conditions closely related to the primary cancer of interest (including potential metastatic sites) or its treatment were excluded, as were any acute/self-limiting or gender-specific conditions. This resulted in the identification of 50 condition categories which were then assigned relevant codes according to the ICD-10-AM system.[555]

The development cohort included 14 096 patients diagnosed with breast, colorectal, gynaecological, upper gastrointestinal, or urological cancers between 2006-2008, identified from the NZCR and linked via NHI with the NMDS and Mortality Collection.[116] All ICD-10-AM codes for primary and secondary diagnoses were recorded from any hospital admissions occurring within 5 years preceding cancer diagnosis, with identification of the 50 selected conditions. A prevalence threshold of ≥0.5% was applied, resulting in the selection of 42 conditions for ultimate inclusion.[32] Weighting coefficients were assigned to each condition according to their log HR for 1-year non-cancer mortality using age- and stage-adjusted Cox regression models. Total C3 score is obtained by summation of these weights. Indices were developed for the 5 cancer-specific sites, as well as all-sites-combined. Performance was then compared with the CCI and NCI in a validation cohort of 11 014 patients, with correlation coefficients ranging between 0.61-0.78.

4.8.2. Application of the C3 Index

The all-sites-combined index was selected for use in this thesis rather than the breast-specific index. This was due to the superior performance of the all-sites-combined index in the validation study, as well as the reduced number of conditions ultimately included in the breast-specific index due to the smaller sample size.[32⑭]

⑭ Within the smaller sample size of the breast cohort (*n*=4,059), only 33 of the 42 conditions met the 0.5% threshold to enable the derivation of an appropriately stable weight.

Following the C3 methodology, study participants were linked via their NHI with the NMDS to obtain ICD-10-AM codes for all diagnoses recorded from hospital admissions with a 5-year lookback period preceding the date of breast cancer diagnosis. From these codes the 42 C3 index conditions were identified and their weighting coefficients assigned using a SAS macro. If no admissions occurred within the 5 year lookback period, subjects were allocated a C3 score of 0.

The identified conditions were then used in various ways to assign comorbidity, depending on the study analysis. Comorbidity was assessed in relation to the 42 individual conditions, a count of these conditions, and as a summed weighted C3 index. Weighted C3 score was analysed on a continuous scale and as a categorical variable with 3 defined categories: ≤0, 0.1-2.00, and >2.00. Due to the right-skewed distribution of C3 scores within the cohort, these boundaries reflected a desire to include adequate numbers of participants within each category, whilst reflecting subgroups with zero, low, and high levels of comorbidity.

4.9. Outcome Variable: Mortality

Date and cause of death for deaths occurring up to the date of censoring (01/01/2018) was identified from the Mortality Collection database. Occurrence of death was also cross-referenced with data stored on the breast cancer registers. Participants without a record of death from either data source were assumed to be alive at the date of censoring. The ICD-10-AM code for underlying cause of death was used to classify deaths occurring up to 01/01/2015. Coding for deaths occurring after this date were not yet available and cause of death was therefore assigned based on free text information from medical certificates of death, following the WHO Rules and Guidelines for Mortality and Morbidity Coding.[101] Cause of death was classified as being due to breast cancer or not due to breast cancer, with the occurrence of either contributing to all-cause mortality. For 6 patients with pending coroner's reports, cause of death was classified as unknown. Subjects with unknown cause of death contributed to all-cause but not breast cancer-specific mortality.

4.10. Data Analysis

This section will discuss the actions taken to ensure the integrity of the data analyses. General statistical methods are presented here, with detail pertaining to the specific analyses of Studies 1-3 outlined in the results chapters to follow.

Statistical analyses were performed using Stata for Macintosh, Version 14.0[559] unless otherwise specified. Community-contributed programs were installed from the Boston College Statistical Software Components archive[611] and are referenced accordingly.

4.10.1. Descriptive Analysis

Descriptive statistics for study variables were computed using complete cases. Categorical variables are displayed as actual numbers and percentages. Continuous variables were largely nonparametric and are presented as medians and interquartile ranges (IQRs). Categorical variables were compared between groups using Fisher's exact tests or χ^2 tests where these failed to converge. Comparison of continuous variables was by Wilcoxon rank-sum tests. All tests of significance were 2-tailed. P<.05 was considered significant.

4.10.2. Missing Data

4.10.2.1. Missing Values Analysis

Each variable was evaluated for missing values. Overall, 13 independent variables were incomplete; affecting 3037 cases (23.7%) with at least 1 missing value. As a consequence of study design and assumptions, comorbidity and treatment receipt were completely observed. Age at diagnosis and mode of presentation were also complete. The majority of casewise missingness was driven by HER2 status, which was missing in 19.6% of cases. Additional variables with >1% unobserved values included: stage (4.07%), grade (2.77%), histopathologic type (1.01%), focality/centricity (1.25%), ER status (1.36%), and PR status (1.89%). Stage at diagnosis was derived from the individually collected component variables T and N stage, with both components required for the overall stage variable to be observed.

Missing data patterns were assessed by evaluating the distribution of observed and missing values within the multivariate dataset. Matrices summarising the frequencies of each pattern of missingness were examined, which revealed general (arbitrary) missing data patterns, with missing values dispersed throughout the dataset.[612] Missing data mechanisms were determined by examining for systematic differences between missing and observed values. Reasons for missing data are often classified as per Little and Rubin's framework[613] as missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). For each analysis, missing data was tested for MCAR using Little's χ^2 test of MCAR[614] via the `mcartest` command.[615] As Little's test statistic was significant for almost all study analyses, the data could not be assumed MCAR. Using binary indicator variables denoting missingness, differences in the distributions of other study variables were then assessed using a series of Fisher's exact and Wilcoxon rank-sum tests, with listwise deletion. Significant predictors of missingness were identified for every incomplete variable, indicating that MAR was a reasonable assumption.

4.10.2.2. Multiple Imputation

Given that the data could not be proven MCAR, statistical procedures based on completely observed individuals were inappropriate.[616] As MAR was considered plausible, a data imputation

procedure could be justified. Multiple imputation involves creating multiple copies of the dataset (*m*), replacing missing values in each copy with different *imputed* values sampled from their posterior predictive distribution, using a Bayesian framework based on the observed data (imputation phase). Each complete dataset is then analysed using standard statistical methods (analysis phase). Finally, the parameter estimates obtained from each analysed dataset are combined to yield a single estimate of the parameter for inference (pooling phase). Standard errors are calculated using Rubin's combination rules, which take into account variability within and between imputed datasets, reflecting the uncertainty in the estimate due to missing data.[617]

Imputation models were created for each planned analysis. All covariates and outcome variables destined for inclusion in the final analysis model were included. For time to event analyses, event indicator variables and Nelson-Aalen estimators of the cumulative baseline hazard $H(T)$ (as an approximation of the cumulative baseline hazard $H_0(T)$) were also included[618] (Resche-Rignon, White, & Chevret, 2012, cited by Bartlett & Taylor[619]). Splined terms and interactions were constructed passively post-imputation, using an *impute then transform* approach.[620,621] For simplicity, and to avoid issues with multicollinearity and non-convergence, stage was derived from its individual components and imputed directly.[622] Auxiliary variables were also included. An auxiliary variable is ancillary to the substantive analysis model itself, but is a correlate of an incomplete variable, or of its missingness mechanism.[623] A data-driven but inclusive approach to selection was adopted,[624] with potential variables screened based on their correlation with incomplete variables or their missing value indicators using a threshold for inclusion of $r>0.15$.[625]

Multiple imputation was performed using chained equations.[625,626] Unlike multiple imputation using multivariate normal distribution[623] (another common imputation algorithm), chained equations allows separate conditional distributions for each imputed variable. Binomial logistic regression was used to impute the binary variables of treatment facility, residential status, ER, PR, and HER2 status; multinomial logistic regression was used for the imputation of ethnicity and histopathologic type; while ordered logistic regression was used for categorical variables with ordinal sequence (NZDep2013, stage, and grade). Augmented regression was performed in the presence of perfect prediction.[627] Forty imputed datasets were produced, based on an assessment of relative efficiency[617,623] and Monte Carlo errors[628] of estimates from final analysis models. Imputation model fit was checked by examining cross-tabulations and histograms comparing observed and imputed values for incomplete variables across the imputed datasets.[629]

The estimation package `mim2`[630] was used where the required analytic model was not compatible with standard Stata commands. Where predictions were not directly obtainable from models fit to imputed data (such as point estimates from splined terms), separate predictions were obtained from models fit to each of the *m* datasets and manually combined using Rubin's standard formulae.[617] Normalising logarithmic transformations were applied prior to the combination of risk ratios (RRs), followed by back-transformation to the original scale prior to presentation.[631]

4.10.3. Regression Modelling

4.10.3.2. Modelling Strategy

An explanatory modelling strategy was employed, whereby the statistical model aimed to capture the underlying theoretical causal model, analysing the exposure-outcome relationship with consideration of potential confounding, mediating, and effect-modifying factors.[632] Identification of these factors was grounded in the hypothesised conceptual framework, based on subject matter knowledge from literature review and exploratory data analysis. Direct acyclic graphs were used to plot the assumed causal relationships to be investigated.[633] These are causal diagrams in which the direction of arrows indicates the assumed causal relationships. The software DAGitty, Version 2.3[634] was used as a graphical tool to identify minimal sufficient covariate adjustment sets.

Confounding occurs when an extraneous factor, which is a common cause of both the exposure and outcome and not on the intervening causal pathway, creates a spurious association, leading to an under- or overestimation of the exposure effect.[635,636] Variables identified a priori as potential confounders were entered into univariate and multivariate models with full adjustment.

A mediating variable is one which acts as an intermediary on the pathway between an exposure and outcome.[637] It partially or fully explains the total effect of the causal path. As only the total effect of exposure variables was desired in this thesis, formal mediation analysis was not performed.

Effect-measure modification (or heterogeneity of effect) has been described as "…departure from additivity of effects on the chosen outcome scale."[636(p95)] It is distinct from confounding and occurs when the magnitude of the effect of the exposure on the outcome differs depending on the level of a third variable. The presence of effect modification was assessed by evaluating statistical interaction. When bias is controlled (ie, there is adjustment for confounders), statistical interaction is logically equivalent to effect-measure modification.[636] Variables identified as potential effect-modifiers were entered into models as both main effects and interaction (product) terms with the exposure variable of interest. Wald tests of interaction were performed with p values <.05 indicative of effect modification.

Diagnostic procedures were performed on final multivariate models. Poisson model misspecification was assessed using Pearson and Deviance goodness-of-fit tests and link tests. Multicollinearity was evaluated by computing variance inflation factors, with variables considered for exclusion if these exceeded 5. Outliers and over-influential observations were identified from Pearson and Deviance residuals. Where events per variable numbered <10, estimates were withheld, due to the increase in bias and unreliability in confidence intervals which may occur under such circumstances.[638]

4.10.3.1. Relative Risk Regression

Binary outcomes in epidemiological studies are commonly analysed using logistic regression to estimate ORs.[639] However several criticisms of ORs in non-case control studies have been made, including its difficulty in interpretation, non-collapsibility across categorical strata, and misappropriation as an estimate of the RR.[639-641] Many argue that RRs provide a more useful summary of associations.

As a first approach to multivariate estimation of RRs, the log-binomial generalised linear model were attempted, a cousin to the logistic model which uses a log rather than logit link function between the predictors and outcome.[642] However, as is not uncommon due to parameter constraints which prevent unrealistic probabilities, failure of model convergence meant an alternative method was required. As such, modified Poisson regression with robust sandwich SE estimates[643-645] was selected, which is a popular approximation to log binomial estimates.[642] While Poisson regression is typically concerned with modelling count data, its estimating equations are also unbiased when the outcome is binary.[642] However, due to over-dispersion of the variance, the standard Poisson model gives SEs which are too large.[643] This error can be removed by using robust SE estimates, the so-called *modified Poisson approach*.[644,645]

4.10.3.3. Modelling Nonlinear Relationships

An important consideration in regression modelling is the assumption of linearity, where the outcome variable is a linear combination of the predictor variables. This was assessed by performing Box-Tidwell power transformation modelling,[646,647] Wald hypothesis tests for linearity using the postestimation `nlcheck` command,[648] and likelihood ratio tests comparing models with and without splines. For time to event analyses, the functional form of the relationship between continuous predictors and survival time was also evaluated with lowess plots of Martingale residuals. As nonlinearity was not infrequent, a nonlinear modelling approach was required.

In order to retain the advantages of continuous variables,[649] flexibly model, and visually display the shape of associations, spline regression using restricted cubic splines was conducted. In spline regression, the range of values is subdivided into intervals over a set of knots, with *piecewise* regression curves fit between each knot. With cubic splines, cubic polynomials are used, which enable the individual curves to meet smoothly at each knot.[649] Restricted cubic splines (RCSs) impose an additional constraint of linearity in the tails beyond the first and last knot, ensuring a more realistic relationship at the extremes of data where observations may be sparse and reducing the degrees of freedom in the model.[650] The degree of smoothing is determined by the number of knots. Simple 3 knot spline functions are preferable when adjusting for confounders, since they are more parsimonious and remove the majority of residual confounding.[651,652] While a higher-dimensional spline function may be more precise for explanatory analyses involving the primary exposure variable,[652] exploratory analyses using C3

score revealed no advantage in model fit (using serial comparison of Akaike information criterion [AIC] values[652]) beyond 3 knots.

Where nonlinearity was detected, RCS functions were created using 3 knots at locations assigned according to Durrleman and Simon[653] at the default percentiles of 5, 50, and 95. In analyses involving the entire cohort, for age, this corresponded to knot placements at 38, 57, and 84 years. Due to the right-skewed distribution of C3 scores, use of standard percentiles was not possible due to the first and second consecutive knots being of equal value (0). Following an iterative process involving examination of plots of estimates, knots were placed over the range of maximum expected change, at values of 0, 0.1 (approximately the 80th percentile), and 2.8 (95th percentile).[650,652] As splines do not provide easily interpretable raw parameters, point estimates for predictions at values of interest were calculated using the `xblc` postestimation command,[654] with other covariates fixed at their reference category (Ref) or median value (for continuous variables). For C3, these estimates were calculated with reference to a score of 0, while for age, the median value was selected. Graphs modelling the relationship between outcomes and C3 spline functions were plotted. The range of reported estimates and plotted values was limited between the 1st and 99th centiles. Graphs were created using complete cases and checked within individual imputed datasets. As these were similar, only graphs from complete case analysis are presented.

4.10.4. Time to Event Analysis

4.10.4.1. Cox Proportional Hazards Regression

Univariate and multivariate associations between covariates and survival time were assessed using Cox proportional hazards models,[655] producing HRs. Date of breast cancer diagnosis was used as the time of entry. Failure events included all-cause and breast cancer-specific mortality. For cause-specific survival, subjects dying from a competing cause of death were censored at their date of death. Individuals who remained alive at the conclusion of study follow-up were censored as of 01/01/2018. The Breslow method for handling tied failure events was employed due to the low average number of ties,[656] with sensitivity analyses using exact methods and the Efron approximation yielding near identical results.

The semi-parametric Cox model relies on a fundamental assumption; the proportionality of hazards, which implies that covariates have a constant impact on the hazard of the outcome event over time.[657] Departure from proportionality was evaluated for each covariate in fully adjusted models by visually inspecting smoothed plots of Shoenfeld residuals against time and formally testing for evidence of a nonzero slope. Additional confirmatory testing was performed by assessing the significance of time-by-covariate interactions added to the model. Where possible, major departures from proportionality were dealt with through stratification, where the analysis

was stratified by the time dependent covariate. When such a covariate was of substantive interest to the analysis, a second method was employed; whereby the time axis was partitioned at the median event time, creating 2 subsets of data, with different Cox models fit to each time period.[657] In general, a reduced or nonsignificant effect size was observed in the later time subset, likely due to the smaller number of individuals remaining in the split analysis with a consequent reduction in power. However, as none of the estimates in the earlier time subset were substantially different from the initial models, and no strong theoretical time interactions were supposed, original HRs are presented, representing an average effect over the total time.[656]

4.10.4.2. Competing Risks Regression

Competing risks are encountered when an individual can potentially fail from 2 or more mutually exclusive event types, with the occurrence of one precluding the other. In this instance, if the event of interest is breast cancer mortality, death from other causes serves as a competing event. In order to negate the risk of selection bias due to informative censoring,[658] competing risks methodology was also employed to evaluate mortality due to breast cancer. Cumulative incidence functions estimating the marginal probabilities of each competing event (breast cancer-specific and non-breast cancer-specific death) were modelled using Fine and Gray competing risks regression, producing subdistribution hazard ratios (sHRs) and cumulative incidence function curves for breast cancer mortality.[659]

4.10.5. Propensity Score Analysis

4.10.5.1. The Counterfactual Framework

Of fundamental interest to the estimation of causal effects is the notion of *potential outcomes*, formalised as the *Neyman-Rubin counterfactual framework of causality*.[660,661] Under this framework, for any given subject *i*, there are 2 potential outcomes; $Y_i(1)$ under treatment and $Y_i(0)$ under control. Depending on whether the treatment or control is received, only 1 outcome can be observed, with the unobserved outcome termed the counterfactual. To overcome this *fundamental problem of causal inference,*[662] investigations typically focus on the average treatment effect (ATE) ($E[Y_i(1) - Y_i(0)]$; which is the average effect, at the population level, of moving an entire population from untreated to treated.[663] A related measure is the average treatment effect on the treated (ATT) ($E[Y_i(1) - Y_i(0) \mid Z_i=1]$, where Z denotes the treatment received; Z=0 for control vs Z=1 for treatment); which is the average treatment effect in a population with a covariate distribution similar to that of the group who ultimately received the treatment.[663] In randomised experiments, the 2 measures of treatment effect coincide, and ATEs can be directly computed from the study data. This does not hold in observational designs, where systematic differences between treatment groups may result in *confounding by indication,* thus an unbiased estimate of the ATE cannot be obtained by a direct comparison of outcomes.[664]

4.8.5.2. Propensity Score Estimation

Propensity score analysis, as formalised by Rosenbaum and Rubin,[665] is a class of statistical methods which enable the counterfactual framework to be extended to observational studies, mimicking the design of a randomised trial. By definition, the propensity score *e* for a study participant *i*, is the conditional probability of assignment to the treatment of interest (Z = 1) (vs non-treatment; Z = 0), given their observed baseline characteristics (X)[665]:

$$e(X_i) = \Pr(Z_i = 1 \mid X_i)$$

Guo and Fraser conceptualise the propensity score as "…a balancing score representing a vector of covariates."[666(p130)] Treated and non-treated subjects sharing a similar propensity score are viewed as comparable, even though they may differ on values of specific covariates. This property means that, conditional on the propensity score, each participant has the same probability of treatment, as in a randomised experiment. This is a key component of the *strongly ignorable treatment assignment assumption*,[665] otherwise known as *exchangeability*. The second condition of this assumption is that of *positivity* (*common support*), where there is a positive probability of receiving treatment for all values of X. If treatment assignment is strongly ignorable, then conditioning on the propensity score will enable unbiased estimation of ATEs.

In order to meet the requirements of strongly ignorable treatment assignment, all variables known to relate to both treatment and outcome were included in propensity score models.[667-669] While several methods of predicting propensity scores exist,[664,666] the prevailing approach; multivariable logistic regression, was used in this thesis. Missing data in the vector of covariates contributing to the propensity score was dealt with by multiple imputation. Two main approaches to multiple imputation in combination with propensity score methods have been described. Following the imputation of covariates and estimation of the propensity score model; (1) propensity scores for an individual may be combined across imputed datasets and the average score used to estimate a single treatment effect; or (2) treatment effects may be estimated within each imputed dataset and the results combined using Rubin's rules. Mitra and Reiter,[670] refer to these methods as the *across* and *within* approaches respectively. In this study, a within approach was used, as it has been shown that this results in the least amount of selection and confounding biases,[671,672] particularly in the context of inverse probability of treatment (IPT) weighting.[672]

4.10.5.3. Propensity Score Implementation

Several different techniques may be used to control for propensity scores; including regression, matching, or stratification on the propensity score,[665] or weighting (standardisation).[673] The choice of method depends upon the ability to achieve balance between treatment groups, the desired measure of treatment effect, and the outcome model. In time to event analysis, unbiased estimates of marginal HRs have been reported with the use of matching and weighting (using IPT-weights),[674,675] with weighted analyses resulting in estimates with the best precision.[675]

Propensity score weighting creates a *pseudo-population,* where the distribution of baseline covariates is independent of treatment assignment (a property expected under randomisation). A differential amount of information is taken from each participant depending on their conditional probability of receiving treatment. Two types of weighting may be used: IPT and standardised mortality ratio (SMR) weights (otherwise known as weighting by the odds). Weighting by the IPT results in estimates generalisable to the entire analysis population; enabling estimation of the ATE. With IPT-weighting, each subject is given a weight *w* proportional to the inverse of their probability of receiving treatment[673,676]:

$$w_i = \frac{Z_i}{e_i} + \frac{(1 - Z_i)}{1 - e_i}$$

When the estimand of interest is the ATT, SMR-weights[677] are used, where treated patients are given a weight of 1 while control patients receive weights defined as the ratio of the estimated propensity score to 1 minus the propensity score (essentially reweighting controls to be representative of the treated population)[673]:

$$w_i = Z_i + (1 - Z_i)\frac{e_i}{1 - e_i}$$

For treated subjects with a very low probability of treatment (or control subjects with a high probability of treatment), weights may be large and influential, resulting in imprecise and possibly biased estimates of the treatment effect.[678-680] To address this, the use of stabilising weights has been proposed, standardising the previously defined weights by the marginal probability of treatment.[681] Stabilised weights are thus:

$$sw_i = \frac{Z_i \Pr(Z = 1)}{e_i}$$

for treated participants and:

$$sw_i = \frac{(1 - Z_i) \Pr(Z = 0)}{1 - e_i}$$

for controls, where Pr(*Z*=1) and Pr(*Z*=0) denote the marginal probabilities of treatment and control. In addition,[682,683] weight trimming (truncation) may be employed, where outlying weights outside some pre-specified centile w_0 are fixed as $w_{0.}$[680] In the setting of logistic regression-estimated weights, trimming reduces bias and variability of the estimated treatment effects.[684]

The resulting covariate balance in the observed and imputed, trimmed, weighted samples between treatment groups was assessed by computing standardised differences in covariate means. Standardised differences compare the proportional differences in treated and untreated means for each covariate, in units of the pooled SD.[664] Their use in examining balance is recommended over hypothesis-based tests of statistical significance, which are influenced by sample size and do not quantify the magnitude of difference.[664,685]

Survival models were then estimated within IPT- and SMR-weighted samples to obtain estimates of the ATE and ATT respectively. Robust variance estimators were applied to account for uncertainty due to the estimation of propensity scores and treatment effects in separate steps.[686,687]

4.11. Sample Size Estimation

Sample size calculations were performed for each of the planned treatment effects analyses in Study 3 using Stata's `power logrank` command. Sample size analysis was based upon a 2-sample comparison of survivor functions using the log-rank test (Freedman method[688]). Calculations are presented with respect to the primary outcome variable; all-cause survival. Where possible, the expected effect size was based on the absolute difference in 5-year probability of all-cause survival by treatment status from relevant EBCTCG Overviews. From this, the expected HR was derived as the ratio of:

$$\ln(S_1) / \ln(S_2)$$

where S_1 is the survival probability in the untreated group and S_2 is the survival probability in the treated group. Group ratios were expected to differ by treatment modality and are based on the key performance indicator (KPI) thresholds from the Breast Surgeons of Australia and New Zealand (BreastSurgANZ) Quality Audit.[689] Primary calculations were performed assuming a 2-sided significance level of α=.05 with 80% power, although simulations assuming different levels of power were also explored (**Figure 8**).

Estimations were based on a standard randomised controlled trial design, although the planned use of an observational design with propensity score methods added an additional level of complexity. To meet the positivity component of the strongly ignorable treatment assignment assumption, observations outside common support are discarded from the analysis, thus the final sample size is unknown until after the propensity score has been constructed and balanced. In order to account for this, an expected withdrawal rate of 5% was applied.

Given the intended use of interaction and subgroup analysis to investigate heterogeneity in treatment effects by comorbidity, the estimated sample sizes were required within each comorbidity subgroup. Further adjustment was also required due to the generally low power of interaction tests to detect true differences in effect.[690] Sample sizes were therefore inflated by a factor of 4, in order to detect interaction effects with the same power (ie, 80%) as the overall treatment effect.[690,691]

The following will outline the assumptions applied to the sample size calculations for each of the treatment effects analyses, with a summary of the estimated required unadjusted and adjusted sample sizes provided in **Table 6**.

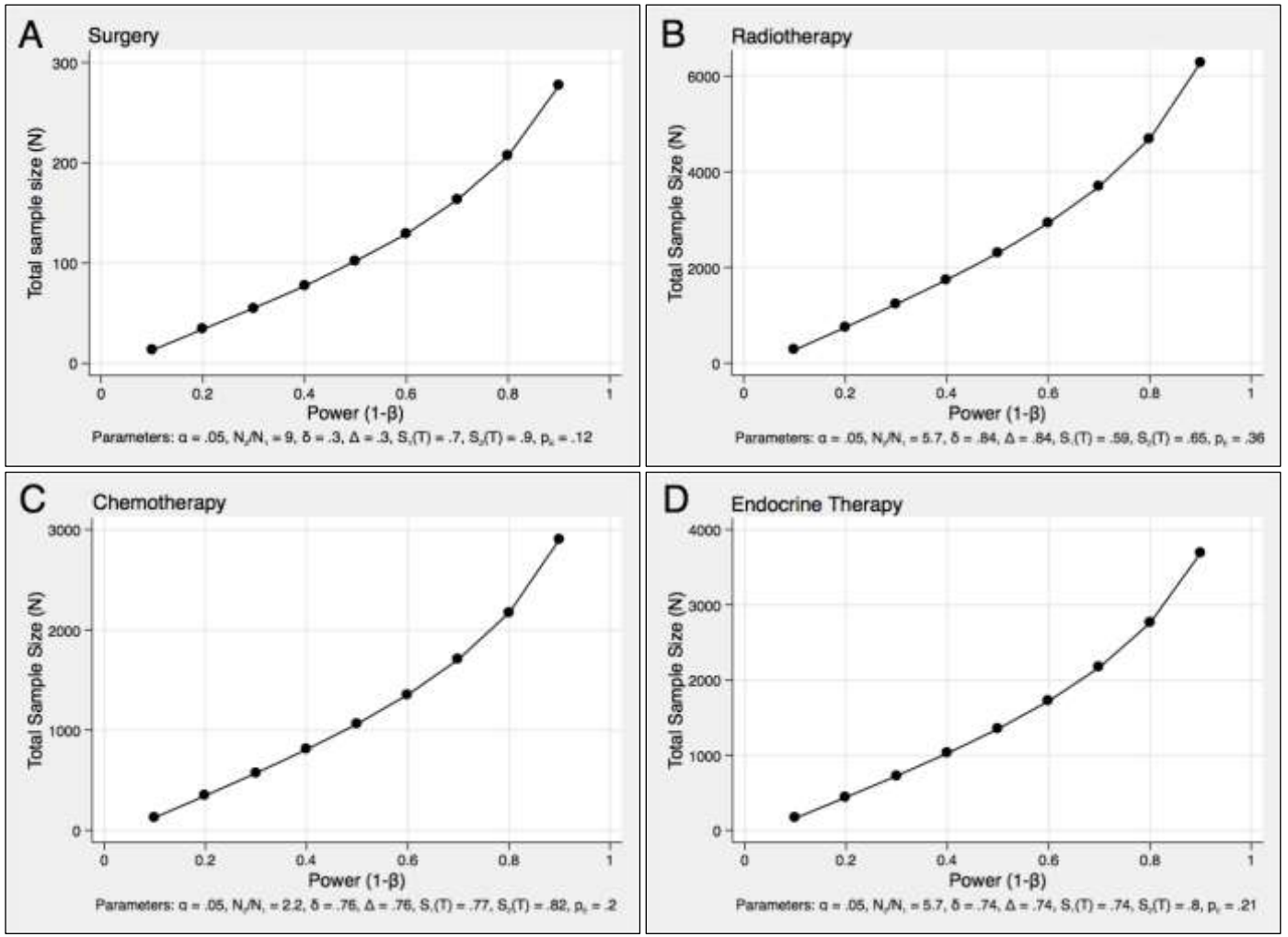


Figure 8. Power Simulations for Treatment Effects Analyses

Abbreviations: N_2/N_1, treatment/no treatment group ratio; p_E, overall probability of death event; $S_1(T)$, survival probability in the no treatment group; $S_2(T)$, survival probability in the treatment group; α, significance level; β, probability of type II error; δ effect size; Δ HR.

Table 6. Estimated Sample Sizes Required for Treatment Effects Analyses

Treatment	Outcome	Expected Survival Probability		Expected Effect Size		Group Ratio	Required Sample Size (N_2:N_1)[a]		
		S_1 Treatment	S_2 No Treatment	Survival Difference[b]	HR		Unadjusted	+ 5% Withdrawal[c]	+ 4x Inflation Factor[d]
Surgery	5-year all-cause survival	89.7%	70.0%	19.7%	0.30	9.00	207 (186:21)	217 (195:22)	868 (781:87)
Radiotherapy	15-year all-cause survival	64.8%	59.5%	5.30%	0.84	5.67	4,689 (3986:703)	4923 (4186:737)	19 692 (16 738:2954)
Chemotherapy	5-year all-cause survival	82.0%	76.9%	5.10%	0.76	2.23	2,169 (1497:672)	2277 (1571:706)	9108 (6285:2823)
Endocrine	5-year all-cause survival	80.1%	74.2%	5.90%	0.74	5.67	2,758 (2344:414)	2896 (2462:434)	11 584 (9846:1738)

[a] N_2:N_1 is the required sample size ratio for treatment vs no treatment groups.
[b] Absolute difference in survival probability.
[c] 5% withdrawal rate for loss to off-support.
[d] 4-fold inflation factor to detect interaction.

Breast and Axillary Surgery

Given the well-established role of surgery in the treatment of non-metastatic breast cancer, the survival benefit of surgery versus no surgery has not been explicitly examined by the EBCTCG. Observational studies which examine the survival impact of untreated disease can however shed some light on this. Older series of patients with untreated breast cancer report 5-year survival rates between 16-22% (although it should be noted that this includes patients presenting with metastatic disease).[692] A more recent Canadian study found that amongst 87 women aged ≤75 years with non-metastatic breast cancer who refused all recommended standard treatments, the 5-year all-cause survival was 43.2%.[693] Given the present study requires the receipt of both breast and axillary surgery to be considered concordant, and that non-concordant patients are likely to have received some form of additional treatment (particularly endocrine therapy), a more optimistic 5-year all-cause survival estimate of 70% was assumed. An estimated survival gain of approximately 20% with the addition of surgery was therefore expected, using as reference the 5-year overall survival estimate of 89.7% from the SEER Cancer Statistics Review 1975-2015.[153] Thus the anticipated treatment effect of surgery was a 70% proportional reduction in the hazard of overall death (HR=0.30). Based on the BreastSurgANZ KPI for the proportion of invasive cases undergoing axillary surgery, 90% of the sample were expected to receive surgical treatment (group ratio 9.00).[689] Under these assumptions, the required sample size for this analysis was therefore 186 in the surgery group and 21 in the no surgery group (total sample 207). Allowing for withdrawal due to off-support, plus inflation for the detection of interaction, an adjusted sample size of 868 (781:87) was required.

Adjuvant Radiotherapy

From the 2005 EBCTCG Overview, the addition of radiotherapy resulted in minimal gains in 5-year all-cause survival (1.00% following BCS, 1.90% following mastectomy). Basing the sample size calculation on such a small expected effect resulted in an unfeasible number of required participants (>30 000) in relation to the number recorded in the combined breast cancer registers. As such, the sample size calculation for the radiotherapy analysis was based on the expected absolute difference in survival at 15 years. Unfortunately, an overall estimate of all-cause survival due to radiotherapy is not available from the EBCTCG, with outcomes stratified by type of surgery. As the majority of patients received radiotherapy following BCS, the expected survival post-BCS was applied to the sample size calculations in this analysis. Ergo, a 5.3% absolute difference in all-cause survival (64.8% vs 59.5%) was expected, corresponding to an anticipated treatment effect of HR=0.84.[208] In accordance with the BreastSurgANZ KPI targets for invasive cancers referred for radiotherapy after BCS, and high risk invasive cancers referred for radiotherapy post-mastectomy, 85% of the sample were expected to receive radiotherapy.[689] The required sample size for the radiotherapy analysis was therefore calculated as 3986 in the radiotherapy group and 703 in the no radiotherapy group (total sample size 4689), with adjusted estimated sample size of 19 692 (16 738:2954).

Adjuvant Chemotherapy

From the 2012 EBCTCG Overview comparing outcomes from any anthracycline-based chemotherapy regime versus no chemotherapy, a 5.1% absolute difference in 5-year all-cause mortality was expected (23.1% vs 18.0%), with the estimated treatment effect HR=0.76.[248] While the BreastSurgANZ KPI stipulates that 90% of high risk cases should be referred for chemotherapy,[689] a recent study using Waikato registry data found that only 69% of women meeting eligibility criteria for chemotherapy actually received treatment.[524] Using a group ratio of 2.23 based on this Waikato study, the required sample size for the chemotherapy analysis was 1497 in the chemotherapy group and 672 in the no chemotherapy group (total sample 2169), with an adjusted estimated sample size of 9108 (6285:2823).

Endocrine Therapy

Based on the 1998 EBCTCG Overview comparing 5 years of tamoxifen versus no tamoxifen in node-positive[⑮] women with ER-positive disease, a 5.9% absolute difference in 5-year all-cause mortality was expected, with the corresponding treatment effect HR=0.74.[275] According to the BreastSurgANZ KPI, 85% of invasive ER-positive cancers should be referred for endocrine therapy.[689] The required sample size for the endocrine therapy analysis was therefore 2344 in the endocrine therapy group and 414 in the no endocrine therapy group (total sample 2758), with an adjusted estimated sample size of 11 584 (9846:1738).

[⑮] Mortality outcomes were subdivided by nodal status. Assuming an effect size based on node-negative participants (91.8% vs 88.3% all-cause 5-year survival, absolute gain 3.5%) an estimated unadjusted sample size of 3902 (3317:585) would be required.

Chapter 5. Study 1

The Burden of Comorbidity amongst Patients with Breast Cancer

5.1. Introduction

This is the first of 3 chapters detailing the studies of this thesis. In Chapter 5, Study 1 is presented, which broadly aims to determine the burden of coexistent comorbidity amongst patients with breast cancer. Baseline characteristics of the study cohort are described, along with prevalence estimates for individual comorbid conditions and the distribution of comorbidity severity. The survival impacts of individual conditions and overall comorbidity burden are investigated. Baseline sociodemographic factors associated with the presence and severity of comorbidity in this cohort are explored in a nested cross-sectional study.

5.1.1. Aims

Study 1 focuses on the second research objective:

- To describe the burden of comorbidity in a diverse population of New Zealand women with primary breast cancer and factors associated with its presence.

The aims specific to Study 1 were:

1. To estimate the prevalence of comorbid conditions and the distribution of comorbidity severity in a cohort of New Zealand women with primary breast cancer.
2. To determine the age (and stage) -adjusted survival impacts of individual comorbid conditions and overall comorbidity burden within this cohort.
3. To evaluate sociodemographic factors associated with the presence of comorbidity and burden of comorbidity severity.

5.2. Methods

5.2.1. Variables

Study 1 is comprised of multiple sections of results targeted toward the specific study aims. Following on from Section 1 which provides a description of the study cohort, Section 2 evaluates the prevalence of the 42 individual comorbid conditions making up the C3 index. The distribution of comorbidity as an overall measure is also described, using C3 index score as a continuous, ordinal, and categorical variable.

In the third section, the survival impacts of the individual C3 conditions and overall comorbidity burden are examined, using breast cancer-specific and all-cause death as outcome variables. Age and stage at diagnosis were considered the most important confounders of the relationship between comorbidity and mortality, and therefore required adjustment both sets of analyses.

The fourth section evaluates the associations between baseline sociodemographic factors and the presence and severity of comorbidity at breast cancer diagnosis. Exposure variables were selected based on their presumed relationships with comorbidity from literature review (**Appendix A**, **Figure 33a**). Minority ethnicity, advancing age, and socioeconomic deprivation were thought to be strongly linked with comorbidity. A component of the impact of ethnicity is likely to be mediated through deprivation. Treatment facility and NZDep2013 were considered proxy variables for deprivation. While demographic differences were thought to explain any potential association between geographic region and comorbidity, an independent effect could not be discounted. Residential status (rurality) may also be associated with comorbidity, although the direction of this is unclear. Comorbidity was evaluated in 2 ways. Firstly, comorbidity was dichotomised, differentiating patients with at least 1 of the 42 C3 index conditions from those with none. Secondly, comorbidity was treated as a count, modelling the number of C3 conditions present.

5.2.2. Data Analysis

5.2.2.1. Description of the Study Cohort and Prevalence of Comorbidity

Baseline characteristics of the study cohort and prevalence of comorbid conditions are presented using descriptive statistics. Direct age-standardisation of crude proportions was performed using the WHO World Population Standard (2000-2025),[694] yielding age-adjusted prevalence estimates.

5.2.4.2. Impact of Comorbidity on Mortality

The associations between the C3 conditions and breast cancer-specific and all-cause mortality were assessed in Cox models. The mortality impact of overall comorbidity burden was analysed by C3 category and continuous C3 score. Initial crude HRs were estimated, followed by models controlling for age and stage. Stage information was missing for 4.07% of the cohort, with the probability of its missingness related to age and comorbidity (Wilcoxon rank-sum tests p<.001, Little's χ^2 test of MCAR p<.001). For simplicity, missing stage was treated as a separate category; given it was the only covariate with missing data, and of no substantive interest itself. Proportionality was violated for stage in the breast cancer models, and age plus stage in the all-cause models. Stratified regression was therefore performed, stratifying by stage in the breast cancer mortality models, and age category plus stage in the all-cause mortality models. Proportionality was also violated for paralysis and urinary tract disorder in the all-cause mortality models, thus the effect estimate presented is an average over the total study time.

5.2.4.3. Factors Associated with the Presence of Comorbidity

The associations between exposure variables and binary comorbidity were modelled using univariate and multivariate modified Poisson regression to obtain crude and adjusted prevalence risk ratios (PRRs). Comorbidity was then modelled as a count variable using zero-inflated negative binomial regression. While the most common distribution for counts is Poisson, in this dataset, over-dispersion was present; resulting in a variance larger than the mean thereby contraindicating the use of standard Poisson regression.[695] Over-dispersion in this case was due to the heavily right-skewed count distribution, with a high frequency of zeros. This was influenced by 1 of 2 processes: firstly, a participant may have had a hospital admission within the 5-year lookback period but had no relevant coded comorbidity; or secondly, no hospital admission occurred within the lookback period, and a zero score was assigned accordingly.

Zero-inflated models are a class of regression methods which model the excess number of zeros in the outcome variable by fitting a mixture model.[696] The first component of the model examines whether the outcome event ever occurred using logistic regression, producing ORs. The second examines how frequently an event occurred, through either Poisson or negative binomial regression, producing PRRs. The fit of various potential count models was compared using likelihood ratio tests, differences in AIC, and differences between observed and predicted count probabilities using the program `countfit`.[697] This confirmed the zero-inflated negative binomial model as providing the best fit to the data. Univariate and multivariate analytic models were estimated from the imputed datasets using the `mim2` package.[630] Exposure variables were the same in both components of the model. Age was incorporated as a categorical variable, due to nonlinearity in its relationship with condition count.

5.3. Results

5.3.1. Description of the Study Cohort

A total of 12 834 patients were eligible for inclusion in the study cohort. **Table 7** shows the crude and age-standardised proportions of study participants by baseline characteristics, treatments received, and disease outcomes. A wide age distribution was observed within the study cohort, with a median age of 57 years (IQR 19, range 21-104) and the majority of patients postmenopausal (62.5%). Europeans constituted the ethnic majority (age-standardised prevalence 60.2%), with Māori and Pacific peoples comprising 16.5% and 8.39% of the cohort respectively. The Auckland register contributed over three-quarters of participants to the study. The majority of patients lived in an urban setting (92.9%) and nearly two-thirds received treatment in the public sector. The distribution of NZDep2013 quintile scores was roughly equivalent. Fewer cancers were detected through screening (40.8%) than following a symptomatic presentation.

Table 7. Characteristics of the Study Population: Crude and Age-standardised Proportions

Characteristic	*n*	Crude%	Age-Standardised%
Age at diagnosis, years			
≤49	3636	28.3	
50-59	3517	27.4	
60-69	3027	23.6	
≥70	2654	20.7	
Median (IQR) [range]	57	(19)	[21-104]
Ethnicity			
European	8641	67.3	60.2
Māori	1377	10.7	16.5
Pacific peoples	912	7.11	8.39
Asian	1055	8.22	8.65
Other ethnic groups	750	5.84	5.71
Missing	99	0.77	0.55
Treatment facility			
Public	8019	62.5	65.9
Private	4807	37.5	34.0
Missing	8	0.06	0.07
NZDep2013, quintile			
1	2857	22.3	18.0
2	2381	18.6	18.2
3	2494	19.4	23.3
4	2342	18.2	18.9
5	2722	21.2	21.0
Missing	38	0.30	0.52
Residential status			
Urban	11 921	92.9	92.8
Rural	900	7.01	7.12
Missing	13	0.10	0.11
Region			
Auckland	10 083	78.6	76.8
Waikato	2751	21.4	23.2
Mode of detection			
Screen-detected	5241	40.8	22.1
Non-screen-detected	7593	59.2	77.9
Stage			
I	5637	43.9	36.3
II	4723	36.8	42.4
III	1952	15.2	19.4
Missing	522	4.07	1.77
Grade			
1	3078	24.0	16.7
2	5864	45.7	40.2
3	3537	27.6	41.4
Missing	355	2.77	1.70
Histopathological type			
Invasive carcinoma NST	10 490	81.7	88.4
Lobular	1465	11.4	6.69
Other	750	5.84	4.44
Missing	129	1.01	0.45
Focality/centricity			
Unifocal & unicentric	10 305	80.3	52.2
Multifocal &/or multicentric	2369	18.5	12.7
Missing	160	1.25	1.05
ER status			
Negative	2333	18.2	25.4
Positive	10 326	80.5	73.7
Missing	175	1.36	0.96
PR status			
Negative	3963	30.9	37.1
Positive	8628	67.2	61.5
Missing	243	1.89	1.47

Table 7 continued. Characteristics of the Study Population: Crude and Age-standardised Proportions

Characteristic	*n*	Crude%	Age-Standardised%
HER2 status			
Negative	8632	67.3	65.1
Positive	1684	13.1	19.5
Missing	2518	19.6	15.4
Surgery			
No	530	4.13	1.79
Yes	12 304	95.9	98.2
Radiotherapy			
No	4739	36.9	29.9
Yes	8095	63.1	70.1
Chemotherapy			
No	8409	65.5	40.5
Yes	4425	34.5	59.5
Biological therapy			
No	11 905	92.8	87.9
Yes	929	7.24	12.1
Endocrine therapy			
No	4682	36.5	37.3
Yes	8152	63.5	62.7
Breast cancer death			
No	11 281	87.9	82.2
Yes	1553	12.1	17.8
All-cause death			
No	9834	76.6	77.4
Yes	3000	23.4	22.6
Year of diagnosis			
2000-2003	2547	19.8	21.8
2004-2007	3096	24.1	22.8
2008-2011	3634	28.3	29.1
2012-2015	3557	27.7	26.3
Follow-up time, months			
Median (IQR) [range]	87	(83.5)	[0.26-211.3]

Overall, 80.7% of cancers were stage I-II, while 69.7% were grade 1-2. Invasive carcinoma NST was the most common subtype (81.7%), and the majority were unifocal and unicentric (80.3), hormone receptor-positive (81.7%), and HER2-negative (83.7% of cases with complete data). Most patients received surgery (95.9%), radiotherapy (63.1%), and endocrine therapy (63.5%), while only a third received chemotherapy (34.5%). HER2-directed therapy was received by 7.24% of the cohort overall, rising to 10.7% of cases diagnosed in 2007 or later. Locoregional or metastatic recurrence occurred in 14.6% of patients. Overall, 23.4% of the cohort died during the follow-up period, including 12.1% who died from breast cancer. The number of cancers diagnosed per calendar year rose steadily over the study period. A total of 102 109 person-years follow-up was observed, with a median of 87.0 months (IQR 83.5, range 0.26-211.3).

5.3.2. Prevalence of Comorbidity

Comorbidity data from the NMDS was available for 48.4% of the cohort. Crude and age-standardised proportions of the 42 C3 conditions are shown in **Table 8**. At least 1 major comorbid condition was experienced by 21.5% of the study population. The most common condition was hypertension, with a crude prevalence of 7.83%. Cardiac conditions were also prevalent (angina 1.70%, cardiac arrhythmias 3.24%, CHF 1.78%, MI 1.43%, and other cardiac conditions 2.16%), as well as metabolic disorders (3.67%), COPD/asthma (2.70%), and diabetes (4.21% overall).

Table 8 also shows descriptive statistics by C3 score, with the distribution of scores displayed in **Figure 9**. While there was a wide range of severity (-0.03-13.1), scores were greatly right-skewed, with a high proportion of patients possessing a score ≤0. When operationalised as a count, the distribution of comorbidity was also right-skewed, with a range of 0-17 conditions.

5.3.3. Impact of Comorbidity on Mortality

Table 9 shows crude and age-adjusted HRs for breast cancer-specific mortality. Crude HRs for most conditions were >1, indicating higher mortality than for those without the condition. Dementia (HR 4.09, 95% CI 2.50-6.70, p<.001) and epilepsy (HR 3.18, 95% CI 1.71-5.92, p<.001) had the highest impact on crude breast cancer mortality. Following adjustment for age/stage, only a few conditions retained statistical significance: epilepsy, connective tissue disease, dementia, malnutrition, renal disease, joint or spinal disorder, and COPD/asthma.

Dementia (HR 9.87, 95% CI 7.77-12.6, p<.001) and CHF (HR 6.17, 95% CI 5.30-7.17, p<.001) had the largest impact on crude all-cause mortality, although their effects were heavily confounded by age/stage (**Table 10**). Following stratification by age and stage, the conditions with the greatest impact were: dementia (aHR 3.32, 95% CI 2.59-4.25, p<.001), alcohol abuse (aHR 3.31, 95% CI 1.92-5.74), CHF (aHR 3.06, 95% CI 2.61-3.58), and renal disease (aHR 2.89, 95% CI 2.40-3.47, p<.001).

Table 8. Crude and Age-standardised Proportions of the C3 Conditions in the Study Cohort

	n	Crude%	Age-standardised%
Conditions			
Alcohol abuse	31	0.24	0.10
Anaemia	205	1.60	0.84
Angina	218	1.70	0.45
Anxiety & behavioural disorder	130	1.01	0.44
Cardiac arrhythmia	416	3.24	0.97
Cardiac valve disorder	123	0.96	0.30
Cerebrovascular disease	245	1.91	0.62
Coagulopathy/blood disorder	232	1.81	0.78
CHF	228	1.78	0.48
Connective tissue disease	73	0.57	0.17
COPD & asthma	347	2.70	1.16
Dementia	77	0.60	0.12
Diabetes with complications	329	2.56	0.78
Diabetes without complications	211	1.64	0.70
Endocrine disorder	139	1.08	0.41
Epilepsy	33	0.26	0.11
Eye problem	189	1.47	0.63
Gastrointestinal disease	107	0.83	0.23
Hepatitis: chronic viral	58	0.45	0.29
Hypertension	1005	7.83	2.21
Inflammatory bowel disorder	252	1.96	0.82
Inner ear disorder	129	1.01	0.57
Intestinal disorder	212	1.65	0.44
Joint or spinal disorder	128	1.00	0.37
Liver - moderate/severe disease	50	0.39	0.14
Major psychiatric condition	166	1.29	0.55
Malnutrition	59	0.46	0.14
Metabolic disorder	471	3.67	1.09
MI	183	1.43	0.36
Neurological condition	82	0.64	0.17
Obesity	221	1.72	0.83
Osteoporosis & bone disorder	81	0.63	0.14
Other cardiac condition	277	2.16	0.58
Other malignancy	162	1.26	0.40
Paralysis	113	0.88	0.24
Peripheral nerve or muscular disorder	36	0.28	0.09
Peripheral vascular disease	99	0.77	0.20
Pulmonary circulation disorder	60	0.47	0.30
Renal disease	170	1.32	0.39
Sleep disorder	40	0.31	0.14
Urinary tract disorder	37	0.29	0.12
Venous insufficiency	17	0.13	0.03
C3 Category			
0 (≤0)	10144	79.0	86.6
1 (0.01-2.00)	1726	13.5	10.1
2 (>2)	964	7.51	3.31
Median (IQR) [range]	0	(0)	[-0.03-13.1]

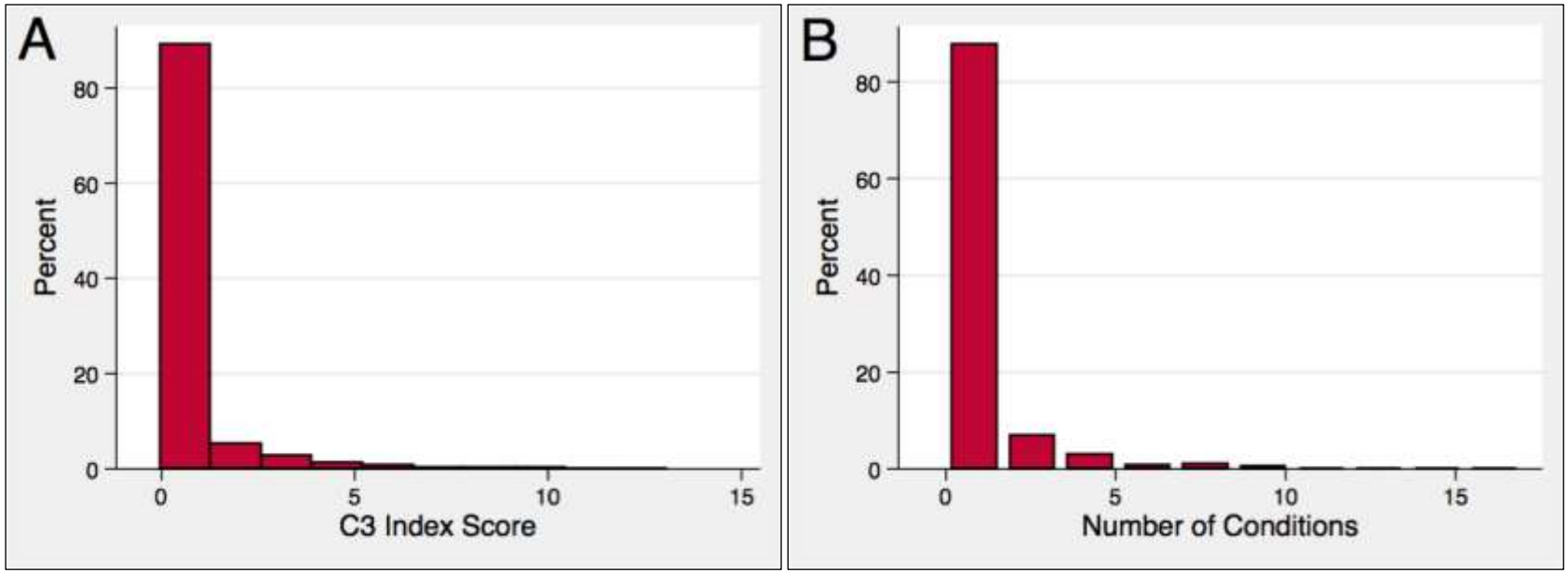


Figure 9. Distribution of Comorbidity Severity in the Study Cohort

(A) C3 index score (B) Count of conditions

Table 9. Crude and Adjusted Hazard Ratios of Breast Cancer Mortality by C3 Conditions

		Crude			Age & Stage-adjusted		
Condition	**Deaths (*n*)**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Alcohol abuse	4	1.46	0.55-3.92	.44	1.71	0.64-4.58	.28
Anaemia	35	1.90	1.36-2.66	<.001	1.40	1.00-1.96	.05
Angina	27	1.16	0.79-1.70	.44	0.88	0.60-1.30	.53
Anxiety & behavioural disorder	15	1.24	0.74-2.06	.41	1.06	0.64-1.76	.83
Cardiac arrhythmia	53	1.43	1.08-1.88	.01	1.07	0.81-1.42	.63
Cardiac valve disorder	13	1.18	0.69-2.05	.54	0.91	0.52-1.57	.73
Cerebrovascular disease	37	1.64	1.18-2.27	.003	1.08	0.77-1.51	.66
Coagulopathy/blood disorder	33	1.56	1.10-2.20	.01	1.16	0.82-1.65	.39
CHF	36	2.15	1.54-2.99	<.001	1.37	0.98-1.92	.07
Connective tissue disease	18	2.53	1.59-4.03	<.001	2.08	1.30-3.31	.002
COPD & asthma	61	1.73	1.34-2.24	<.001	1.61	1.24-2.08	<.001
Dementia	16	4.09	2.50-6.70	<.001	2.05	1.24-3.39	.01
Diabetes with complications	40	1.42	1.04-1.95	.03	1.17	0.85-1.60	.34
Diabetes without complications	30	115	0.80-1.65	.44	1.01	0.71-1.46	.94
Endocrine disorder	24	1.66	1.11-2.48	.01	1.40	0.94-2.11	.10
Epilepsy	10	3.18	1.71-5.92	<.001	2.71	1.46-5.06	.002
Eye problem	29	1.77	1.23-2.56	.002	1.30	0.90-1.89	.16
Gastrointestinal disease	13	1.23	0.71-2.13	.45	1.05	0.61-1.82	.85
Hepatitis: chronic viral	9	1.46	0.76-2.82	.26	1.47	0.76-2.83	.25
Hypertension	145	1.47	1.24-1.74	<.001	1.14	0.95-1.37	.15
Inflammatory bowel disorder	36	1.45	1.04-2.02	.03	1.24	0.89-1.74	.20
Inner ear disorder	25	1.88	1.27-2.80	.002	1.38	0.92-2.05	.12
Intestinal disorder	20	0.93	0.60-1.45	.75	0.81	0.52-1.26	.35
Joint or spinal disorder	28	2.56	1.76-3.72	<.001	1.73	1.19-2.53	.01
Liver - moderate/severe disease	7	1.27	0.61-2.68	.52	1.24	0.59-2.61	.57
Major psychiatric condition	25	1.49	1.01-2.22	.047	1.48	0.99-2.19	.05
Malnutrition	10	2.55	1.37-4.76	.003	1.91	1.02-3.56	.04
Metabolic disorder	66	1.38	1.08-1.77	.01	1.19	0.92-1.52	.18
MI	22	1.34	0.88-2.04	.17	0.92	0.60-1.41	.71
Neurological condition	16	2.40	1.47-3.93	<.001	1.63	0.99-2.68	.06
Obesity	29	1.20	0.83-1.73	.34	1.10	0.76-1.59	.61
Osteoporosis & bone disorder	18	2.75	1.73-4.38	<.001	1.44	0.89-2.31	.14
Other cardiac condition	36	1.31	0.94-1.82	.11	0.97	0.69-1.36	.86
Other malignancy	28	1.74	1.20-2.52	.004	1.40	0.96-2.04	.08
Paralysis	18	1.71	1.08-2.72	.02	1.14	0.71-1.82	.58
Peripheral nerve or muscular disorder	6	2.32	1.04-5.18	.04	1.39	0.62-3.11	.42
Peripheral vascular disease	17	2.01	1.24-3.23	.004	1.21	0.74-1.96	.44
Pulmonary circulation disorder	10	1.67	0.90-3.11	.11	1.36	0.73-2.53	.34
Renal disease	31	2.61	1.83-3.73	<.001	1.83	1.27-2.62	.001
Sleep disorder	4	0.95	0.36-2.53	.92	1.29	0.49-3.46	.61
Urinary tract disorder	5	1.15	0.48-2.76	.76	0.92	0.38-2.21	.85
Venous insufficiency	2	1.57	0.39-6.27	.53	0.78	0.20-3.15	.73

Table 10. Crude and Adjusted Hazard Ratios of All-cause Mortality by C3 Conditions

		Crude			Age & Stage-stratified		
Condition	**Deaths (*n*)**	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Alcohol abuse	13	2.58	1.50-4.45	.001	3.31	1.92-5.74	<.001
Anaemia	102	3.05	2.50-3.72	<.001	1.94	1.59-2.37	<.001
Angina	115	2.64	2.19-3.18	<.001	1.33	1.10-1.61	.003
Anxiety & behavioural disorder	58	2.62	2.02-3.40	<.001	1.78	1.37-2.31	<.001
Cardiac arrhythmia	241	3.70	3.24-4.22	<.001	1.94	1.69-2.22	<.001
Cardiac valve disorder	82	4.11	3.30-5.12	<.001	2.09	1.67-2.62	<.001
Cerebrovascular disease	149	3.62	3.07-4.26	<.001	1.69	1.42-1.99	<.001
Coagulopathy/blood disorder	133	3.43	2.88-4.08	<.001	2.10	1.76-2.51	<.001
CHF	181	6.17	5.30-7.17	<.001	3.06	2.61-3.58	<.001
Connective tissue disease	45	3.35	2.50-4.50	<.001	2.04	1.52-2.75	<.001
COPD & asthma	193	2.90	2.51-3.36	<.001	2.15	1.85-2.49	<.001
Dementia	69	9.87	7.77-12.6	<.001	3.32	2.59-4.25	<.001
Diabetes with complications	143	2.89	2.44-3.42	<.001	1.77	1.50-2.10	<.001
Diabetes without complications	99	1.95	1.60-2.39	<.001	1.42	1.16-1.74	.001
Endocrine disorder	77	2.77	2.21-3.48	<.001	1.88	1.50-2.36	<.001
Epilepsy	19	3.31	2.11-5.20	<.001	2.36	1.50-3.71	<.001
Eye problem	101	3.42	2.80-4.17	<.001	1.90	1.55-2.32	<.001
Gastrointestinal disease	48	2.48	1.86-3.30	<.001	1.45	1.09-1.93	.01
Hepatitis: chronic viral	19	1.64	1.04-2.57	.03	1.99	1.26-3.12	.003
Hypertension	533	3.15	2.87-3.46	<.001	1.66	1.50-1.84	<.001
Inflammatory bowel disorder	106	2.34	1.93-2.84	<.001	1.47	1.21-1.78	<.001
Inner ear disorder	67	2.64	2.08-3.37	<.001	1.59	1.24-2.02	<.001
Intestinal disorder	82	2.09	1.68-2.61	<.001	1.16	0.93-1.44	.20
Joint or spinal disorder	80	3.93	3.14-4.90	<.001	1.81	1.44-2.26	<.001
Liver - moderate/severe disease	23	2.19	1.45-3.30	<.001	1.80	1.19-2.72	.01
Major psychiatric condition	85	2.70	2.18-3.35	<.001	2.29	1.85-2.85	<.001
Malnutrition	39	5.56	4.05-7.62	<.001	2.69	1.96-3.71	<.001
Metabolic disorder	216	2.46	2.14-2.82	<.001	1.50	1.30-1.73	<.001
MI	116	3.93	3.26-4.73	<.001	1.77	1.46-2.12	<.001
Neurological condition	55	4.49	3.44-5.87	<.001	2.03	1.55-2.66	<.001
Obesity	97	2.11	1.73-2.59	<.001	1.80	1.47-2.21	<.001
Osteoporosis & bone disorder	65	5.33	0.17-6.81	<.001	1.86	1.44-2.40	<.001
Other cardiac condition	161	3.20	2.73-3.75	<.001	1.47	1.25-1.73	<.001
Other malignancy	77	2.56	2.04-3.20	<.001	1.57	1.25-1.97	<.001
Paralysis	61	3.07	2.38-3.95	<.001	1.53	1.18-1.97	.001
Peripheral nerve or muscular disorder	25	5.42	3.65-8.03	<.001	2.88	1.93-4.28	<.001
Peripheral vascular disease	73	4.71	3.74-5.95	<.001	1.85	1.46-2.34	<.001
Pulmonary circulation disorder	31	2.78	1.95-3.96	<.001	1.73	1.21-2.47	.003
Renal disease	123	5.83	4.87-6.99	<.001	2.89	2.40-3.47	<.001
Sleep disorder	13	1.64	0.95-2.83	.08	2.06	1.19-3.56	.01
Urinary tract disorder	21	2.52	1.64-3.88	<.001	1.76	1.14-2.71	<.001
Venous insufficiency	14	6.03	3.56-10.2	<.001	2.35	1.39-3.99	.002

C3 score was associated with both mortality outcomes in a dose-dependent fashion (**Figure 10**). As with the individual conditions, there was substantial confounding by age and stage, as evidenced by the reductions in mortality risk following adjustment for these variables. Despite this, there was still a significantly elevated risk of death amongst patients with any degree of comorbidity compared to those without, for both breast cancer-specific (C3 category 1: aHR 1.24, 95% CI 1.07-1.42, p=.003; C3 category 2: aHR 1.41, 95% CI 1.17-1.69, p<.001) and all-cause mortality (C3 category 1: aHR 1.50, 95% CI 1.36-1.65, p<.001; C3 category 2: aHR 2.53, 95% CI 2.28-2.80, p<.001) in the adjusted models.

5.3.4. Factors Associated with the Presence of Comorbidity

Descriptive analysis revealed significant differences in the distributions of sociodemographic factors by comorbidity severity, with the proportions of older, Māori/Pacific, socioeconomically deprived, and urban individuals increasing with C3 category (Wilcoxon rank-sum tests p<.001). All exposure variables except geographic region were significant in the univariate binary comorbidity model (**Table 11**). In the multivariate model, residential status lost evidence of an association, while region gained statistical significance, with lower likelihood of comorbidity in the Waikato region. No large differences in PRRs before and after adjustment were noted for age, ethnicity, treatment facility, and deprivation score. Age was predictive of comorbidity in a nonlinear fashion (p<.001), with a steep increase from approximately 70 years, as shown in **Figure 11**.

Modelling comorbidity as a count produced similar results, though with slightly different interpretations. Firstly, in the multivariate logistic zero-inflation model which examined the non-occurrence of comorbidity; advancing age, ethnicity (Māori and other), public treatment, and increasing deprivation were associated with reduced likelihood of a comorbidity count of zero (**Table 12**). In the second part of the model, which analysed comorbidity severity amongst those with a nonzero count; increasing age, ethnicity (Māori and Pacific), public treatment, and Auckland region were associated with higher number of conditions. Residential status was not associated with comorbidity in either component of the model.

5.4. Conclusions

This chapter presented the results of Study 1, which examined the burden of coexistent comorbidity amongst patients with breast cancer in New Zealand. In the study cohort, comorbidity was common, although most patients possessed a low burden of disease. Comorbidity was more strongly associated with all-cause mortality than breast cancer-specific mortality, with variable impact depending on the condition. A number of sociodemographic factors associated with the presence and burden of comorbidity were identified; providing insight as to potential confounders of the comorbidity – cancer treatment – survival pathway, which will be the subject of investigation over the next 2 chapters.

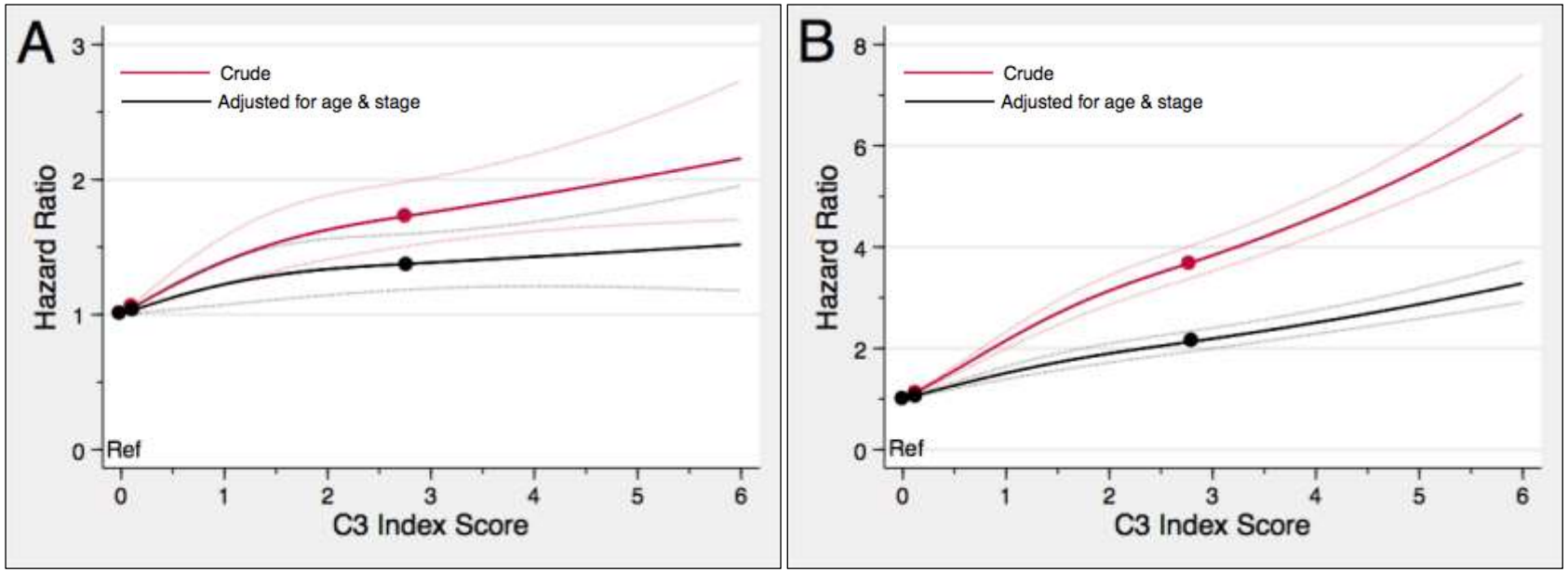


Figure 10. Crude and Age/Stage-adjusted Hazard Ratios of Mortality by C3 Score

(A) Breast cancer-specific mortality (B) All-cause mortality

Dotted lines indicate 95% CIs. C3 is a RCS with reference value 0. Dots indicate the x-axis position of spline knots.

Table 11. Prevalence Risk Ratios for Binary Comorbidity by Sociodemographic Factors

	Univariate			Multivariate		
Characteristic	**PRR**	**95% CI**	**P value**	**PRR**	**95% CI**	**P value**
Age at diagnosis, years[a]						
30	0.39	0.31-0.48	<.001	0.39	0.32-0.48	<.001
50	0.70	0.67-0.73		0.70	0.67-0.74	
60	[Ref]			[Ref]		
70	1.52	1.49-1.55		1.51	1.48-1.54	
90	3.94	3.63-4.31		3.74	3.42-4.10	
Ethnicity						
European	[Ref]		<.001	[Ref]		<.001
Māori	1.49	1.36-1.64		1.53	1.39-1.68	
Pacific peoples	1.39	1.24-1.55		1.35	1.20-1.51	
Asian	0.68	0.59-0.80		0.86	0.74-1.01	
Other ethnic groups	1.38	1.22-1.56		1.16	1.03-1.30	
Treatment facility						
Public	[Ref]		<.001	[Ref]		<.001
Private	0.37	0.33-0.40		0.50	0.46-0.55	
NZDep2013, quintile						
1	[Ref]		<.001	[Ref]		<.001
2	1.29	1.15-1.46		1.16	1.03-1.30	
3	1.51	1.34-1.69		1.24	1.11-1.38	
4	1.62	1.44-1.81		1.23	1.10-1.38	
5	1.96	1.76-2.18		1.39	1.25-1.54	
Residential status						
Urban	[Ref]		<.001	[Ref]		.14
Rural	0.75	0.64-0.87		0.89	0.77-1.04	
Region						
Auckland	[Ref]		.07	[Ref]		.01
Waikato	1.08	0.99-1.16		0.90	0.83-0.97	

[a] RCS.

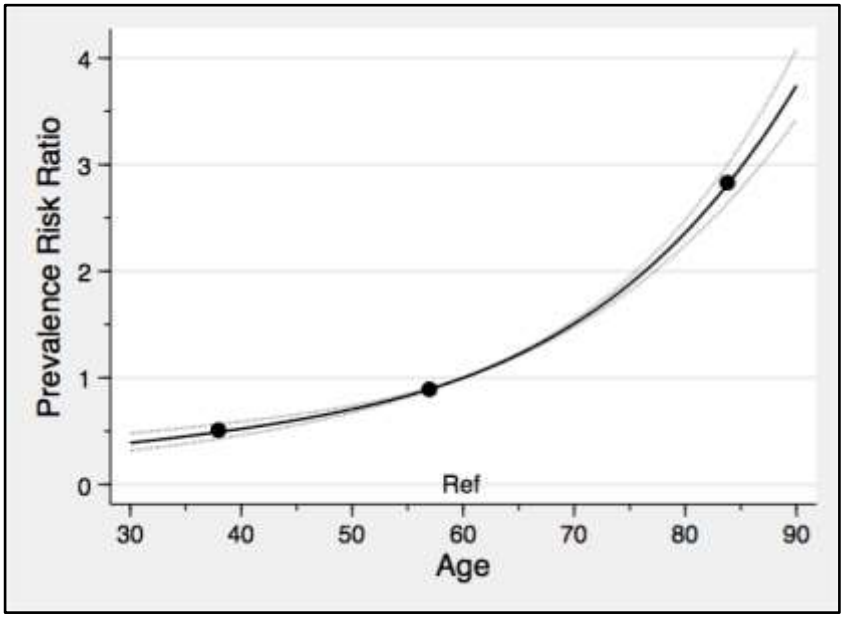


Figure 11. Adjusted Prevalence Risk Ratios for Binary Comorbidity by Age

Age is a RCS with reference value 60 years. Complete case analysis; *n*=12 691.

Table 12. Zero-inflated Negative Binomial Regression: Count of Comorbid Conditions

	Univariate				Multivariate			
	Negative Binomial Model		Logistic Inflation Model		Negative Binomial Model		Logistic Inflation Model	
Characteristic	**PRR**	**95% CI**	**OR**	**95% CI**	**PRR**	**95% CI**	**OR**	**95% CI**
Age, years								
≤49	[Ref]		[Ref]		[Ref]		[Ref]	
50-59	2.03	1.65-2.50	1.16	0.91-1.48	1.98	1.61-2.43	1.19	0.91-1.54
60-69	2.36	1.94-2.88	0.67	0.52-0.85	2.37	1.95-2.88	0.69	0.53-0.89
>70	3.62	3.01-4.34	0.16	0.11-0.22	4.00	3.30-4.84	0.19	0.14-0.26
Ethnicity								
European	[Ref]		[Ref]		[Ref]		[Ref]	
Māori	1.07	0.91-1.26	0.45	0.32-0.61	1.34	1.15-1.57	0.55	0.43-0.72
Pacific	1.29	1.06-1.56	0.64	0.47-0.85	1.43	1.19-1.71	0.79	0.60-1.05
Asian	0.69	0.53-0.90	1.42	1.03-1.95	0.89	0.69-1.14	1.20	0.87-1.68
Other	0.87	0.70-1.09	0.44	0.28-0.68	0.81	0.67-0.98	0.55	0.38-0.80
Treatment facility								
Public	[Ref]		[Ref]		[Ref]		[Ref]	
Private	0.55	0.47-0.64	3.52	2.85-4.34	0.66	0.56-0.77	2.35	1.93-2.86
NZDep2103, quintile								
1	[Ref]		[Ref]		[Ref]		[Ref]	
2	1.03	0.84-1.26	0.67	0.53-0.86	0.95	0.79-1.13	0.71	0.55-0.92
3	0.97	0.80-1.17	0.48	0.37-0.63	0.90	0.76-1.08	0.61	0.47-0.79
4	1.01	0.83-1.22	0.43	0.33-0.57	0.97	0.81-1.16	0.65	0.50-0.84
5	1.18	0.99-1.41	0.32	0.24-0.43	1.09	0.91-1.29	0.56	0.43-0.72
Residence								
Urban	[Ref]		[Ref]		[Ref]		[Ref]	
Rural	0.77	0.60-0.997	1.38	0.99-1.91	0.91	0.71-1.16	1.11	0.78-1.58
Region								
Auckland	[Ref]		[Ref]		[Ref]		[Ref]	
Waikato	0.85	0.74-0.98	0.76	0.61-0.93	0.84	0.73-0.95	1.06	0.86-1.31

Chapter 6. Study 2

The Impacts of Comorbidity on Breast Cancer Diagnosis and Standards of Treatment

6.1. Introduction

This chapter presents the second study of this thesis, which broadly aims to establish the extent to which comorbidity impacts upon the diagnosis of breast cancer and the standards of treatment received. The results are split into 4 sections. The first section, which examines the impact of comorbidity on breast cancer diagnosis, consists of 3 sets of analyses modelling the impacts of comorbidity on screen-detection of breast cancer, missing cancer stage, and stage at diagnosis. Subsequent sections evaluate the impact of comorbidity on guideline-non-concordant treatment in 3 ways: receipt of treatment, quality of treatment, and timeliness of treatment.

6.1.1. Aims

Study 2 addresses the third research objective:

- To determine the impacts of comorbidity on breast cancer diagnosis and standards of treatment.

The specific study aims were:

1. To examine the impact of comorbidity on breast cancer diagnosis by screen-detection.
2. To determine the effect of comorbidity on missing breast cancer stage.
3. To investigate the influence of comorbidity on breast cancer stage at diagnosis.
4. To estimate the impacts of comorbidity on the receipt of treatments for breast cancer.
5. To evaluate the impacts of comorbidity on the quality of treatments for breast cancer.
6. To examine the effects of comorbidity on the timeliness of treatments for breast cancer.

6.2. Methods

6.2.1. Population

Separate eligibility criteria were applied to each of the analyses performed in this study. For the analysis examining the impact of comorbidity on screen-detection, the population was limited to the BSA target screening age range. Participants were eligible for inclusion if they were aged between 50-64 with a diagnosis of breast cancer made prior to 01/07/2004; or aged between 45-

69 with a breast cancer diagnosis later than this date.[194][16] The impact of comorbidity on missing stage used the entire cohort, while the analysis examining actual stage was limited to those with observed stage data. The analyses pertaining to the impact of comorbidity on treatment concordance utilised a variety of selection criteria, which are outlined in detail in Section 4.6.

6.2.2. Variables

6.2.2.1. Primary Exposure Variable: Comorbidity

In addition to C3 index score, 5 important individual conditions were selected as exposure variables of interest in this study. From the results of Study 1 (Sections 5.3.2-3), these were defined as conditions with crude prevalence >2.5% and HR of all-cause mortality >1.5. Applying this criteria; cardiac arrhythmia, COPD/asthma, diabetes (with and without complications[17]), hypertension, and metabolic disorder were selected for further investigation. In order to determine their individual impacts on cancer diagnosis and treatment, these conditions were included in the multivariate models in this study along with continuous C3 score. As a sensitivity analysis, models exclusive of these conditions were also produced, however as results were similar, only models including the conditions are displayed. To examine the impact of comorbidity as an overall measure of disease burden, graphs exploring the relationships between C3 index score and outcome variables were produced from models excluding individual conditions.

6.2.2.2. Covariates and Effect-modifying Variables

Covariates were selected based on their presumed relationships with comorbidity and the outcome variables, as established by the conceptual framework developed through literature review (**Figure 7**) and the results of Study 1. The pathways hypothesised to be involved are shown in **Appendix A**, **Figure 33** (**b-d**).

The first section of analyses examines the impact of comorbidity on the diagnosis of breast cancer. In the first analysis, screen-detection of cancer was modelled. In addition to the age restriction imposed on the analysis population, age was included in the model because of its nonlinear association with comorbidity within this age range (**Figure 11**), as well as known variations in screening coverage by age, even within the target range.[698] Variations in screening coverage have also been documented by ethnicity (and thus, probably by deprivation) and BSA lead provider (region). Residential status was not included because, despite its documented impact on screening uptake internationally,[546] BSA's mobile outreach services mean no substantial national differences in screening equity by rurality were expected[194] and (less crucially) no association between residential status and comorbidity was found in Study 1.

[16] From 1st July 2004, the age range for free breast screening in New Zealand was extended from 50-64 to 45-69 years.
[17] Unlike the findings of the C3 development study, which noted a slight survival advantage for uncomplicated diabetes (coefficient -0.03), no substantive differences in survival between diabetic patients with and without complications were found; hence, they were combined as a single subgroup.

The second model in this section evaluates the impact of comorbidity on missing stage at diagnosis. It was presumed that the pathway from comorbidity to missing stage was largely mediated through non-receipt of surgery (with consequent lack of pathological staging information), with nonparticipation in screening (contributing to a lack clinical staging information) thought to play a more minor role. Sociodemographic factors (namely age, ethnicity, and socioeconomic deprivation) with influence over these mediating pathways were considered to be confounders requiring adjustment. Geographic region and residential status were not expected to have an impact on missing stage[550] other than a possible indirect effect through reduced screening,[698] and were therefore omitted from the model.

Thirdly, the impact of comorbidity on stage at diagnosis was modelled. Screen-detection status is closely linked with stage; with screen-detected cancers showing more favourable tumour characteristics, including earlier stage at diagnosis.[196] Mode of detection was therefore a mediating factor on the comorbidity – cancer stage pathway, and did not require adjustment.

In the next 3 sections, the focus was the impact of comorbidity on standards of treatment for breast cancer. Age, ethnicity, and deprivation were considered confounders as they drive inequities in both comorbidity burden and cancer treatment. As treatment between regions was expected to be equivalent, region was not considered a confounder in this set of models. Given the hypothesised associations between comorbidity and stage, and between stage and cancer treatment, stage was considered a potential mediator of the pathway between comorbidity and treatment. As only the total effect of comorbidity on treatment was desired, stage did not require formal adjustment in these models. Tumour factors were identified as potential effect-modifiers of the relationship between comorbidity and cancer treatment. It was hypothesised that comorbid patients with worse prognosis cancers, or tumour biology precluding alternative treatment options (such as hormone receptor-negative tumours contraindicating the use of endocrine therapy) may be more likely to receive guideline-concordant treatment compared with a similar patient without such features. Cancer variables (stage, grade, histopathological type, hormone receptor status, and HER2 status) were therefore assessed for evidence of effect-measure modification.

Effect modification was evaluated in relation to pathological stage, unless neoadjuvant treatment was received, no surgery was performed, or pathological stage was missing, in which case clinical stage was used. Clinical stage was assessed in analyses pertaining to surgery however; as pathological stage is not a baseline variable in this context (being derived from histopathological reports obtained after surgery has been performed). Only clinical T stage was examined, as a large number of cases on the Auckland breast cancer register were missing clinical N stage. As potential responsiveness to endocrine therapy is a function of either ER or PR-positivity,[699] these were combined as a single binary variable termed *hormone receptor status* in these models, where either ER or PR-positivity was taken to be positive hormone receptor status, while double ER and PR-negativity was taken to be negative.

6.2.2.3. Outcome Variables

Presentation with a screen-detected breast cancer was modelled as a binary variable, the alternative being non-screen-detected cancer. Stage at diagnosis was examined in 2 ways. Firstly, missing stage as a binary variable (missing/observed) was modelled. Secondly, for participants with observed stage information, stage as a 3 level ordinal variable (stage I, II, or III) was evaluated.

Standards of breast cancer treatment were modelled in terms of binary guideline-non-concordance (vs guideline-concordance). The specific standards used to define this were outlined in **Table 3**. Modelling inappropriate treatment (as opposed to its inverse) was considered a better fit to a major underlying hypothesis of Study 2; that comorbidity results in inferior treatment for breast cancer, a consistent theme identified from the literature.

6.2.3. Data Analysis

6.2.3.1. Impacts of Comorbidity on Breast Cancer Diagnosis

The impact of comorbidity on diagnosis was evaluated in 3 ways using a nested cross-sectional design. Firstly, the likelihood of presenting with a screen-detected cancer was modelled using univariate and multivariate modified Poisson regression; producing crude and adjusted RRs.

Secondly, the likelihood of missing stage was modelled, also using modified Poisson regression.

Lastly, univariate and multivariate ordered logistic regression was used to model stage as a 3 level ordinal variable, obtaining crude and adjusted proportional ORs. Ordered logistic regression is otherwise known as the proportional odds model because it assumes that the relationship between the coefficients for each pair of outcome groups (ie, between the lowest and all higher categories of the outcome variable) is the equal. Models were tested for the proportional odds assumption using Brant tests from the package `omodel`,[700] with $p<.05$ considered indicative of non-proportional odds. As age and treatment facility displayed evidence of non-proportionality, generalised ordered logistic regression models were fit using the `gologit2` program.[701] Rather than using a non-ordinal model, such as multinomial regression, generalised ordered logistic regression provides a more interpretable model with greater parsimony. Generalised ordered logistic regression estimate partial proportional odds models, which relax the proportional odds assumption for variables which violate this assumption, enabling coefficients to vary between outcome categories. Age was entered into the models as a categorical variable, due to evidence of nonlinearity in addition to non-proportionality. Multiple imputation for cases with missing data on ethnicity, treatment facility, NZDep2013, and stage was performed, however cases with missing values for stage (n=522) were dropped prior to model estimation.[628,702] Using imputed values of outcome variables provides minimal gain in information recovery whilst adding needless noise to

estimates.[628,702] Sensitivity analysis was performed retaining these cases, however as the estimates were largely similar, but with greater fraction of missing information (0.18 vs 0.01) and average relative increase in variance (0.06 vs 0.002), only results from the *imputed then deleted* model are presented.

6.2.3.2. Impacts of Comorbidity on Non-concordant Treatment

Guideline-non-concordant treatment was modelled using univariate and multivariate modified Poisson regression to obtain RRs. For the receipt of treatment analyses, the presence of effect-measure modification by cancer factors was assessed for tumour variables as appropriate. All tumour variables identified as potential effect-modifiers were entered into multivariate models (exclusive of individual comorbid conditions) as main effects and interaction terms. Wald tests of interaction were requested and a hierarchical backward elimination procedure employed, whereby nonsignificant interaction terms and their main effects were sequentially removed.[703] Where evidence of effect modification was uncovered, multivariate stratum-specific estimates were inspected and interaction plots (displaying the effect of continuous C3 score on treatment-non-concordance within each category of the modifying tumour variable) were produced, with covariates set at their reference category or median value (for continuous variables). Interaction plots were produced from imputed data, using the module `mimrgns`.[704] While there was a moderate proportion of missing data (2.08-39.6%) in tumour variables, as there were no substantive differences between complete case and multiply imputed estimates, only results from multiple imputation are presented.

6.3. Results

6.3.1. Impacts of Comorbidity on Breast Cancer Diagnosis

6.3.1.1. Impact of Comorbidity on Screen-detection of Breast Cancer

From the total cohort, 7751 patients (60.4%) were of screening age, 4564 (58.9%) of whom had a screen-detected cancer. Roughly equivalent proportions of screen-detected tumours (approximately 60%) were noted by C3 category (p=.36). In multivariate analysis, there was moderate evidence of an association between C3 score and screen-detection status, with an adjusted RR of 0.96 (95% CI 0.93-1.00, p=.05) per 1.0 unit change in C3 score (**Table 13**). Hypertension displayed an association in the opposite direction; increasing the likelihood of presentation with a screen-detected tumour (aRR 1.19, 95% CI 1.07-1.32, p=.001). Younger age and private treatment were additional factors associated with reduced likelihood of screen-detection.

Table 13. Risk Ratios for Screen-detected Breast Cancer

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	1.00	0.98-1.02	.90	0.96	0.93-1.00	.05
Cardiac arrhythmia	0.96	0.82-1.12	.60	0.93	0.79-1.10	.42
COPD/asthma	1.01	0.89-1.15	.87	1.00	0.87-1.16	.93
Diabetes	1.00	0.90-1.11	.98	0.94	0.83-1.06	.31
Hypertension	1.11	1.03-1.20	.01	1.19	1.07-1.32	.001
Metabolic disorder	1.01	0.91-1.13	.83	0.98	0.86-1.13	.82
Age at diagnosis, years[a]						
45	0.72	0.67-0.78	<.001	0.72	0.67-0.78	<.001
50	0.82	0.79-0.85		0.83	0.79-0.85	
60	[Ref]					
69	1.11	1.04-1.16		1.08	1.03-1.15	
Ethnicity						
European	[Ref]		.41	[Ref]		.12
Māori	0.95	0.89-1.01		0.92	0.86-0.98	
Pacific peoples	0.99	0.92-1.07		0.96	0.89-1.04	
Asian	0.96	0.89-1.03		0.98	0.92-1.05	
Other ethnic groups	1.00	0.92-1.09		0.97	0.90-1.06	
Treatment facility						
Public	[Ref]		<.001	[Ref]		<.001
Private	0.86	0.83-0.90		0.85	0.82-0.89	
NZDep2013, quintile						
1	[Ref]		.35	[Ref]		.78
2	0.99	0.93-1.05		0.98	0.92-1.04	
3	1.03	0.97-1.09		1.00	0.94-1.06	
4	1.01	0.95-1.07		0.97	0.91-1.03	
5	1.05	0.99-1.11		0.99	0.94-1.06	
Region						
Auckland	[Ref]		.13	[Ref]		.77
Waikato	1.03	0.99-1.08		1.01	0.96-1.06	

[a] RCS.

6.3.1.2. Impact of Comorbidity on Breast Cancer Stage at Diagnosis

Stage was missing in 522 cases (4.07%). In addition to being older (median age 81, IQR 22; p<.001) and more comorbid (median C3 score 0.63, IQR 2.84; p<.001), patients with missing stage had less aggressive tumours (grade 1 p<.001, hormone receptor-positive p<.001, and HER2-negative tumours p<.001), and were less likely to receive all types of treatment (p values <.001). In multivariate analysis, missing stage was associated with increasing comorbidity (p<.001) and age (p<.001), as well as non-European ethnicity (p<.001) (**Table 14**). The relationship between C3 and missing stage is shown in **Figure 12**. Individual conditions, whilst statistically significant in univariate analysis, did not retain any associations in the multivariate model.

Amongst patients with observed stage information (*n*=12 312), comorbidity was associated with higher stage at diagnosis, in linear fashion (**Table 15**). In the multivariate model, for every 1.0 increase in C3 score, the proportional odds of presenting with a higher stage tumour were 1.09-times greater. Other factors associated with higher stage at presentation were more advanced age, non-European ethnicity, and greater deprivation. Individual conditions were not statistically significant in the multivariate model.

Table 14. Risk Ratios for Missing Breast Cancer Stage

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score[a]						
0	[Ref]		<.001	[Ref]		<.001
1	3.29	2.80-3.86		1.48	1.21-1.82	
2	5.26	4.35-6.42		1.79	1.36-2.34	
3	6.17	5.10-7.39		1.96	1.48-2.61	
6	8.85	7.32-10.8		2.51	1.77-3.60	
Cardiac arrhythmia	5.64	4.56-6.99	<.001	1.07	0.84-1.38	.56
COPD/asthma	3.56	2.69-4.71	<.001	1.28	0.96-1.71	.10
Diabetes	2.47	1.87-3.25	<.001	0.97	0.73-1.29	.85
Hypertension	4.31	3.59-5.18	<.001	0.92	0.73-1.17	.51
Metabolic disorder	2.60	1.95-3.45	<.001	0.83	0.62-1.11	.21
Age at diagnosis, years[a]						
30	1.30	0.77-2.18	<.001	1.21	0.72-2.05	<.001
50	0.76	0.68-0.85		0.76	0.68-0.86	
60	[Ref]			[Ref]		
70	2.80	2.64-2.97		2.64	2.46-2.86	
90	26.3	21.3-32.5		22.0	17.1-28.2	
Ethnicity						
European	[Ref]		<.001	[Ref]		<.001
Māori	0.79	0.57-1.07		1.53	1.13-2.08	
Pacific peoples	1.33	0.99-1.79		2.43	1.82-3.26	
Asian	0.72	0.50-1.04		1.64	1.15-2.34	
Other ethnic groups	1.77	1.34-2.34		1.39	1.07-1.79	
Treatment facility						
Public	[Ref]		<.001	[Ref]		.64
Private	0.52	0.43-0.64		1.05	0.86-1.29	
NZDep2013, quintile						
1	[Ref]		.36	[Ref]		.07
2	1.56	0.89-1.50		1.03	0.81-1.31	
3	0.93	0.71-1.22		0.79	0.62-1.02	
4	0.92	0.70-1.21		0.76	0.59-0.99	
5	1.10	0.86-1.42		0.95	0.74-1.21	

[a] RCS.

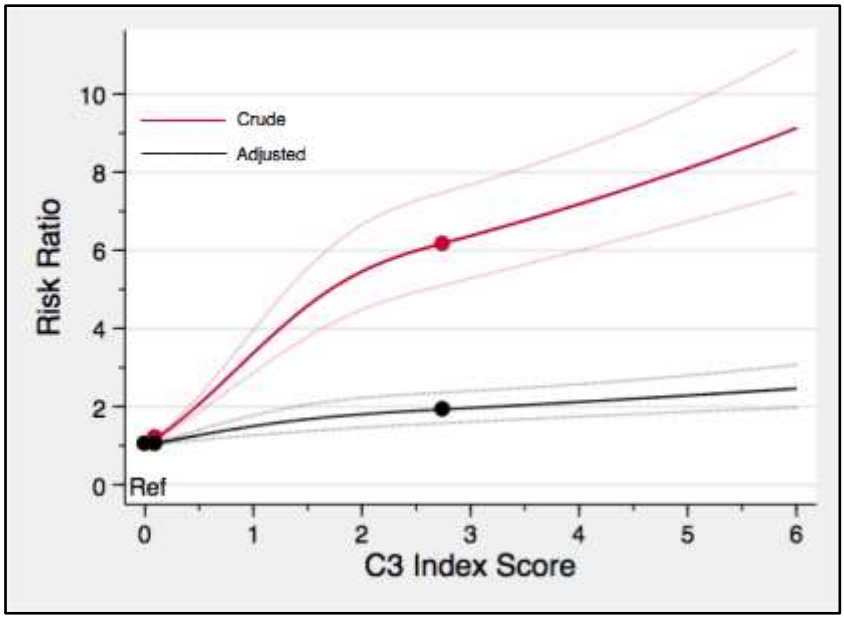


Figure 12. Risk Ratios for Missing Breast Cancer Stage by C3 Score

C3 is a RCS with reference value 0. Complete case analysis; *n*=12 691.

Table 15. Generalised Ordered Logistic Regression: Breast Cancer Stage at Diagnosis

	Univariate				Multivariate			
	Stage III vs I + II		Stage II + III vs I		Stage III vs I + II		Stage II + III vs I	
Characteristic	**POR**	**95% CI**	**POR**	**95% CI**	**POR**	**95% CI**	**POR**	**95% CI**
C3 score	1.08	1.05-1.11	1.08	1.05-1.11	1.09	1.03-1.14	1.09	1.03-1.14
Cardiac arrhythmia	1.12	0.91-1.37	1.12	0.91-1.37	0.86	0.68-1.08	0.86	0.68-1.08
COPD/asthma	1.08	0.87-1.34	1.08	0.87-1.34	0.84	0.66-1.07	0.84	0.66-1.07
Diabetes	1.36	1.15-1.61	1.36	1.15-1.61	1.07	0.87-1.32	1.07	0.87-1.32
Hypertension	1.19	1.05-1.36	1.19	1.05-1.36	0.86	0.71-1.03	0.86	0.71-1.03
Metabolic disorder	1.26	1.05-1.51	1.26	1.05-1.51	1.02	0.82-1.28	1.02	0.82-1.28
Age, years								
≤49	[Ref]		[Ref]		[Ref]		[Ref]	
50-59	0.62	0.56-0.67	0.62	0.56-0.67	0.62	0.57-0.68	0.62	0.57-0.68
60-69	0.43	0.40-0.48	0.43	0.40-0.48	0.44	0.40-0.48	0.44	0.40-0.48
>70[a]	1.09	0.98-1.21	0.75	0.65-0.85	1.09	0.98-1.23	0.74	0.64-0.84
Ethnicity								
European	[Ref]		[Ref]		[Ref]		[Ref]	
Māori	1.35	1.21-1.50	1.35	1.21-1.50	1.26	1.12-1.41	1.26	1.12-1.41
Pacific	2.01	1.77-2.30	2.01	1.77-2.30	1.77	1.54-2.04	1.77	1.54-2.04
Asian	1.10	0.98-1.25	1.10	0.98-1.25	1.01	0.89-1.15	1.01	0.89-1.15
Other	1.02	0.88-1.18	1.02	0.88-1.18	1.02	0.88-1.18	1.02	0.88-1.18
Facility								
Public	[Ref]		[Ref]		[Ref]		[Ref]	
Private[a]	0.84	0.79-0.91	0.75	0.68-0.84	0.98	0.90-1.06	0.86	0.77-0.96
NZDep2103, quintile								
1	[Ref]		[Ref]		[Ref]		[Ref]	
2	1.03	0.92-1.14	1.03	0.92-1.14	0.99	0.89-1.11	0.99	0.89-1.11
3	1.12	1.01-1.24	1.12	1.01-1.24	1.07	0.96-1.19	1.07	0.96-1.19
4	1.25	1.12-1.38	1.25	1.12-1.38	1.14	1.02-1.28	1.14	1.02-1.28
5	1.34	1.21-1.48	1.34	1.21-1.48	1.15	1.03-1.28	1.15	1.03-1.28

Abbreviation: POR, proportional odds ratio.
[a] Non-proportional odds.

6.3.2. Impacts of Comorbidity on Receipt of Treatment

6.3.2.1. Receipt of Surgery: Breast

Overall, 542 out of 12 830 eligible participants (4.22%) did not receive surgery of their breast primary. In descriptive analysis, patients who did not receive surgery were significantly more comorbid than those who did (median C3 score 1.01 vs 0; p<.001). Comorbidity was associated with non-receipt of breast surgery, with significantly higher risk of non-treatment with increasing level of comorbidity (p<.001) (**Figure 13, Table 16**). This effect was greatly confounded by other patient and healthcare access factors, with large reductions in the risk of non-concordance following adjustment, although a strong relationship remained. The 5 individual conditions were related to non-concordance in univariate analysis, but not multivariate. Other variables displaying an increased likelihood of non-treatment were extremes of age, Māori/Pacific ethnicity, and public treatment. Effect-measure modification of the association between C3 and non-receipt of breast surgery was detected for clinical T stage (p=.004). **Figure 14** is an interaction plot showing the relationships between C3 score and predicted risk of non-concordance within each strata of clinical T stage. Compared to patients with clinical T stage 0-I and II tumours, the risk of non-concordant breast surgery was greater amongst patients with stage III and IV disease, at all levels of comorbidity severity.

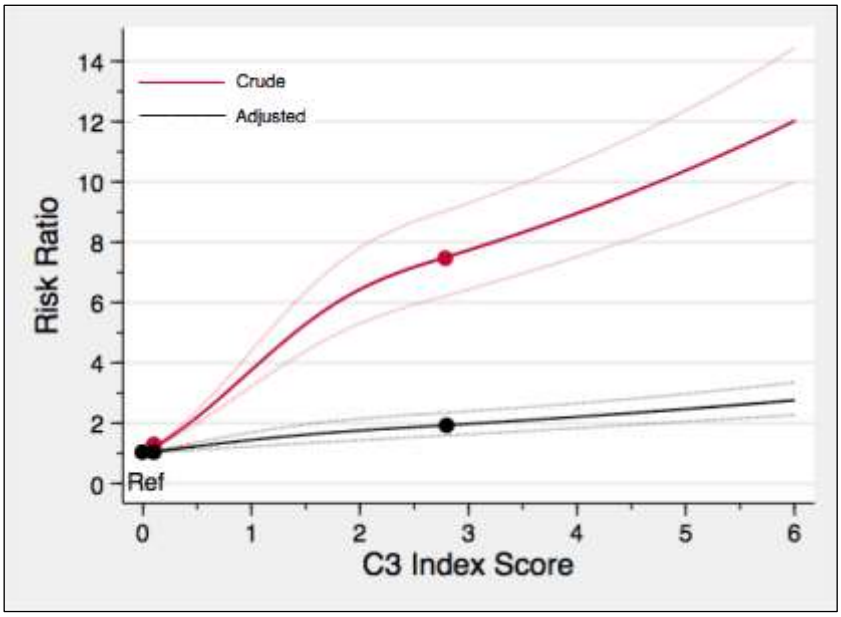


Figure 13. Risk Ratios for Non-concordant Treatment by C3 Score: Receipt of Breast Surgery

C3 is a RCS with reference value 0. Complete case analysis; *n*=12 687.

Table 16. Risk Ratios for Non-concordant Treatment: Receipt of Breast Surgery

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score[a]						
0	[Ref]		<.001	[Ref]		<.001
1	3.74	3.22-4.39		1.53	1.27-1.86	
2	6.42	5.31-7.85		1.92	1.49-2.48	
3	7.77	6.42-9.30		2.20	1.70-2.89	
6	12.1	9.97-14.4		3.23	2.36-4.48	
Cardiac arrhythmia	6.01	4.90-7.37	<.001	0.93	0.75-1.16	.75
COPD/asthma	3.28	2.47-4.37	<.001	0.91	0.69-1.21	.69
Diabetes	2.92	2.27-3.75	<.001	0.84	0.65-1.10	.65
Hypertension	5.21	4.39-6.19	<.001	0.91	0.73-1.14	.73
Metabolic disorder	3.42	2.67-4.38	<.001	1.04	0.80-1.36	.80
Age at diagnosis, years[a]						
30	1.58	1.03-2.46	<.001	1.73	1.15-2.61	<.001
50	0.82	0.74-0.90		0.85	0.77-0.94	
60	[Ref]			[Ref]		
70	2.32	2.20-2.44		2.17	2.05-2.29	
90	30.6	25.8-36.6		24.6	19.9-30.6	
Ethnicity						
European	[Ref]		<.001	[Ref]		<.001
Māori	1.10	0.84-1.44		1.90	1.47-2.47	
Pacific peoples	1.97	1.53-2.52		3.14	2.42-4.07	
Asian	0.46	0.29-0.73		1.07	0.69-1.66	
Other ethnic groups	1.59	1.18-2.14		1.17	0.91-1.51	
Treatment facility						
Public	[Ref]		<.001	[Ref]		<.001
Private	0.19	0.14-0.25		0.41	0.32-0.54	
NZDep2013, quintile						
1	[Ref]		.001	[Ref]		.68
2	1.39	1.05-1.85		1.10	0.86-1.42	
3	1.32	0.99-1.75		0.94	0.73-1.22	
4	1.57	1.19-2.08		1.06	0.83-1.50	
5	1.71	1.31-2.22		1.09	0.85-1.39	

[a] RCS.

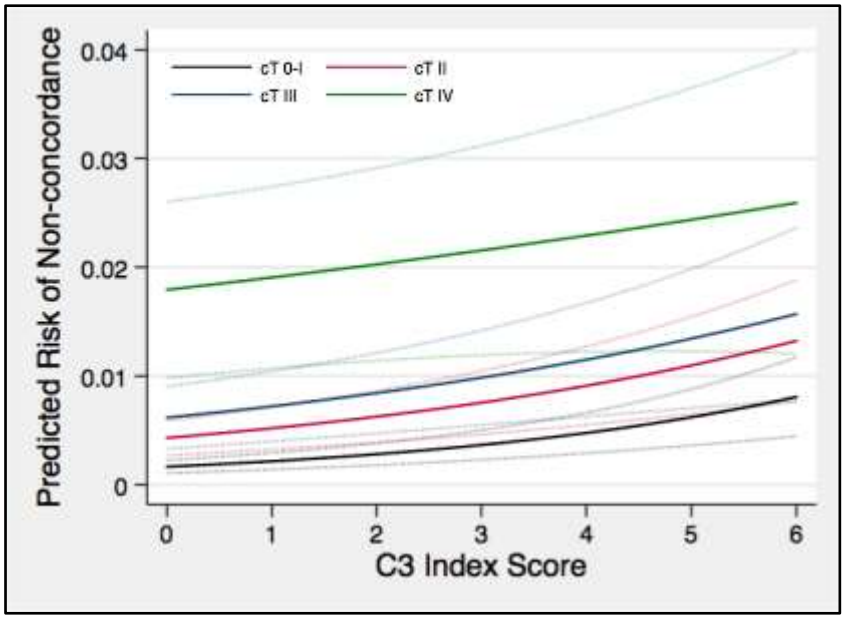


Figure 14. Interaction Plot Showing Adjusted Predicted Risk of Non-concordant Treatment by C3 Score within Strata of Clinical T Stage: Receipt of Breast Surgery

Abbreviation: cT, clinical T stage. C3 is a RCS.

6.3.2.2. Receipt of Surgery: Axilla

A total of 890 study participants (6.93%) did not receive axillary surgery. As seen in the former analysis, patients who did not undergo axillary surgery were significantly more comorbid than those who did (median C3 score 0.69 vs 0; p<.001). Increasing comorbidity severity (but not individual conditions) was associated with greater risk of non-treatment in the multivariate model (p<.001) (**Table 17**, **Figure 15**). Once again, age (with a J-shaped relationship), Māori/Pacific ethnicity, and public treatment were additional factors associated with greater likelihood of not undergoing axillary surgical treatment.

Interaction analysis revealed evidence of effect modification of the relationship between C3 and non-receipt of axillary surgery by both clinical T stage (p=.001) and tumour grade (p=.002). Interaction plots of these relationships are shown in **Figure 16**. At all levels of comorbidity severity, more advanced stage tumours were associated with greater predicted risk of non-concordant surgical treatment. Conversely, with higher grade tumours, the risk of non-concordance was reduced.

Table 17. Risk Ratios for Non-concordant Treatment: Receipt of Axillary Surgery

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score[a]						
0	[Ref]		<.001	[Ref]		<.001
1	3.22	2.89-3.63		1.40	1.22-1.62	
2	5.21	4.53-6.05		1.70	1.40-2.05	
3	6.23	5.42-7.10		1.92	1.57-2.34	
6	9.39	8.25-10.8		2.69	2.12-3.42	
Cardiac arrhythmia	5.38	4.61-6.28	<.001	0.97	0.82-1.15	.74
COPD/asthma	3.65	2.99-4.46	<.001	1.19	0.97-1.45	.09
Diabetes	2.44	1.98-2.99	<.001	0.86	0.70-1.05	.14
Hypertension	4.45	3.89-5.08	<.001	0.94	0.80-1.11	.46
Metabolic disorder	2.66	2.16-3.28	<.001	0.85	0.70-1.04	.12
Age at diagnosis, years[a]						
30	0.87	0.59-1.27	<.001	0.90	0.62-1.31	<.001
50	0.73	0.66-0.79		0.75	0.68-0.81	
60	[Ref]			[Ref]		
70	2.25	2.16-2.34		2.14	2.03-2.23	
90	22.9	20.1-26.3		18.8	16.1-22.4	
Ethnicity						
European	[Ref]		<.001	[Ref]		<.001
Māori	0.97	0.79-1.21		1.63	1.34-1.99	
Pacific peoples	1.38	1.11-1.71		2.20	1.76-2.75	
Asian	0.54	0.39-0.74		1.21	0.90-1.62	
Other ethnic groups	1.41	1.12-1.77		1.10	0.90-1.35	
Treatment facility						
Public	[Ref]		<.001	[Ref]		<.001
Private	0.34	0.28-0.40		0.70	0.59-0.82	
NZDep2013, quintile						
1	[Ref]		<.001	[Ref]		.15
2	1.25	1.003-1.55		1.06	0.88-1.27	
3	1.27	1.03-1.58		1.00	0.83-1.21	
4	1.43	1.16-1.76		1.08	0.90-1.29	
5	1.61	1.32-1.97		1.22	1.02-1.46	

[a] RCS.

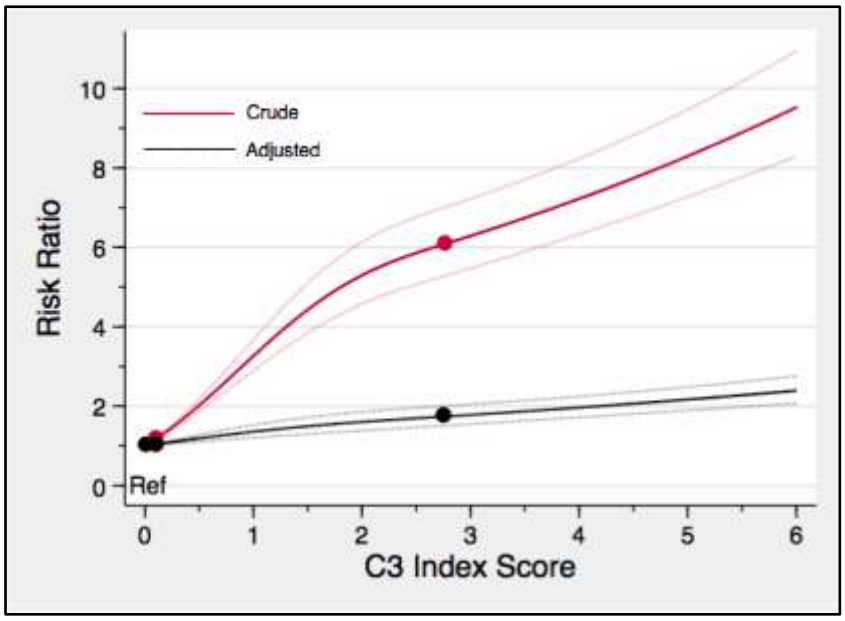


Figure 15. Risk Ratios for Non-concordant Treatment by C3 Score: Receipt of Axillary Surgery

C3 is a RCS with reference value 0. Complete case analysis; *n*=12 691.

6.3.2.3. Receipt of Adjuvant Radiotherapy

This analysis included 7717 patients, 5931 (76.9%) of which had a minimum indication for radiotherapy following BCS, and 1786 (23.1%) after mastectomy. In total, 807 (10.5%) of the analysis population did not receive adjuvant radiotherapy. Of these 807 non-concordant cases, 497 (61.5%) had received BCS, while the remaining 310 (38.4%) had undergone mastectomy.

Patients who did not receive radiotherapy as recommended had higher levels of comorbidity than those who did (median C3 score 0.95 vs 0; p<.001). Comorbidity as an overall measure had an adverse impact on the likelihood of receiving adjuvant radiotherapy, with greater risk of non-treatment seen at higher levels of comorbidity severity (**Table 18**, **Figure 17**). Conversely, diabetes increased the likelihood of receiving radiotherapy, although this association was lost if C3 score was removed from the model. Extremes of age, minority ethnicity, and public treatment were also associated with greater risk of non-concordance.

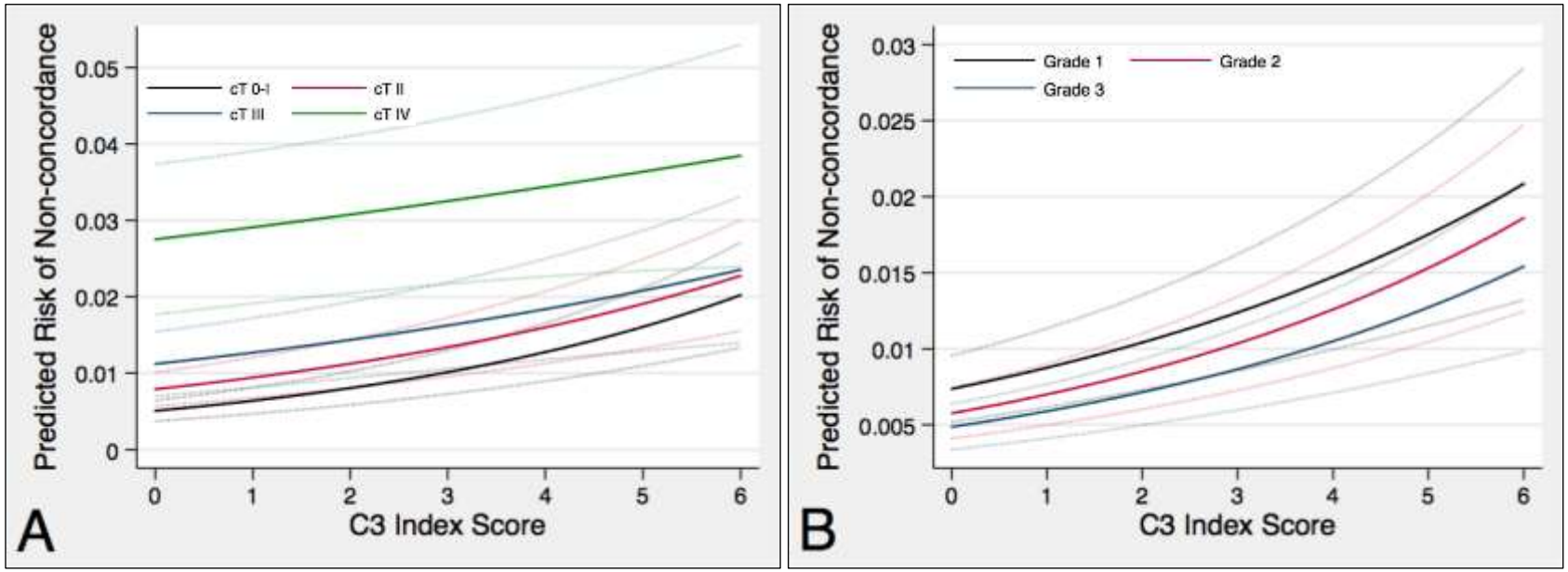


Figure 16. Interaction Plot Showing Adjusted Predicted Risk of Non-concordant Treatment by C3 Score within Strata of Tumour Factors: Receipt of Axillary Surgery

(A) Clinical T stage (B) Grade

Abbreviation: cT, clinical T stage.
C3 is a RCS.

Table 18. Risk Ratios for Non-concordant Treatment: Receipt of Adjuvant Radiotherapy

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score[a]						
0	[Ref]		<.001	[Ref]		<.001
1	1.86	1.60-2.16		1.43	1.19-1.72	
2	2.44	2.08-2.86		1.73	1.39-2.16	
3	2.89	2.51-3.35		2.01	1.60-2.53	
5	4.10	3.53-4.76		2.72	2.05-3.60	
Cardiac arrhythmia	3.17	2.51-4.01	<.001	0.94	0.75-1.19	.63
COPD/asthma	2.78	2.16-3.57	<.001	1.11	0.85-1.46	.44
Diabetes	1.85	1.44-2.38	<.001	0.87	0.66-1.14	.30
Hypertension	2.38	1.99-2.85	<.001	0.78	0.61-0.99	.04
Metabolic disorder	1.86	1.41-2.45	<.001	0.79	0.59-1.05	.10
Age at diagnosis, years[b]						
40	1.23	1.05-1.45	<.001	1.16	0.99-1.38	<.001
50	0.92	0.87-0.98		0.92	0.86-0.98	
60	[Ref]			[Ref]		
70	1.73	1.67-1.80		1.65	1.57-1.73	
80	3.86	3.49-4.31		3.40	2.97-3.86	
Ethnicity						
European	[Ref]		<.001	[Ref]		<.001
Māori	1.15	0.93-1.42		1.27	1.02-1.58	
Pacific peoples	1.72	1.39-2.12		1.88	1.51-2.35	
Asian	1.11	0.86-1.43		1.47	1.14-1.90	
Other ethnic groups	1.09	0.81-1.45		1.05	0.80-1.37	
Treatment facility						
Public	[Ref]		<.001	[Ref]		.02
Private	0.60	0.52-0.69		0.83	0.71-0.96	
NZDep2013, quintile						
1	[Ref]		<.001	[Ref]		.03
2	0.96	0.76-1.20		0.89	0.72-1.10	
3	1.32	1.08-1.62		1.17	0.96-1.42	
4	1.09	0.88-1.34		0.96	0.77-1.18	
5	1.45	1.19-1.77		1.15	0.94-1.41	

[a] RCS.

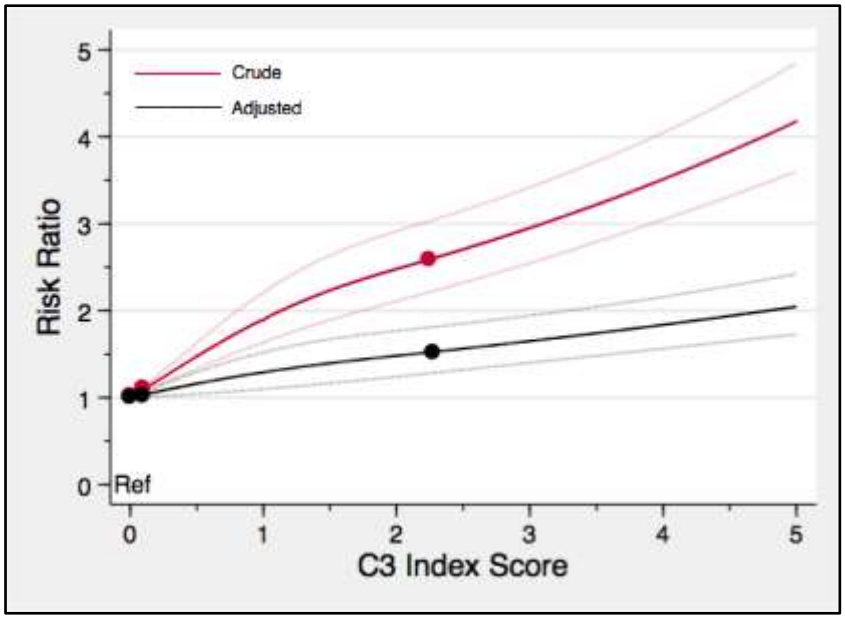


Figure 17. Risk Ratios for Non-concordant Treatment by C3 Score: Receipt of Radiotherapy

C3 is a RCS with reference value 0. Complete case analysis; *n*=7618.

6.3.2.4. Receipt of Adjuvant Chemotherapy

This analysis included 4119 patients, 1540 (37.4%) of whom did not receive chemotherapy as indicated. Non-treatment was more frequent amongst comorbid patients (64.8% of C3 category 2 and 45.4% of C3 category 1 vs 35.1% of C3 category 0; p<.001). Comorbidity severity was associated with non-treatment in a linear fashion, with an adjusted RR of 1.11 (95% CI 1.06-1.16, p<.001) per 1.0 unit change in C3 score (**Table 19**). Individual conditions showed associations in univariate analysis only. Other factors associated with non-concordance in the multivariate model were increasing age and Pacific ethnicity. The relationship between C3 score and chemotherapy was modified by tumour stage (p<.001) and grade (p<.001). While non-concordance was higher for lower stage and grade tumours overall, there were greater increases in the risk of non-concordance for higher stage and grade tumours with rising comorbidity severity (**Figure 18**).

Table 19. Risk Ratios for Non-concordant Treatment: Receipt of Adjuvant Chemotherapy

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	1.14	1.12-1.16	<.001	1.11	1.06-1.16	<.001
Cardiac arrhythmia	1.82	1.54-2.16	<.001	0.94	0.76-1.18	.61
COPD/asthma	1.61	1.33-1.96	<.001	1.01	0.80-1.27	.93
Diabetes	1.63	1.41-1.89	<.001	1.11	0.93-1.32	.24
Hypertension	1.57	1.38-1.79	<.001	0.78	0.64-0.94	.01
Metabolic disorder	1.54	1.29-1.83	<.001	0.88	0.73-1.06	.17
Age at diagnosis, years	1.05	1.05-1.05	<.001	1.05	1.04-1.05	<.001
Ethnicity						
European	[Ref]		.046	[Ref]		.19
Māori	0.88	0.77-1.01		0.98	0.85-1.12	
Pacific peoples	1.09	0.95-1.25		1.15	1.01-1.30	
Asian	0.86	0.74-0.99		1.05	0.91-1.20	
Other ethnic groups	1.00	0.84-1.20		0.95	0.80-1.13	
Treatment facility						
Public	[Ref]		<.001	[Ref]		.08
Private	0.85	0.78-0.92		0.93	0.85-1.01	
NZDep2013, quintile						
1	[Ref]		.45	[Ref]		.76
2	0.93	0.82-1.06		0.93	0.83-1.05	
3	0.95	0.84-1.08		0.94	0.84-1.06	
4	1.02	0.90-1.16		0.95	0.84-1.06	
5	1.03	0.92-1.16		0.95	0.85-1.07	

6.3.2.5. Receipt of HER2-directed Therapy

Of the 1010 patients included in this analysis, 173 (17.1%) did not receive treatment. Again, comorbidity severity was tied to non-receipt of treatment in a linear fashion, with an adjusted RR of 1.32 (95% CI 1.15-1.52, p<.001) per 1.0 unit change in C3 score (**Table 20**). While cardiac arrhythmia and COPD/asthma showed lower risk of non-concordance in the full model, neither retained statistical significance when C3 score were omitted. Advancing age, Pacific ethnicity, and public treatment were also associated with greater risk of not receiving HER2-directed therapy.

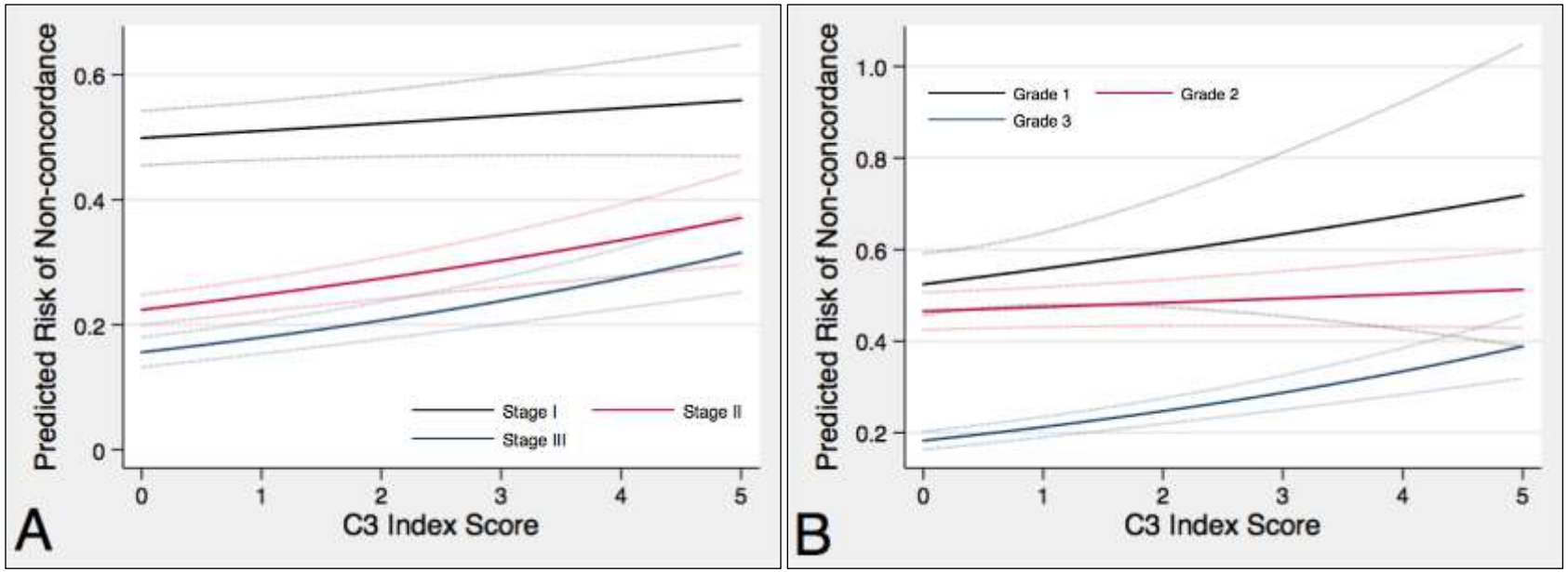


Figure 18. Interaction Plots Showing Adjusted Predicted Risk of Non-concordant Treatment by C3 Score within Strata of Tumour Factors: Receipt of Adjuvant Chemotherapy

(A) Stage (B) Grade

Table 20. Risk Ratios for Non-concordant Treatment: Receipt of HER2-directed Therapy

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	1.21	1.16-1.27	<.001	1.32	1.15-1.52	<.001
Cardiac arrhythmia	2.15	0.97-4.76	.06	0.32	0.10-0.99	.049
COPD/asthma	1.47	0.55-3.95	.45	0.31	0.14-0.70	.01
Diabetes	1.94	1.14-3.29	.02	0.80	0.41-1.58	.53
Hypertension	1.95	1.17-3.23	.01	0.61	0.29-1.29	.19
Metabolic disorder	1.30	0.54-3.13	.56	0.57	0.25-1.29	.18
Age at diagnosis, years[a]						
30	0.65	0.35-1.24	<.001	0.60	0.32-1.10	<.001
40	0.76	0.58-1.00		0.72	0.55-0.95	
50	[Ref]			[Ref]		
60	1.85	1.65-2.07		1.92	1.70-2.18	
70	4.34	3.29-5.71		4.68	3.51-6.24	
Ethnicity						
European	[Ref]		.01	[Ref]		.03
Māori	1.32	0.92-1.91		1.43	0.99-2.07	
Pacific peoples	1.75	1.24-2.48		1.82	1.23-2.70	
Asian	0.70	0.40-1.24		0.95	0.54-1.65	
Other ethnic groups	1.14	0.54-2.42		0.94	0.50-1.77	
Treatment facility						
Public	[Ref]		<.001	[Ref]		.002
Private	0.43	0.30-0.61		0.56	0.39-0.82	
NZDep2013, quintile						
1	[Ref]		.003	[Ref]		.34
2	1.05	0.61-1.80		0.86	0.53-1.41	
3	1.64	1.02-2.61		1.22	0.79-1.89	
4	1.25	0.75-2.06		0.94	0.59-1.50	
5	2.00	1.30-3.07		1.26	0.83-1.93	

[a] RCS.

6.3.2.6. Receipt of Endocrine Therapy

Endocrine therapy was indicated for 10 465 of the cohort, with 2475 (23.7%) non-concordant. There was a linear increase in the likelihood of non-treatment by comorbidity severity, with an adjusted RR of 1.05 (95% CI 1.01-1.10, p=.02) per 1.0 unit change in C3 score (**Table 21**). There was evidence of effect modification of this relationship by tumour grade (p<.001). Overall, non-concordance was higher for lower grade tumours; however, as the severity of comorbidity rose, the risk of non-concordance amongst patients with higher grade tumours increased, while non-concordance amongst patients with lower grade tumours was reduced (**Figure 19**).

None of the individual comorbidities examined were significantly associated with endocrine treatment in multivariate analysis. Extremes of age were associated with a lower likelihood of non-treatment, as well as Māori ethnicity and higher levels of socioeconomic deprivation.

Table 21. Risk Ratios for Non-concordant Treatment: Receipt of Endocrine Therapy

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	1.04	1.01-1.06	.002	1.05	1.01-1.10	.02
Cardiac arrhythmia	1.15	0.96-1.37	.14	0.99	0.81-1.21	.90
COPD/asthma	1.13	0.93-1.39	.22	1.01	0.81-1.26	.91
Diabetes	1.01	0.85-1.19	.93	0.88	0.72-1.07	.21
Hypertension	1.18	1.05-1.32	.01	1.08	0.91-1.28	.39
Metabolic disorder	1.04	0.87-1.24	.69	0.84	0.67-1.05	.12
Age at diagnosis, years[a]						
30	0.42	0.35-0.51	<.001	0.41	0.34-0.50	<.001
50	0.82	0.79-0.85		0.83	0.79-0.86	
60	[Ref]			[Ref]		
70	1.02	0.99-1.05		1.00	0.96-1.03	
90	0.81	0.70-0.94		0.74	0.63-0.88	
Ethnicity						
European	[Ref]		.001	[Ref]		.03
Māori	0.76	0.66-0.86		0.81	0.71-0.93	
Pacific peoples	0.91	0.79-1.05		1.01	0.87-1.18	
Asian	0.95	0.84-1.09		1.03	0.91-1.18	
Other ethnic groups	0.99	0.85-1.15		0.97	0.84-1.13	
Treatment facility						
Public	[Ref]		.25	[Ref]		.63
Private	1.04	0.97-1.12		0.98	0.91-1.07	
NZDep2013, quintile						
1	[Ref]		<.001	[Ref]		<.001
2	1.03	0.93-1.14		1.04	0.94-1.15	
3	0.88	0.79-0.98		0.88	0.79-0.97	
4	0.71	0.63-0.80		0.72	0.64-0.81	
5	0.85	0.76-0.94		0.86	0.77-0.96	

[a] RCS

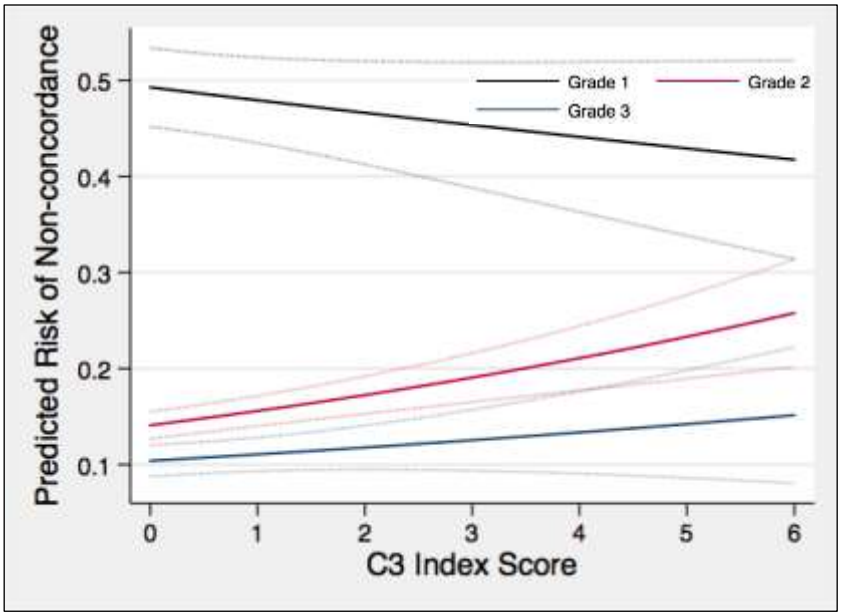


Figure 19. Interaction Plot Showing Adjusted Predicted Risk of Non-concordant Treatment by C3 Score within Strata of Tumour Grade: Receipt of Endocrine Therapy

6.3.3. Impacts of Comorbidity on Quality of Treatment

6.3.3.1. Quality of Surgery: Breast

A total of 12 275 patients were eligible for this analysis, of which 6001 (48.9%) received BCS, while 6274 (51.1%) underwent mastectomy. A greater proportion of comorbid patients underwent mastectomy than BCS (61.4% vs 38.6% in C3 category 2; 52.4% vs 47.6% in C3 category 1) compared with patients without comorbidity, where the split was even (**Figure 20**).

A total of 795 (6.48%) patients received non-concordant surgery, with no large differences by C3 category (p=.17). C3 score was not associated with the overall quality of breast surgery received in either univariate or multivariate analysis (**Table 22**). While diabetes was associated with lower risk of non-concordance (aRR 0.53, 95% CI 0.31-0.92, p=.02), a greater proportion of diabetic patients underwent mastectomy than BCS (56.8% vs 43.1%). Younger age (<60 years) and public treatment were additional factors related to lower risk of non-concordance.

Restricting the analysis to 6001 patients who underwent BCS as their final surgery revealed an association between C3 score and non-concordant breast surgery (ie, an inadequate surgical margin) in the multivariate model, with an adjusted RR of 1.12 (95% CI 1.01-1.24, p=.04).

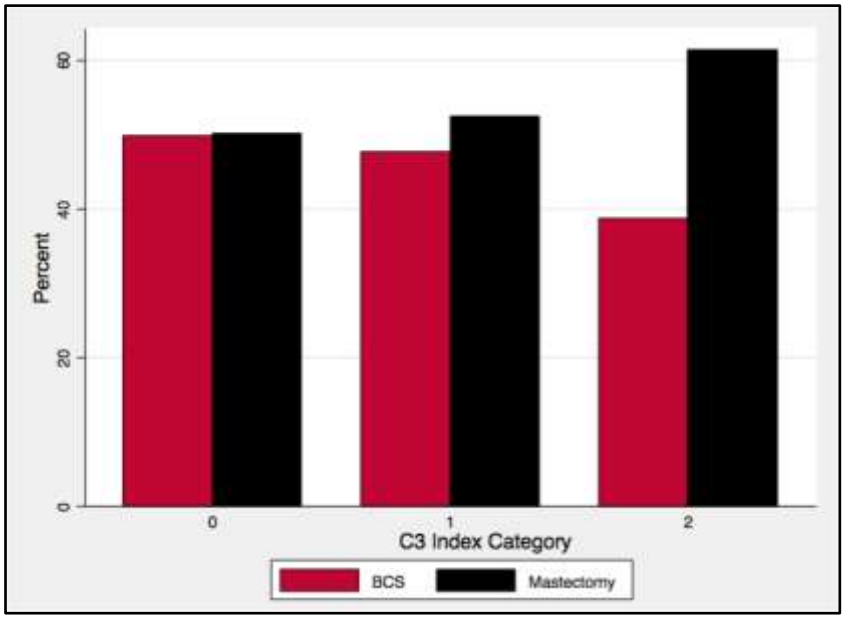


Figure 20. Final Breast Surgery by C3 Category

Table 22. Risk Ratios for Non-concordant Treatment: Quality of Breast Surgery

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	0.95	0.88-1.02	.15	1.04	0.94-1.16	.43
Cardiac arrhythmia	0.85	0.54-1.35	.50	0.86	0.52-1.42	.55
COPD/asthma	0.71	0.43-1.19	.20	0.75	0.43-1.31	.32
Diabetes	0.51	0.31-0.83	.01	0.53	0.31-0.92	.02
Hypertension	0.84	0.63-1.12	.23	0.93	0.66-1.33	.71
Metabolic disorder	0.79	0.52-1.21	.28	0.97	0.58-1.62	.91
Age at diagnosis, years[a]						
30	0.40	0.28-0.57	<.001	0.38	0.27-0.55	<.001
50	0.82	0.76-0.89		0.81	0.75-0.87	
60	[Ref]			[Ref]		
70	1.00	0.92-1.08		1.03	0.95-1.12	
90	0.79	0.57-1.11		0.88	0.63-1.22	
Ethnicity						
European	[Ref]		.01	[Ref]		.85
Māori	0.69	0.54-0.89		0.89	0.68-1.16	
Pacific peoples	0.67	0.49-0.92		0.92	0.67-1.28	
Asian	0.92	0.73-1.18		1.06	0.83-1.36	
Other ethnic groups	0.92	0.69-1.24		0.95	0.71-1.28	
Treatment facility						
Public	[Ref]		<.001	[Ref]		<.001
Private	1.49	1.30-1.70		1.38	1.19-1.60	
NZDep2013, quintile						
1	[Ref]		<.001	[Ref]		.19
2	0.83	0.68-1.02		0.88	0.72-1.07	
3	0.77	0.63-0.94		0.83	0.68-1.02	
4	0.73	0.59-0.90		0.83	0.67-1.03	
5	0.65	0.52-0.79		0.78	0.63-0.98	

[a] RCS.

6.3.3.2. Quality of Surgery: Axilla

Of 11 925 patients included in this analysis, 898 (7.53%) did not receive concordant axillary surgery, with no large differences by C3 category (p=.11). A greater proportion of comorbid patients underwent level II/III ALND compared with SLNB only (58.4% vs 36.9% in C3 category 2; 54.4% vs 41.5% in C3 category 1), than patients with no comorbidity (52.0% vs 45.4%) (**Figure 21**). Axillary sampling or level I ALND was also slightly more common amongst patients with a high level of comorbidity (4.7% in C3 category 2 vs 2.6% in C3 category 0).

There was no association between comorbidity and the overall quality of axillary surgery received in either univariate or multivariate analysis (**Table 23**). Age >60 years, other ethnicity, and private treatment were associated with lower concordance, while Asian ethnicity was associated with higher concordance.

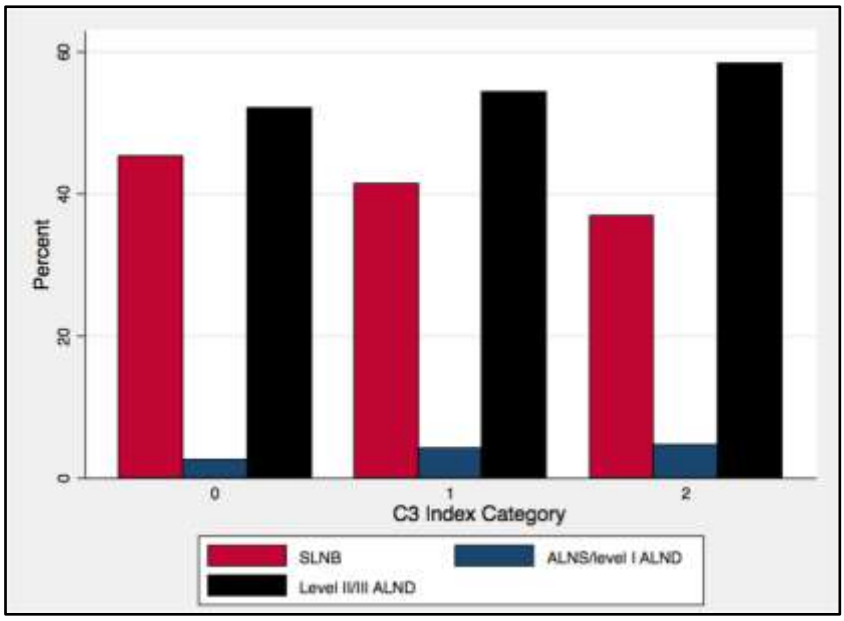


Figure 21. Final Axillary Surgery by C3 Category

Abbreviation: ALNS, axillary lymph node sampling.

Table 23. Risk Ratios for Non-concordant Treatment: Quality of Axillary Surgery

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	1.05	1.00-1.11	.07	1.01	0.91-1.12	.92
Cardiac arrhythmia	1.20	0.82-1.76	.34	0.99	0.63-1.53	.95
COPD/asthma	1.21	0.82-1.78	.34	1.22	0.80-1.89	.36
Diabetes	1.15	0.85-1.56	.37	1.20	0.84-1.73	.32
Hypertension	1.32	1.05-1.66	.02	1.16	0.84-1.59	.37
Metabolic disorder	1.13	0.81-1.58	.47	0.93	0.61-1.40	.72
Age at diagnosis, years[a]						
40	0.95	0.81-1.12	<.001	0.98	0.84-1.16	<.001
50	0.92	0.87-0.98		0.93	0.89-0.99	
60	[Ref]			[Ref]		
70	1.23	1.15-1.32		1.23	1.15-1.32	
80	1.63	1.38-1.93		1.63	1.36-1.93	
Ethnicity						
European	[Ref]		<.001	[Ref]		.004
Māori	0.61	0.48-0.79		0.77	0.60-1.01	
Pacific peoples	0.61	0.45-0.82		0.76	0.55-1.05	
Asian	0.65	0.50-0.86		0.75	0.57-0.99	
Other ethnic groups	1.25	0.99-1.58		1.29	1.02-1.64	
Treatment facility						
Public	[Ref]		<.001	[Ref]		<.001
Private	1.55	1.37-1.76		1.60	1.39-1.83	
NZDep2013, quintile						
1	[Ref]		.02	[Ref]		.78
2	0.94	0.78-1.14		1.00	0.83-1.21	
3	1.01	0.84-1.21		1.10	0.92-1.33	
4	0.84	0.69-1.02		0.99	0.81-1.21	
5	0.75	0.62-0.92		0.99	0.80-1.22	

[a] RCS.

6.3.3.3. Quality of Adjuvant Radiotherapy

Quality of adjuvant radiotherapy was evaluated in 7871 of the study cohort, with 5419 (68.8%) receiving radiotherapy following BCS, and 2452 (31.2%) after mastectomy. Non-concordant doses of radiation were received by 959 (12.2%) of the analysis cohort. Of the 368 patients receiving non-concordant radiation post-mastectomy, 139 (37.8%) received a hypofractionated regime (between 40 and 45Gy in 15-24 fractions).

Comorbidity (overall) (RR 1.12, 95% CI 1.07-1.18, p<.001) and diabetes (RR 1.51, 95% CI 1.16-1.97, p=.002) were associated with a higher likelihood of receiving non-concordant doses of radiotherapy in univariate analysis, but not multivariate (**Table 24**). In the adjusted model, extremes of age, Asian ethnicity, public treatment, and increasing levels of socioeconomic deprivation were associated with non-concordance.

Table 24. Risk Ratios for Non-concordant Treatment: Quality of Adjuvant Radiotherapy

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 index score	1.12	1.07-1.18	<.001	1.09	0.98-1.20	.10
Cardiac arrhythmia	1.23	0.82-1.85	.32	0.79	0.52-1.20	.27
COPD/asthma	1.25	0.84-1.87	.27	0.88	0.57-1.37	.58
Diabetes	1.51	1.16-1.97	.002	1.04	0.76-1.42	.82
Hypertension	1.26	1.00-1.59	.06	0.77	0.56-1.07	.12
Metabolic disorder	1.29	0.94-1.77	.11	0.87	0.60-1.27	.48
Age at diagnosis, years[a]						
40	1.31	1.15-1.49	<.001	1.25	1.09-1.42	<.001
50	0.99	0.94-1.03		0.97	0.93-1.02	
60	[Ref]			[Ref]		
70	1.45	1.35-1.54		1.40	1.31-1.51	
80	2.41	2.05-2.83		2.29	1.93-2.69	
Ethnicity						
European	[Ref]		<.001	[Ref]		<.001
Māori	1.42	1.19-1.68		1.11	0.93-1.33	
Pacific peoples	1.36	1.09-1.69		1.02	0.81-1.28	
Asian	1.48	1.21-1.79		1.43	1.17-1.74	
Other ethnic groups	0.70	0.50-0.98		0.64	0.46-0.89	
Treatment facility						
Public	[Ref]		<.001	[Ref]		<.001
Private	0.36	0.31-0.42		0.41	0.35-0.49	
NZDep2013, quintile						
1	[Ref]		<0.001	[Ref]		.02
2	1.12	0.90-1.39		1.01	0.81-1.25	
3	1.50	1.23-1.83		1.24	1.02-1.51	
4	1.71	1.40-2.07		1.28	1.04-1.56	
5	1.89	1.57-2.28		1.33	1.09-1.62	

[a] RCS.

6.3.3.4. Quality of Chemotherapy

A total of 4385 patients were included in this analysis, with half (51.2%) receiving a suboptimal number of cycles for their intended chemotherapy regime. Comparatively few patients with comorbidity were included in this analysis (C3 category 1: 443 [10.1%]; C3 category 2: 93 [2.12%]). Overall, more than half of patients received a combination anthracycline/taxane regime (60.7%), with an additional 36.9% receiving an anthracycline-containing regime without a taxane. Only 8 patients (0.18%) received CMF. The majority of patients with C3 category 2 comorbidity received combination anthracycline/taxane chemotherapy (73.1%), with only 1 receiving CMF alone (**Figure 22**).

Overall, comorbidity showed a strong negative association with the likelihood of completing the intended number of chemotherapy cycles, with an adjusted RR of non-concordance of 1.15 (95% CI 1.09-1.21, p<.001) per 1.0 unit change in C3 score (**Table 25**). Diabetes, hypertension, and metabolic disorders were also associated with non-concordance in univariate analysis, but lost statistical significance the multivariate model. In the adjusted model, COPD/asthma showed a reduced likelihood of non-concordance, which lost statistical significance if overall C3 score was omitted. Other factors associated with non-concordance in the multivariate model were increasing age, Pacific/Asian ethnicity, and public treatment. Increasing levels of socioeconomic deprivation were associated with reduced likelihood of non-concordant chemotherapy.

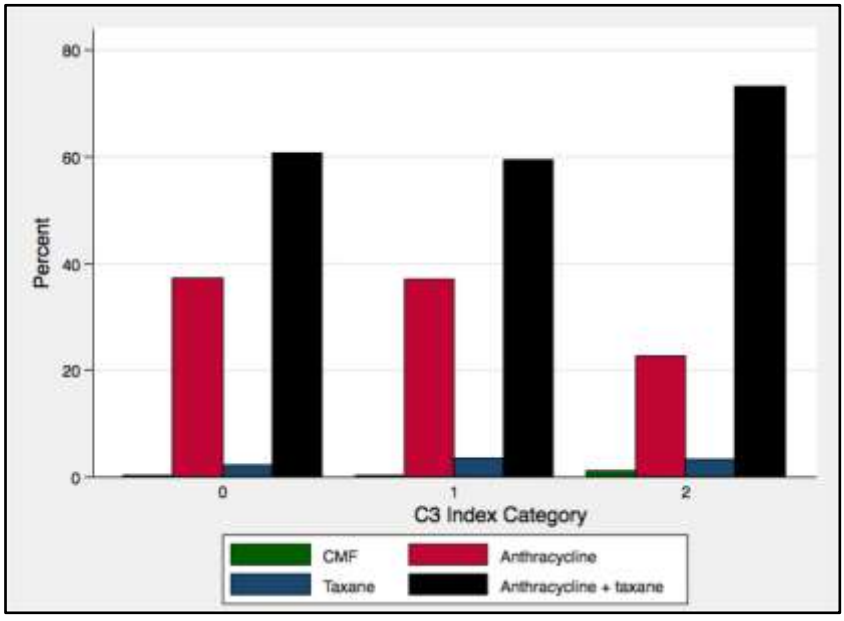


Figure 22. Chemotherapy Regime by C3 Category

Table 25. Risk Ratios for Non-concordant Treatment: Quality of Chemotherapy

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	1.11	1.08-1.14	<.001	1.15	1.09-1.21	<.001
Cardiac arrhythmia	1.21	0.96-1.52	.10	0.91	0.70-1.18	.47
COPD/asthma	0.93	0.72-1.21	.58	0.72	0.56-0.94	.02
Diabetes	1.24	1.05-1.46	.01	0.97	0.81-1.16	.74
Hypertension	1.29	1.13-1.47	<.001	0.95	0.79-1.14	.55
Metabolic disorder	1.28	1.07-1.52	.01	0.92	0.75-1.12	.41
Age at diagnosis, years	1.01	1.01-1.01	<.001	1.01	1.01-1.01	<.001
Ethnicity						
European	[Ref]		<.001	[Ref]		<.001
Māori	0.95	0.86-1.05		1.00	0.90-1.11	
Pacific peoples	1.20	1.09-1.31		1.29	1.17-1.43	
Asian	1.25	1.15-1.36		1.31	1.20-1.42	
Other ethnic groups	1.07	0.94-1.23		1.05	0.92-1.19	
Treatment facility						
Public	[Ref]		.01	[Ref]		.01
Private	0.93	0.87-0.98		0.92	0.87-0.98	
NZDep2013, quintile						
1	[Ref]		<.001	[Ref]		<.001
2	0.97	0.89-1.06		0.95	0.87-1.03	
3	0.93	0.85-1.01		0.90	0.83-0.98	
4	0.82	0.74-0.90		0.76	0.69-0.84	
5	0.89	0.82-0.97		0.82	0.74-0.89	

6.3.3.5. Quality of Adjuvant Endocrine Therapy

A total of 5586 patients were included this analysis, with half (49.3%) deemed to be non-concordant, possessing an MPR <80%. Suboptimal adherence was more frequent amongst patients with no comorbidity (50.3% in C3 category 0 vs 49.0% and 35.2% in C3 categories 1 and 2 respectively; p<.001). **Figure 23** shows the proportions of patients within each MPR decile by C3 category. Overall, the greatest number of patients were in the highest MPR decile (>90% adherence), with C3 category 2 patients comprising the greatest proportion. Tamoxifen was the first prescribed endocrine therapy in 55.7% of the cohort, with the remainder receiving an aromatase inhibitor. Proportionally more C3 category 2 patients received an aromatase inhibitor as initial treatment (56.7%) than C3 category 1 (47.7%), or 0 (43.0%) patients.

Comorbidity was related to endocrine adherence, with reduced likelihood of non-concordance with rising levels of comorbidity (aRR 0.94, 95% CI 0.88-0.997, p=.04) (**Table 26**). The individual comorbidities of cardiac arrhythmia, diabetes, hypertension, and metabolic disorder were associated with lower risk of non-concordance in univariate, but not multivariate analysis. Other factors associated with lower risk of non-concordant-treatment in multivariate analysis were increasing age, other ethnicity, and private treatment. Conversely, Māori and Pacific ethnicity displayed a higher risk of suboptimal adherence.

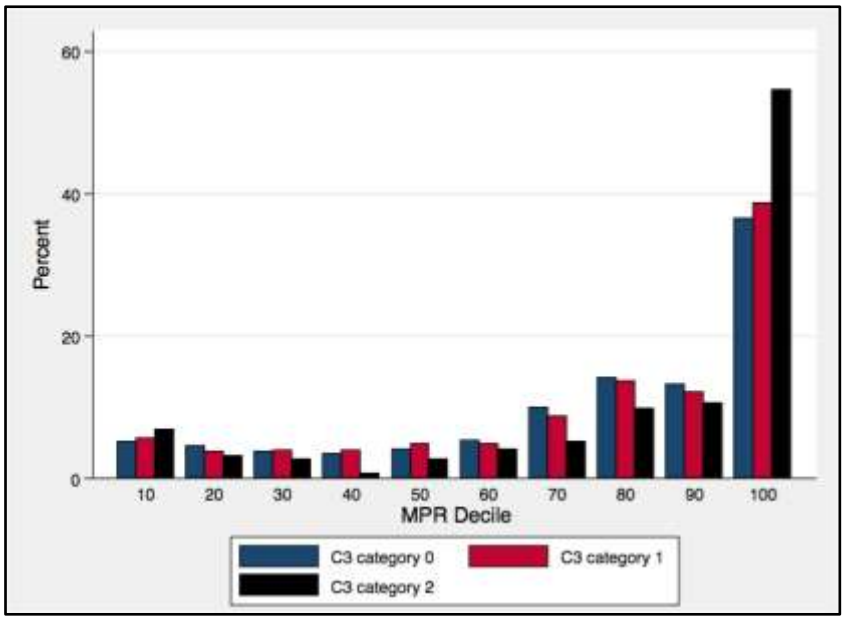


Figure 23. Proportions within MPR Deciles by C3 Category

Table 26. Risk Ratios for Non-concordant Treatment: Quality of Endocrine Therapy

	Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	0.92	0.89-0.96	<.001	0.94	0.88-0.997	.04
Cardiac arrhythmia	0.76	0.61-0.94	.01	0.98	0.78-1.24	.88
COPD/asthma	0.86	0.69-1.07	.19	1.02	0.81-1.28	.87
Diabetes	0.84	0.72-0.99	.03	0.97	0.80-1.18	.74
Hypertension	0.77	0.66-0.88	<.001	0.99	0.82-1.21	.96
Metabolic condition	0.79	0.66-0.94	.01	1.06	0.84-1.33	.64
Age at diagnosis, years	0.99	0.99-0.99	<.001	0.99	0.99-0.99	<.001
Ethnicity						
European	[Ref]		<.001	[Ref]		<.001
Māori	1.18	1.10-1.27		1.12	1.04-1.21	
Pacific peoples	1.29	1.18-1.40		1.19	1.08-1.30	
Asian	1.01	0.91-1.11		0.92	0.83-1.01	
Other ethnic groups	0.84	0.72-0.98		0.85	0.73-0.98	
Treatment facility						
Public	[Ref]		.003	[Ref]		<.001
Private	0.92	0.87-0.97		0.89	0.84-0.95	
NZDep2013, quintile						
1	[Ref]		.002	[Ref]		.03
2	1.05	0.96-1.14		1.03	0.95-1.12	
3	0.92	0.84-0.999		0.91	0.83-0.99	
4	0.97	0.89-1.06		0.94	0.86-1.02	
5	1.07	0.99-1.16		0.99	0.91-1.08	

6.3.4. Impacts of Comorbidity on Timeliness of Treatment

6.3.4.1. Timeliness of Primary Breast Surgery

The timeliness of primary breast surgery was evaluated in 11 621 patients. Non-receipt of surgery within 31 days of diagnosis occurred in 4440 patients (38.2%), with 217 (1.87%) experiencing a further delay beyond 90 days. The relationship between C3 score and non-receipt of surgery by 31 and 90 days for adjusted models is shown in **Figure 24**. In univariate analysis, comorbidity, as both an overall measure (p<.001) and individual conditions (cardiac arrhythmia, diabetes, hypertension, and metabolic disorder), was associated with higher risk of not receiving surgery within 31 days (**Table 27**). In the multivariate model, C3 was no longer associated with delay, while inverse associations for COPD/asthma (aRR 0.76, 95% CI 0.66-0.89, p=.001) and diabetes (aRR 0.82, 95% CI 0.73-0.93, p=.001) became apparent.

In the 90 day models, C3 (p<.001) and the individual comorbidities of COPD/asthma, hypertension, and metabolic disorder were again associated with non-concordance in crude analysis. In the multivariate model, C3 score was associated with non-concordance (p=.01), particularly at high levels of comorbidity severity (point estimate at C3 score 5: aRR 2.49, 95% CI 1.20-5.21). Again, paradoxically, diabetes was associated with a lower risk of non-concordance at 90 days, with an adjusted RR of 0.43 (95% CI 0.24-0.79, p=.01). Other factors associated with non-concordance at 91 days were advanced age, Pacific ethnicity, and public treatment.

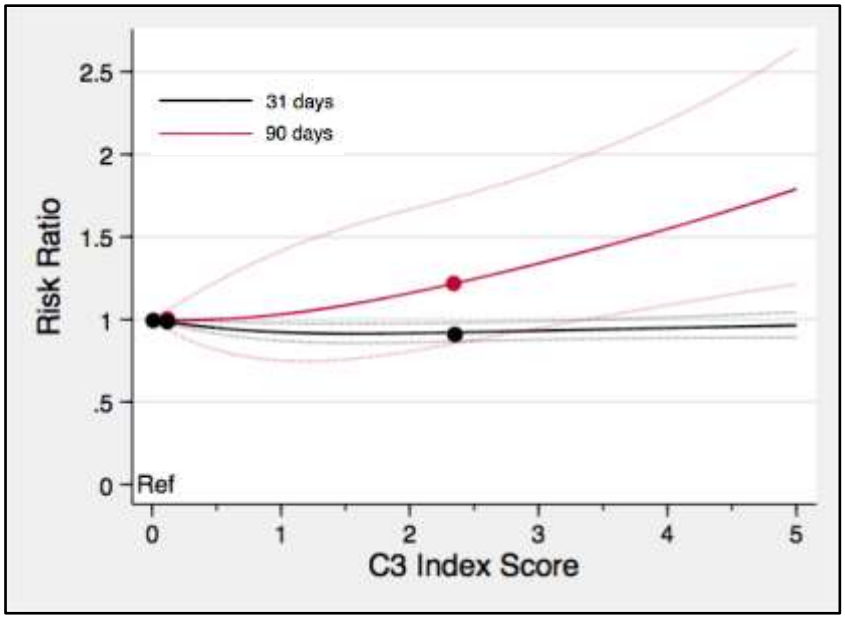


Figure 24. Adjusted Risk Ratios for Non-concordant Treatment by C3 Score: Timeliness of Primary Breast Surgery, 31 and 90 Day Models

C3 is a RCS with reference value 0. Complete case analysis; *n*=11 495.

Table 27. Risk Ratios for Non-concordant Treatment: Timeliness of Breast Surgery

	>31 Days						>90 Days					
	Univariate			Multivariate			Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score[a]												
0	[Ref]		<.001	[Ref]		.05	[Ref]		<.001	[Ref]		.01
1	1.20	1.13-1.27		0.95	0.88-1.02		1.40	1.04-1.92		1.15	0.76-1.73	
2	1.28	1.20-1.36		0.96	0.88-1.05		1.73	1.22-2.46		1.39	0.82-2.34	
3	1.32	1.25-1.40		0.99	0.90-1.11		2.05	1.49-2.86		1.68	0.94-3.00	
5	1.42	1.31-1.54		1.06	0.91-1.23		2.89	2.03-4.10		2.49	1.20-5.21	
Cardiac arrhythmia	1.37	1.23-1.53	<.001	1.07	0.95-1.20	.27	2.51	1.48-4.26	.001	1.07	0.53-2.14	.85
COPD/asthma	1.07	0.92-1.23	.39	0.76	0.66-0.89	.001	1.34	0.63-2.81	.45	0.56	0.25-1.25	.16
Diabetes	1.25	1.13-1.38	<.001	0.82	0.73-0.93	.001	1.44	0.81-2.55	.22	0.43	0.24-0.79	.01
Hypertension	1.32	1.23-1.42	<.001	1.09	0.98-1.21	.10	2.11	1.44-3.10	<.001	1.05	0.59-1.87	.86
Metabolic disorder	1.22	1.09-1.36	<.001	0.92	0.81-1.05	.23	2.12	1.27-3.55	.004	1.15	0.61-2.15	.66
Age, years[a]												
40	0.76	0.70-0.81	<.001	0.78	0.73-0.84	<.001	1.38	1.02-1.84	<.001	1.34	1.00-1.79	.04
50	0.90	0.87-0.91		0.92	0.90-0.94		1.06	0.95-1.17		1.07	0.96-1.20	
60	[Ref]			[Ref]			[Ref]			[Ref]		
70	1.04	1.02-1.07		0.98	0.96-1.01		1.23	1.07-1.40		1.15	0.99-1.34	
80	1.05	0.98-1.12		0.91	0.86-0.97		1.75	1.25-2.46		1.48	1.03-2.14	
Ethnicity												
European	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001
Māori	1.62	1.52-1.71		1.09	1.03-1.15		1.85	1.26-2.71		1.31	0.88-1.96	
Pacific	1.58	1.47-1.70		1.04	0.97-1.12		4.10	2.93-5.73		2.89	2.01-4.16	
Asian	1.14	1.05-1.24		1.01	0.94-1.09		1.13	0.67-1.90		1.07	0.62-1.82	
Other	1.01	0.90-1.12		0.86	0.78-0.95		0.82	0.40-1.67		0.73	0.36-1.48	
Facility												
Public	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001
Private	0.19	0.17-0.20		0.19	0.18-0.21		0.20	0.13-0.30		0.27	0.17-0.42	
NZDep2103, quintile												
1	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001	[Ref]		.19
2	1.18	1.08-1.29		1.01	0.93-1.09		1.19	0.70-2.01		0.97	0.58-1.64	
3	1.37	1.26-1.49		1.03	0.96-1.11		1.49	0.91-2.44		1.09	0.66-1.80	
4	1.63	1.50-1.77		1.06	0.99-1.14		2.51	1.60-3.94		1.55	0.98-2.45	
5	2.06	1.92-2.22		1.21	1.13-1.30		2.65	1.71-4.09		1.26	0.81-1.98	

[a] RCS.

6.3.4.2. Timeliness of Adjuvant Therapy

Overall, 8765 patients were included in the analysis; 4678 (53.4%) of which received radiotherapy as their first adjuvant treatment, with the remaining 4087 (46.6%) undergoing initial chemotherapy and/or HER2-directed therapy. Overall, 76.7% of patients did not receive treatment within 6 weeks, dropping to 16.9% by 12 weeks. Non-concordance was largely driven by patients receiving radiotherapy as their first treatment, with 85.8% experiencing delays >6 weeks and 26.8% >12 weeks. Of the patients who received systemic therapy as their initial treatment, 66.2% experienced delays >6 weeks, improving to 5.48% by 12 weeks post-surgery.

While there was an association between C3 score and delay to first adjuvant therapy beyond 6 (RR 1.05, 95% CI 1.04-1.06, p<.001) and 12 weeks (RR 1.18, 95% CI 1.14-1.22, p<.001) in crude analysis, this was not retained following adjustment in the multivariate models (6 weeks: aRR 1.00, 95% CI 0.99-1.02, p=.74; 12 weeks: aRR 1.00, 95% CI 0.92-1.08, p=.98). Amongst patients who received radiotherapy as their first adjuvant therapy, C3 score was associated with delays beyond 6 and 12 weeks in univariate analysis, but not multivariate (**Table 28**). In multivariate analysis, while there were no associations between individual conditions and delays >6 weeks, patients with COPD/asthma (aRR 1.60, 95% CI 1.25-2.06, p<.001) and hypertension (aRR 1.36, 95% CI 1.09-1.70, p=.01) were more likely to have delays >12 weeks.

Again, amongst patients who received systemic therapy (chemotherapy and/or HER2-directed therapy) as first adjuvant treatment, C3 score was only associated with delays >6 and 12 weeks in univariate analysis (**Table 29**). Cardiac arrhythmia, diabetes, hypertension, and metabolic disorder were related to delays >6 weeks in univariate analyses, with only cardiac arrhythmia retaining significance in the multivariate model (aRR 1.24, 95% CI 1.12-1.38, p<.001). Diabetes and hypertension also showed associations with delay in univariate analyses using a 12 week threshold, although these were no longer observed following adjustment in the multivariate model.

6.4. Conclusions

Chapter 6 outlined the results of Study 2, which investigated the effects of comorbidity on breast cancer diagnosis and the standards of treatments received. Overall, comorbidity burden had a negative impact on diagnosis, reducing the likelihood of screen-detection, and increasing the risks of unknown and higher stage at diagnosis. Comorbidity also reduced the likelihood of receiving all treatment modalities, with relatively greater impacts on surgery, radiotherapy, and HER2-directed therapy than chemotherapy and endocrine therapy. There was also effect modification of some of these relationships by tumour stage and grade. For comorbid patients who did receive treatment, the quality and timeliness of that treatment was variable, depending on the therapeutic modality assessed. An important next step is to examine the impact on survival for comorbid patients who do receive treatment. This will be the subject of investigation in Chapter 7.

Table 28. Risk Ratios for Non-concordant Treatment: Timeliness of Adjuvant Radiotherapy

	>6 Weeks						>12 Weeks					
	Univariate			Multivariate			Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 index score	1.03	1.02-1.03	<.001	1.00	0.99-1.02	.70	1.10	1.06-1.14	<.001	0.98	0.90-1.05	.54
Cardiac arrhythmia	1.03	0.96-1.11	.41	0.96	0.89-1.03	.27	1.27	0.97-1.68	.08	1.04	0.78-1.39	.77
COPD/asthma	1.10	1.04-1.16	<.001	1.03	0.97-1.10	.28	1.88	1.54-2.30	<.001	1.60	1.25-2.05	<.001
Diabetes	1.11	1.07-1.15	<.001	0.99	0.95-1.04	.72	1.32	1.09-1.61	.01	0.90	0.71-1.15	.41
Hypertension	1.07	1.03-1.11	<.001	1.00	0.95-1.05	.93	1.42	1.23-1.65	<.001	1.35	1.08-1.68	.01
Metabolic condition	1.12	1.08-1.16	<.001	1.05	1.00-1.11	.08	1.35	1.10-1.66	.004	1.05	0.80-1.39	.72
Age, years	1.001	1.001-1.002	<.001	1.00	1.00-1.00	.26	1.00	0.99-1.00	.34	1.00	0.99-1.00	.10
Ethnicity												
European	[Ref]		<.001	[Ref]		.54	[Ref]		<.001	[Ref]		<.001
Māori	1.09	1.06-1.12		1.01	0.97-1.04		1.45	1.26-1.67		1.22	1.05-1.41	
Pacific	1.11	1.08-1.15		1.02	0.98-1.06		1.85	1.60-2.15		1.53	1.31-1.80	
Asian	1.05	1.01-1.10		1.03	0.99-1.08		1.02	0.83-1.25		0.98	0.80-1.20	
Other	1.01	0.96-1.06		0.99	0.94-1.04		1.14	0.93-1.39		1.11	0.92-1.35	
Facility												
Public	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001
Private	0.79	0.77-0.82		0.81	0.78-0.83		0.63	0.57-0.70		0.69	0.62-0.78	
NZDep2103, quintile												
1	[Ref]		<.001	[Ref]		.02	[Ref]		<.001	[Ref]		.58
2	1.04	0.99-1.08		1.02	0.98-1.06		1.03	0.88-1.21		0.98	0.83-1.14	
3	1.09	1.05-1.13		1.04	1.00-1.08		1.10	0.94-1.28		1.01	0.86-1.18	
4	1.14	1.10-1.18		1.06	1.02-1.10		1.29	1.11-1.49		1.09	0.94-1.27	
5	1.15	1.10-1.19		1.05	1.01-1.08		1.39	1.20-1.60		1.07	0.92-1.25	

Table 29. Risk Ratios for Non-concordant Treatment: Timeliness of Adjuvant Chemotherapy/HER2-directed Therapy

	>6 Weeks						>12 Weeks					
	Univariate			Multivariate			Univariate			Multivariate		
Characteristic	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**	**RR**	**95% CI**	**P value**
C3 score	1.06	1.03-1.10	<.001	1.00	0.95-1.05	.95	1.24	1.08-1.41	.002	1.12	0.83-1.51	.45
Cardiac arrhythmia	1.35	1.21-1.50	<.001	1.24	1.12-1.38	<.001	2.05	0.89-4.73	.09	1.41	0.52-3.79	.50
COPD/asthma	1.06	0.89-1.26	.50	0.94	0.78-1.13	.52	0.64	0.16-2.50	.52	0.33	0.08-1.31	.11
Diabetes	1.29	1.18-1.42	<.001	1.08	0.97-1.21	.16	2.31	1.27-4.19	.01	1.37	0.70-2.67	.36
Hypertension	1.12	1.005-1.26	.04	0.93	0.81-1.08	.35	1.83	1.03-3.26	.04	0.99	0.41-2.37	.98
Metabolic disorder	1.21	1.07-1.37	.002	1.10	0.96-1.27	.19	1.70	0.79-3.69	.18	0.92	0.32-2.62	.88
Age, years	1.003	1.001-1.01	<.001	1.003	1.001-1.01	.01	1.00	0.99-1.02	.32	1.01	0.99-1.02	.43
Ethnicity												
European	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001	[Ref]		.18
Māori	1.14	1.07-1.22		0.99	0.92-1.05		2.08	1.51-2.87		1.45	1.02-2.06	
Pacific	1.36	1.28-1.43		1.16	1.09-1.23		1.83	1.22-2.74		1.22	0.79-1.88	
Asian	1.12	1.05-1.20		1.05	0.98-1.13		0.96	0.59-1.56		0.82	0.50-1.34	
Other	1.17	1.07-1.28		1.09	1.00-1.18		1.44	0.83-2.51		1.21	0.70-2.09	
Facility												
Public	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001	[Ref]		<.001
Private	0.64	0.60-0.67		0.65	0.62-0.69		0.30	0.21-0.41		0.33	0.23-0.48	
NZDep2103, quintile												
1	[Ref]		<.001	[Ref]		.69	[Ref]		.002	[Ref]		.63
2	1.12	1.04-1.21		1.06	0.98-1.14		1.09	0.69-1.72		0.93	0.59-1.47	
3	1.13	1.05-1.22		1.03	0.96-1.11		1.41	0.92-2.16		1.08	0.70-1.67	
4	1.19	1.11-1.28		1.02	0.95-1.10		1.31	0.85-2.04		0.87	0.55-1.37	
5	1.28	1.19-1.37		1.04	0.97-1.12		2.01	1.37-2.96		1.15	0.75-1.74	

Chapter 7. Study 3

The Effects of Breast Cancer Treatment on Survival in Relation to Comorbidity

7.1. Introduction

Chapter 7 outlines the third study of this thesis, which aims to determine the survival impacts of breast cancer treatments in the context of comorbidity. The results are presented in 4 sections examining the treatment effects of surgery, adjuvant radiotherapy, adjuvant chemotherapy, and endocrine therapy.

7.1.1. Aims

Study 3 focuses on the fourth research objective:

- To determine the effects of breast cancer treatments on survival in relation to comorbidity.

The specific aims of this study were:

1. To obtain estimates of the survival impacts of breast cancer treatments in a real-world population of women with breast cancer.
2. To investigate how treatment effects may be modified by the presence of comorbidity.

7.2. Methods

7.2.1. Population

Separate eligibility criteria were applied to each treatment effects analysis. For adjuvant radiotherapy, adjuvant chemotherapy, and endocrine therapy, the inclusion/exclusion criteria were the same as those applied in Study 2; as specified in **Sections 4.6.1.3-4** and **Section 4.6.1.6**. In Study 2, receipt of surgery was split into analyses examining breast and axillary surgery separately. However, exploratory analyses of the data revealed that there was minimal overlap in propensity scores between patients who did and did not receive singular breast or axillary surgery, which precluded any attempt to estimate their treatment effects individually. Study 3 therefore evaluated the treatment effects of breast and axillary surgery combined, using the eligibility criteria specified in **Section 4.6.1.1.**

7.2.2. Variables

In Study 3, the exposure variables of interest were the receipt of guideline-concordant treatments (breast/axillary surgery, adjuvant radiotherapy, adjuvant chemotherapy, and endocrine therapy), defined as per Section 4.6 (summarised in **Table 3**). For the breast/axillary surgery combined analysis, receipt of both breast and axillary surgery was required for concordance.

Covariates were selected for inclusion in propensity score estimation models based on their hypothesised influence over receipt of treatment and survival. Year of diagnosis was also included in order to account for potential changes in treatment delivery (eg, chemotherapy regime, radiation fractionation schedule) over the study period, which may have affected treatment assignment.[664] While individual, health service access, and cancer factors were the same for each treatment modality under study, the inclusion of other treatment factors differed depending on the analysis. All treatment variables were included in propensity score models for endocrine therapy, as the receipt of treatment was considered irrespective of the temporal setting (primary, neoadjuvant, or adjuvant). Breast surgical status was not required in propensity score models for adjuvant treatments (radiotherapy and chemotherapy). For breast/axillary surgery, all other treatment variables were excluded, as these represented (in most cases, other than the small number who received neoadjuvant therapy) post-baseline variables which may have been influenced by the receipt of surgery.[664,669] However, as the receipt of other treatment is an important predictor of survival, for the surgery analyses, these variables were included instead as covariates in the subsequent weighted outcome models.[669]

Heterogeneity in treatment effects (effect modification) was assessed in relation to comorbidity. Interaction tests were performed using C3 score as a continuous variable. Subgroup analysis was performed within the 3 strata of C3 categories, as well as the 5 selected individual conditions.

All-cause mortality was the primary outcome variable of interest. An important secondary outcome was breast cancer-specific mortality, with non-breast cancer death serving as a competing cause.

7.2.3. Data Analysis

Missing values analysis revealed between 20-24% missing data in covariates. Imputation models for each treatment effects analysis were created including propensity score covariates with missing data, fully observed covariates, relevant auxiliary variables, treatment status, mortality event indicator variables, and Nelson-Aalen estimators of the cumulative baseline hazard $H(T)$. An initially specified, main effects binomial logistic regression model was run within each imputed dataset, regressing covariates on the log odds of concordant treatment. Propensity scores were predicted from the model (as estimated probabilities) for each participant. Propensity score distributions (on the logit scale) between treatment groups were compared graphically using kernel density plots (displayed in **Appendix B**, **Figure 34**) to identify the area of common support,

with off-support individuals discarded.[669,705] Stabilised IPT- and SMR-weights were created using the `propwt` program.[706] Weights smaller than the 1st centile and larger than the 99th centile were then trimmed to the values of the weight representing the 1st and 99th centile respectively.[680,684]

Standardised differences between covariate means for raw (using complete cases; including missing data indicators), SMR- and IPT-weighted treated and untreated pseudo-populations were calculated within each imputed dataset using the `pbalchk` command,[707] with results averaged for display purposes[708] (**Appendix B**, **Figure 35**). A general threshold for imbalance of 0.25 was applied, however, given the bias implications for strongly prognostic covariates, a decision was made to aim for differences of <0.10 for C3 score, age, and stage. If acceptable balance was not achieved as stipulated, an iterative process was followed, reformulating the propensity score model by including higher order polynomial terms, nonlinear terms, and/or interaction terms.

Once balance was acceptable, Cox proportional hazards (producing HRs of all-cause and breast cancer-specific mortality) and Fine and Gray competing risks (for sHRs of breast cancer mortality) regression models were estimated for the overall analysis cohort within SMR- and IPT-weighted samples in each imputed dataset. Results were combined using Rubin's rules with robust standard errors.[686,687] Sensitivity analyses were conducted using bootstrapped SEs with 5000 replications (with empirical analyses suggesting this was sufficient to yield stable estimates). However, as variance estimates were similar, and some iterations failed to converge, only results from robust estimators are presented.

Heterogeneity in treatment effects due to comorbidity was evaluated by Wald tests for interaction between C3 index score and treatment status. As potential effect modification by comorbidity was of a priori interest, confirmatory subgroup analysis was then performed, modelling treatment effects within each C3 index category. Estimated interaction effects were calculated as the ratio of HRs (or sHRs) for C3 category 1 (and 2) with reference to C3 category 0.[709] Treatment effects were also modelled within subgroups of patients possessing the 5 selected individual conditions.

Sensitivity analyses were performed using untrimmed weights and conventional regression methods, with results summarised in **Appendix C**, **Figures 36-39**.

Kaplan-Meier survival curves for all-cause and breast cancer-specific survival, and cumulative incidence function curves for breast cancer mortality by C3 category were produced from both weighted samples for radiotherapy, chemotherapy and endocrine therapy analyses. As these were essentially identical, only plots derived from IPT-weighted samples are presented. Cox tests of equality were used for comparisons of survival curves.[710] For the surgery analyses, adjusted survival curves were predicted from Cox models controlling for other treatment received.

7.3. Results

7.3.1. Surgery

A total of 316 patients outside common support (18 below and 298 above) were truncated from the original analysis population of 12 830, leaving 12 514 in the weighted analysis sample (2.64% loss to off-support). Truncated off-support patients were less comorbid than patients remaining in the analysis (off-support: median C3 score 0, range 0-6.51; on-support: median C3 score 0, range -0.03-13.1; p<.001). As shown in **Appendix B**, **Figure 34a**, there was moderate overlap in propensity scores between groups who did and did not receive surgery. While some initial large weights were observed (SMR: mean 0.94, SD 0.59, range 0.002-18.1; IPT: mean 1.01, SD 0.78, range 0.07-44.7), trimming produced weights within optimal range (SMR: mean 0.90, SD 0.23, range 0.02-2.20; IPT: mean 0.97, SD 0.33, range 0.09-3.14). Optimising covariate balance between treatment groups was difficult, however other than treatment facility in the SMR-weighted sample (standardised difference 0.28); overall balance was achieved (**Appendix B**, **Figure 35a**). Twelve covariates possessed standardised differences >0.10; including age (SMR-sample -0.15, IPT-sample -0.13) and stage (stage I: SMR-sample 0.13, IPT-sample 0.11; stage II: SMR-sample -0.20, IPT-sample -0.16).

Table 30 shows descriptive statistics by treatment status for patients included in the weighted analysis. While the majority of patients received surgery (93.0%), this proportion reduced with increasing level of comorbidity (69.2% of C3 category 2 vs 95.9% of C3 category 0; p<.001). Higher proportions of patients with screen-detected (p<.001) and lower stage (p<.001) tumours received surgery. Patients who received additional treatments (radiotherapy p<.001, chemotherapy p<.001, and HER2-directed therapy p<.001) were also treated with surgery more frequently.

Adjusted predicted survival curves for all-cause and breast cancer-specific mortality by surgical treatment status for each comorbidity category are displayed in **Figure 25**. Results from propensity score-weighted Cox proportional hazards models for treatment effects of surgery are shown in **Table 31**. Surgical treatment halved the risk of all-cause mortality overall (ATE HR 0.52, 95% CI 0.43-0.63, p<.001), and within all categories of comorbidity severity. All-cause mortality benefits were also seen for patients with COPD/asthma (ATE HR 0.34, 95% CI 0.22-0.54, p<.001), diabetes (ATE HR 0.48, 95% CI 0.29-0.80, p=.01), and hypertension (ATE HR 0.50, 95% CI 0.36-0.68 p<.001). Substantial reductions in breast cancer-specific mortality with surgery were also noted, although not within the highest category of comorbidity severity (ATE HR 0.67, 95% CI 0.37-1.24, p=.21). The only condition to display a breast cancer-specific mortality benefit with surgery was COPD/asthma (ATE HR 0.30, 95% CI 0.12-0.72, p=.01). Similarly, taking competing risks into account, breast cancer survival benefits were noted for patients with zero and low levels of comorbidity only (C3 category 0: ATE sHR 0.40, 95% CI 0.29-0.54, p<.001; C3 category 1: ATE sHR 0.38, 95% CI 0.21-0.69, p=.001) (**Table 32**, **Figure 26**).

Table 30. Descriptive Statistics by Surgical Status (Weighted Sample)

Characteristic	Overall	Treated (%)	P value
Total	**12 514**	**11 634 (93.0)**	
C3 category			
0 (≤0)	9849	9446	
1 (0.01-2.00)	1714	1530	
2 (>2)	951	658	
Median (IQR) [range]	0 (0) [-0.03-13.1]	0 (0) [-0.03-12.8]	<.001
Cardiac arrhythmia	409	278 (68.0)	<.001
COPD/asthma	346	265 (76.6)	<.001
Diabetes	537	451 (84.0)	<.001
Hypertension	993	758 (76.3)	<.001
Metabolic disorder	469	388 (82.7)	<.001
Age at diagnosis			
≤49	3546	3463 (97.7)	
50-59	3339	3254 (97.5)	
60-69	2994	2907 (97.1)	
≥70	2635	2010 (76.3)	
Median (IQR) [range]	58 (20) [21-102]	57 (18) [21-95]	<.001
Ethnicity			
European	8350	7765 (93.0)	<.001
Māori	1372	1280 (93.3)	
Pacific Peoples	911	824 (90.5)	
Asian	1044	1003 (96.1)	
Other ethnic groups	739	669 (90.5)	
Missing	98	93 (94.9)	
Treatment facility			
Public	7952	7229 (90.9)	<.001
Private	4555	4403 (96.7)	
Missing	7	2 (28.6)	
NZDep2013 quintile			
1	2743	2592 (94.5)	<.001
2	2309	2152 (93.2)	
3	2422	2263 (93.4)	
4	2302	2123 (92.2)	
5	2700	2471 (91.5)	
Missing	38	33 (86.8)	
Residence			
Urban	11 642	10 803 (92.8)	.001
Rural	859	821 (95.6)	
Missing	13	10 (76.9)	
Region			
Auckland	9864	9164 (92.9)	.31
Waikato	2650	2470 (93.2)	
Mode of detection			
Screen-detected	5125	4972 (97.0)	<.001
Non-screen-detected	7389	6662 (90.2)	
Stage			
I	5479	5389 (98.4)	<.001
II	4580	4422 (96.6)	
III	1943	1820 (93.7)	
Missing	512	3 (0.59)	
Grade			
1	3077	2863 (93.0)	.<.001
2	5730	5416 (94.5)	
3	3374	3244 (96.1)	
Missing	333	111 (33.3)	
Focality/centricity			
Unifocal & unicentric	10 258	9584 (93.4)	<.001
Multifocal &/or multicentric	2102	2041 (97.1)	
Missing	154	9 (5.84)	

Table 30 continued. Descriptive Statistics by Surgical Status (Weighted Sample)

Characteristic	Overall	Treated (%)	P value
ER status			
Negative	2232	2135 (95.7)	<.001
Positive	10 118	9430 (93.2)	
Missing	164	69 (42.1)	
PR status			
Negative	3829	3597 (93.7)	.26
Positive	8455	7915 (93.6)	
Missing	230	122 (53.0)	
HER2 status			
Negative	8451	8029 (95.0)	.12
Positive	1590	1552 (95.7)	
Missing	2473	2083 (84.2)	
Year			
2000-2003	2631	2323 (88.3)	<.001
2004-2007	2988	2822 (94.4)	
2008-2011	3513	3301 (94.0)	
2012-2015	3382	3188 (94.3)	
Radiotherapy			
No	4585	3877 (84.6)	<.001
Yes	7929	7757 (97.8)	
Chemotherapy			
No	8276	7434 (89.8)	<.001
Yes	4238	4200 (99.1)	
HER2-directed therapy			
No	11 655	10 783 (92.5)	<.001
Yes	859	851 (99.1)	
Endocrine therapy			
No	4557	4215 (92.5)	.06
Yes	7957	7419 (93.2)	

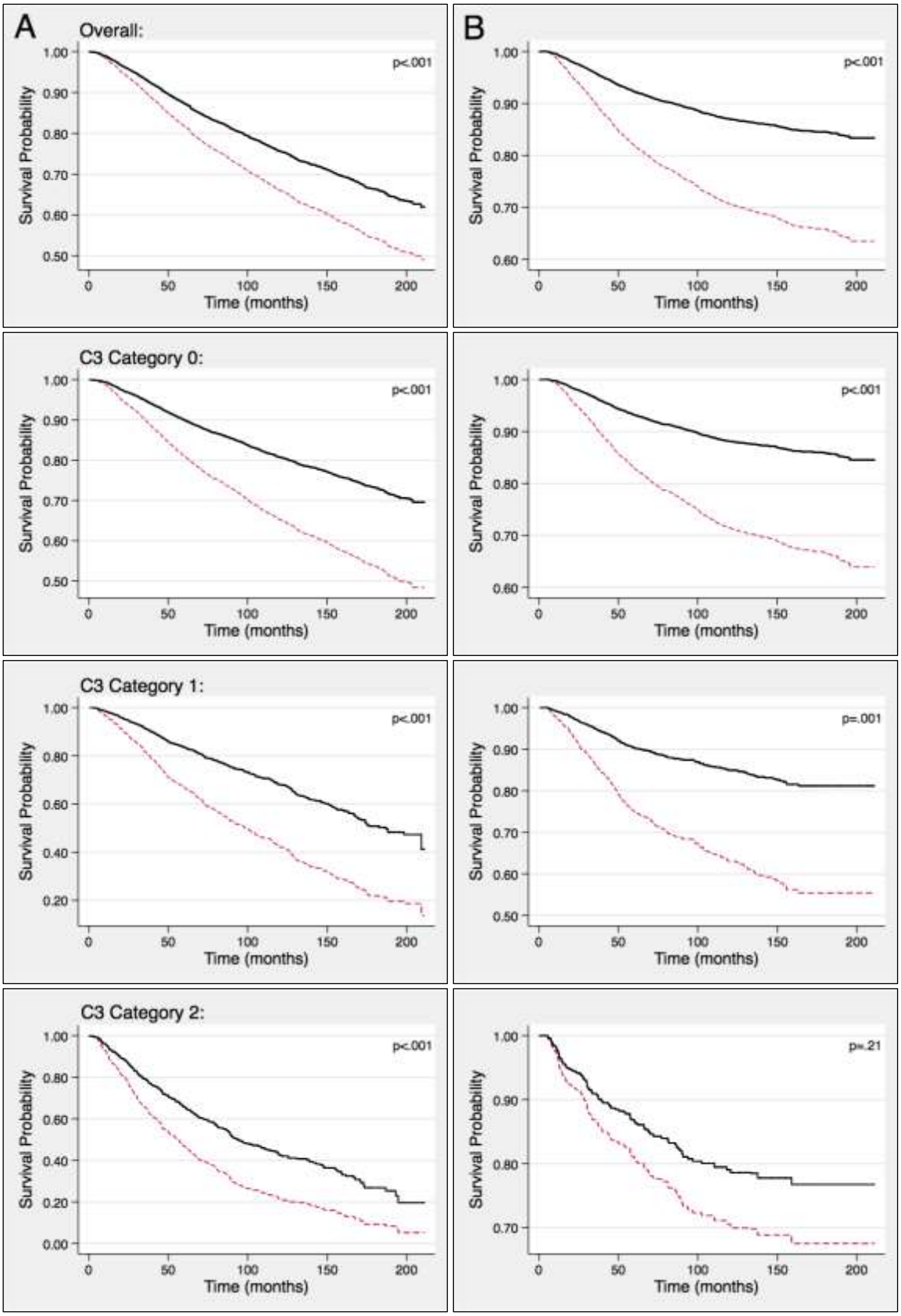


Figure 25. IPT-weighted Adjusted Predicted Survival Curves by Surgical Status: Overall and C3 Categories

(A) All-cause survival (B) Breast cancer-specific survival

Table 31. Propensity Score-weighted Multivariate Cox Regression for All-cause and Breast Cancer-specific Mortality: Treatment Effects of Surgery by Comorbidity Status

	All-cause Mortality				Breast Cancer-specific Mortality			
	ATT		*ATE*		*ATT*		*ATE*	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Overall	0.46[a] (0.38-0.55)	<.001	0.52[a] (0.43-0.63)	<.001	0.37 (0.29-0.47)	<.001	0.40 (0.31-0.52)	<.001
C3 category								
0 (≤0)	0.45[a] (0.35-0.58)	<.001	0.50[a] (0.39-0.64)	<.001	0.36 (0.26-0.48)	<.001	0.38 (0.28-0.51)	<.001
1 (0.1-2.00)	0.41 (0.28-0.60)	<.001	0.45 (0.31-0.65)	<.001	0.33 (0.18-0.60)	<.001	0.35 (0.19-0.64)	.001
2 (>2.00)	0.51 (0.36-0.72)	<.001	0.55 (0.41-0.74)	<.001	0.90[a] (0.28-1.25)	.17	0.67[a] (0.37-1.24)	.21
Condition								
Cardiac arrhythmia	0.63 (0.36-1.12)	.12	0.68 (0.44-1.05)	.08	0.79 (0.29-2.13)	.65	0.76 (0.32-1.80)	.53
COPD/asthma	0.29 (0.17-0.48)	<.001	0.34 (0.22-0.54)	<.001	0.23[a] (0.09-0.57)	.002	0.30 (0.12-0.72)	.01
Diabetes	0.50 (0.27-0.93)	.03	0.48 (0.29-0.80)	.01	0.92 (0.30-2.78)	.88	0.96 (0.37-2.49)	.93
Hypertension	0.48 (0.33-0.70)	<.001	0.50 (0.36-0.68)	<.001	0.51 (0.23-1.12)	.09	0.53 (0.26-1.08)	.08
Metabolic disorder	0.77 (0.35-1.73)	.53	0.65[a] (0.34-1.22)	.18	1.44 (0.39-5.32)	.59	1.17[a] (0.42-3.25)	.76

[a] Time dependent covariate, average effect presented.

Table 32. Propensity Score-weighted Multivariate Competing Risks Regression for Breast Cancer Mortality: Treatment Effects of Surgery by Comorbidity Status

	ATT		*ATE*	
	sHR (95% CI)	**P value**	**sHR (95% CI)**	**P value**
Overall	0.40 (0.31-0.51)	<.001	0.43 (0.34-0.56)	<.001
C3 category				
0 (≤0)	0.38 (0.28-0.51)	<.001	0.40 (0.29-0.54)	<.001
1 (0.1-2.00)	0.36 (0.20-0.64)	.001	0.38 (0.21-0.69)	.001
2 (>2.00)	0.77 (0.36-1.61)	.48	0.87 (0.47-1.58)	.64
Condition				
Cardiac arrhythmia	0.97 (0.38-2.49)	.94	0.91 (0.40-2.05)	.82
COPD/asthma	0.34 (0.13-0.89)	.03	0.42 (0.17-1.05)	.06
Diabetes	1.23 (0.42-3.64)	.71	1.34 (0.52-3.43)	.54
Hypertension	0.64 (0.29-1.44)	.28	0.68 (0.33-1.40)	.29
Metabolic disorder	1.70 (0.49-5.85)	.40	1.49 (0.57-3.86)	.41

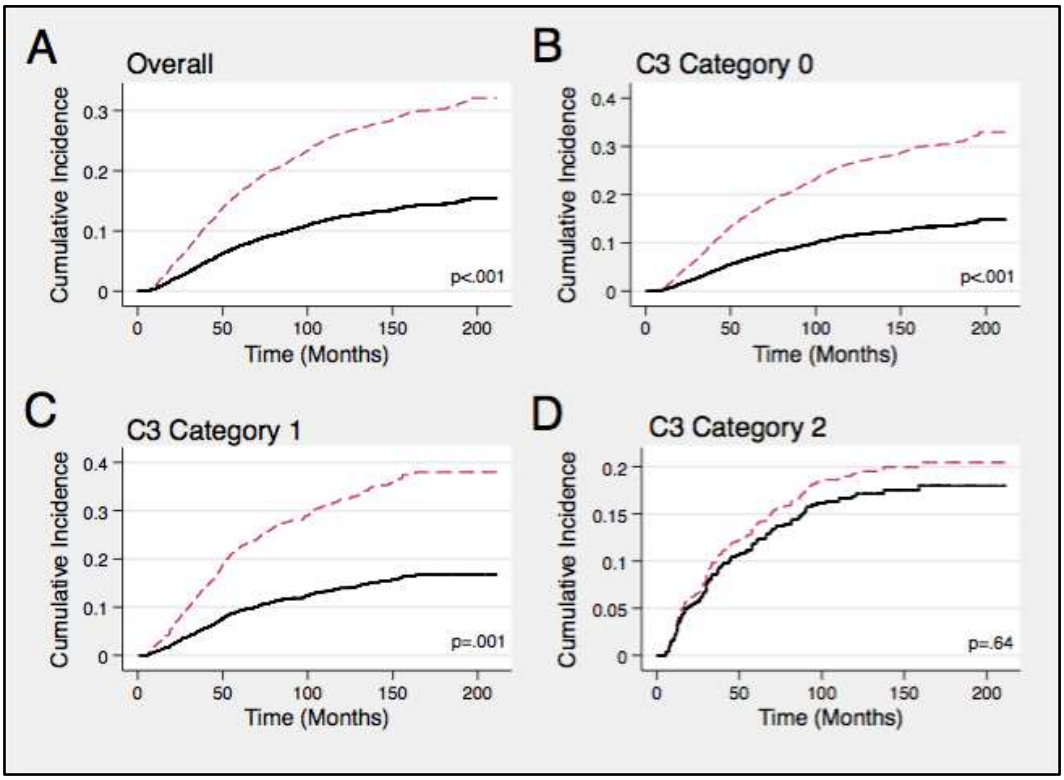


Figure 26. IPT-weighted Adjusted Cumulative Incidence Function Curves for Breast Cancer Mortality by Surgical Status: Overall and C3 Categories

Although Wald tests for overall interaction were insignificant for the survival models assessed (IPT-weighted samples all-cause mortality: p=.42; breast cancer mortality: Cox p=.32, competing risks: p=.09), subgroup analysis revealed evidence of treatment effect heterogeneity by C3 score with respect to breast cancer mortality. In the IPT-weighted Cox model, the ratio of HRs between C3 categories 2 and 0 was 2.50 (95% CI 1.11-5.61, p=.003), indicating lesser benefit from surgery amongst comorbid patients. Similarly, in the IPT-weighted competing risks model, the ratio of sHRs between C3 categories 2 and 0 was 2.18 (95% CI 1.10-4.30, p=.03).

7.3.2. Adjuvant Radiotherapy

There was considerable overlap between radiotherapy treatment groups (**Appendix B**, **Figure 34b**). While only 11 patients below and 3 patients above common support were truncated from an original population of 7717 (0.18% loss to off-support, leaving a weighted analysis sample of 7703), those 14 off-support patients did possess a higher level of comorbidity (off-support: median C3 score 2.68, range 0-9.86; on-support: median C3 score 0, range -0.03-12.8; p<.001). Non-extreme SMR- and IPT-weights were produced, with means of 0.90 (SD 0.40, range 0.01-9.38) and 1.00 (SD 0.48, range 0.11-9.55) respectively. Trimming produced SMR-weights with a mean of 0.88 (SD 0.24, range 0.48-2.40) and IPT-weights with a mean of 0.99 (SD 0.33, range 0.15-3.02). Excellent treatment group balance in the trimmed weighted population was achieved with a propensity score model containing main effects only (**Appendix B**, **Figure 35b**).

Most patients in the weighted cohort received radiotherapy in accordance with guidelines (89.7%), although this was given to relatively fewer patients with severe comorbidity (69.5% of C3 category 2 vs 91.5% of C3 category 0; p<.001) (descriptive statistics shown in **Table 33**).

Kaplan-Meier survival curves for all-cause and breast cancer-specific mortality by comorbidity severity are displayed in **Figure 27**. An all-cause mortality benefit with the addition of radiotherapy was demonstrated in the overall sample, with an ATE HR of 0.58 (95% CI 0.48-0.69, p<.001) (**Table 34**). Radiotherapy also reduced all-cause mortality amongst patients in C3 index stratum 0 (ATE HR 0.56, 95% CI 0.45-0.69, p<.001) and 1 (ATE HR 0.61, 95% CI 0.39-0.98, p=.04), with a trend towards benefit in C3 category 2 (ATE HR 0.69, 95% CI 0.46-1.01, p=.06). Treatment benefits were also noted for patients with cardiac arrhythmias (ATE HR 0.42, 95% CI 0.19-0.91, p=.03) and hypertension (ATE HR 0.54, 95% CI 0.34-0.87, p=.01).

Breast cancer-specific mortality benefits were noted with radiotherapy in the total sample (ATE HR 0.56, 95% CI 0.44-0.70, p<.001) and for patients without comorbidity (C3 category 0: ATE HR 0.54, 95% CI 0.42-0.71, p<.001). While no reduction in the hazard of breast cancer death was found for patients with comorbidity as a summary measure, mortality benefits were present for patients with cardiac arrhythmias (ATE HR 0.28, 95% CI 0.08-0.99, p=.048) and hypertension (ATE HR 0.43, 95% CI 0.24-0.79, p=.01). Similar trends were found using competing risks

Table 33. Descriptive Statistics by Adjuvant Radiotherapy Status (Weighted Sample)

Characteristic	Overall	Treated (%)	P value
Total	**7703**	**6907 (89.7)**	
C3 category			
0 (≤0)	6336	5800 (91.5)	
1 (0.01-2.00)	960	824 (85.8)	
2 (>2)	407	283 (69.5)	
Median (IQR) [range]	0 (0) [-0.03-12.1]	0 (0) [-0.03-11.1]	<.001
Cardiac arrhythmia	161	112 (69.6)	<.001
COPD/asthma	165	121 (73.3)	<.001
Diabetes	281	230 (81.9)	<.001
Hypertension	480	373 (77.7)	<.001
Metabolic disorder	230	188 (81.7)	<.001
Age at diagnosis			
≤49	2170	2002 (92.3)	
50-59	2311	2113 (91.4)	
60-69	2098	1945 (92.7)	
≥70	1124	847 (75.4)	
Median (IQR) [range]	57 (16) [22-98]	56 (17) [22-93]	<.001
Ethnicity			
European	5333	4824 (90.5)	<.001
Māori	816	726 (89.0)	
Pacific Peoples	513	428 (83.4)	
Asian	551	493 (89.5)	
Other ethnic groups	420	376 (89.5)	
Missing	70	60 (85.7)	
Treatment facility			
Public	4566	4003 (87.7)	<.001
Private	3134	2903 (92.6)	
Missing	3	1 (33.3)	
NZDep2013 quintile			
1	1736	1582 (91.1)	<.001
2	1442	1319 (91.5)	
3	1501	1326 (88.3)	
4	1435	1296 (90.3)	
5	1564	1362 (87.1)	
Missing	25	22 (88.0)	
Residence			
Urban	7115	6371 (89.5)	.09
Rural	578	528 (91.3)	
Missing	10	8 (80.0)	
Region			
Auckland	5876	5258 (89.5)	.18
Waikato	1827	1649 (90.3)	
Mode of detection			
Screen-detected	3614	3381 (93.6)	<.001
Non-screen-detected	4089	3526 (86.2)	
Stage			
I	3694	3431 (92.9)	<.001
II	2030	1845 (90.9)	
III	1793	1554 (86.7)	
Missing	186	77 (41.4)	
Grade			
1	2069	1844 (89.1)	.35
2	3479	3140 (90.3)	
3	2097	1875 (89.4)	
Missing	58	48 (82.8)	
Histopathological type			
Invasive carcinoma NST	6356	5735 (90.2)	<.001
Lobular	852	759 (89.1)	
Other	485	406 (83.7)	
Missing	10	7 (70.0)	

Table 33 continued. Descriptive Statistics by Adjuvant Radiotherapy Status (Weighted Sample)

Characteristic	Overall	Treated (%)	P value
Focality/centricity			
Unifocal & unicentric	6710	6032 (89.9)	.07
Multifocal &/or multicentric	983	868 (88.3)	
Missing	10	7 (70.0)	
ER status			
Negative	1332	1172 (88.0)	.02
Positive	6337	5706 (90.0)	
Missing	34	29 (85.3)	
PR status			
Negative	2308	2029 (87.9)	.001
Positive	5326	4815 (90.4)	
Missing	69	63 (91.3)	
HER2 status			
Negative	5410	4890 (90.4)	.13
Positive	950	847 (89.2)	
Missing	1343	1170 (87.1)	
Year			
2000-2003	1537	1357 (88.3)	.06
2004-2007	1875	1687 (90.0)	
2008-2011	2188	1970 (90.0)	
2012-2015	2103	1893 (90.0)	
Axillary surgery			
No	243	100 (41.2)	<.001
Yes	7460	6807 (91.2)	
Chemotherapy			
No	4953	4303 (86.9)	<.001
Yes	2750	2604 (94.7)	
HER2-directed therapy			
No	7157	6394 (89.3)	<.001
Yes	546	513 (94.0)	
Endocrine therapy			
No	2879	2459 (85.4)	<.001
Yes	4824	4448 (92.2)	

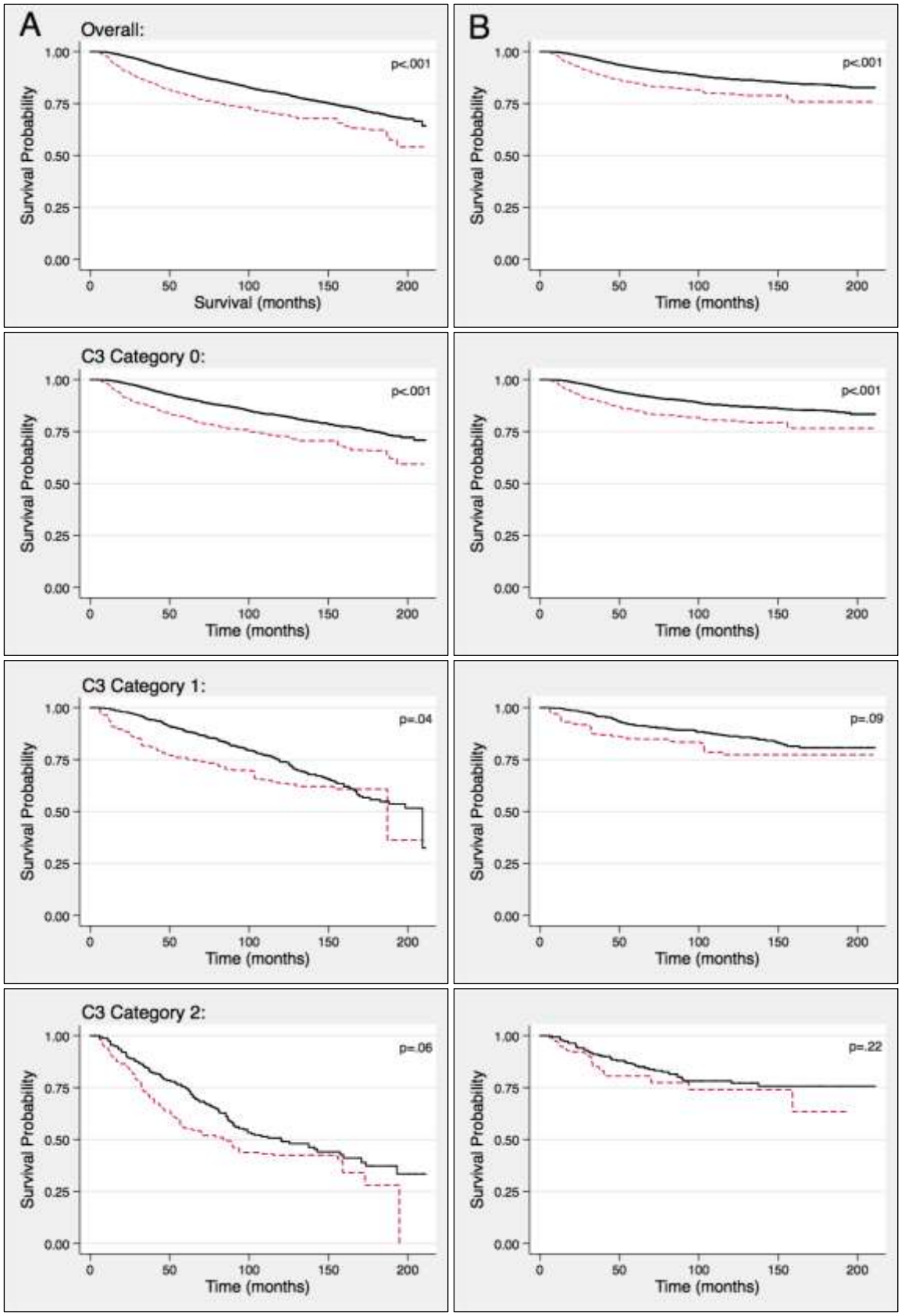


Figure 27. IPT-weighted Kaplan-Meier Survival Curves by Adjuvant Radiotherapy Status: Overall and C3 Categories

(A) All-cause survival (B) Breast cancer-specific survival

Table 34. Propensity Score-weighted Cox Regression for All-cause and Breast Cancer-specific Mortality: Treatment Effects of Adjuvant Radiotherapy by Comorbidity Status

	All-cause Mortality				Breast Cancer-specific Mortality			
	ATT		*ATE*		*ATT*		*ATE*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Overall	0.56[a] (0.46-0.68)	<.001	0.58[a] (0.48-0.69)	<.001	0.55[a] (0.43-0.70)	<.001	0.56[a] (0.44-0.70)	<.001
C3 category								
0 (≤0)	0.55[a] (0.44-0.69)	<.001	0.56[a] (0.45-0.69)	<.001	0.54[a] (0.41-0.71)	<.001	0.54[a] (0.42-0.71)	<.001
1 (0.1-2.00)	0.61[a] (0.37-1.00)	.05	0.61[a] (0.39-0.98)	.04	0.57 (0.29-1.13)	.11	0.57 (0.30-1.08)	.09
2 (>2.00)	0.70 (0.44-1.10)	.12	0.69 (0.46-1.01)	.06	0.60 (0.32-1.15)	.12	0.69 (0.39-1.25)	.22
Condition								
Cardiac arrhythmia	0.40[a] (0.16-0.99)	.048	0.42[a] (0.19-0.91)	.02	0.26 (0.06-1.02)	.05	0.28 (0.08-0.99)	.048
COPD/asthma	0.55 (0.24-1.27)	.16	0.59 (0.27-1.29)	.18	0.47 (0.17-1.32)	.15	0.56 (0.21-1.49)	.24
Diabetes	0.51 (0.25-1.06)	.07	0.60 (0.32-1.14)	.12	0.37 (0.13-1.04)	.06	0.46 (0.18-1.20)	.11
Hypertension	0.52 (0.31-0.87)	.01	0.54 (0.34-0.87)	.01	0.38 (0.20-0.73)	.003	0.43 (0.24-0.79)	.01
Metabolic disorder	0.48 (0.23-0.996)	.049	0.55 (0.28-1.08)	.08	0.35 (0.13-0.99)	.048	0.42 (0.16-1.14)	.09

[a] Time dependent covariate, average effect presented.

regression, with a reduction in breast cancer mortality with the addition of radiotherapy for the overall sample (ATE sHR 0.58, 95% CI 0.46-0.73, p<.001) and C3 category 0 patients (ATE sHR 0.56, 95% CI 0.43-0.73, p<.001), as well as subjects with hypertension (ATE sHR 0.48, 95% CI 0.27-0.87, p=.02) (**Table 35**). Cumulative incidence function curves by C3 category are displayed in **Figure 28**. No evidence of treatment effect heterogeneity by C3 score was uncovered for any of the survival models assessed.

7.3.3. Adjuvant Chemotherapy

Propensity score distributions between chemotherapy treatment groups were poorly overlapping (**Appendix B**, **Figure 34c**). From the original population of 4119, 177 and 557 participants were truncated below and above common support respectively (16.4% loss to off-support), resulting in an analysis population of 3445. There were no major differences in comorbidity between on- and off-support subjects (p=.80). Untrimmed SMR- and IPT-weights had means of 0.64 (SD 2.70, range 0.004-115.9) and 1.05 (SD 3.09, range 0.42-116.3) respectively. Trimming produced SMR-weights with a mean of 0.54 (SD 0.60, range 0.01-4.81) and IPT-weights with a mean of 0.91 (SD 0.96, range 0.42-7.26). Good balance between treatment groups in the trimmed, weighted sample was achieved (**Appendix B**, **Figure 35c**). Five covariates had standardised differences >0.1, including age in the IPT-weighted sample (0.11).

The weighted sample included fewer patients with comorbidity (398 C3 category 1 and 129 C3 category 2 patients) than the other treatment analyses. Overall, 2022 (58.7%) participants received chemotherapy, although this was received by proportionally fewer patients with comorbidity (38.0% of C3 category 2 vs 60.5% of C3 category 0; p<.001) (**Table 36**). Major differences in treatment were also noted by tumour characteristics, with greater proportions of patients with higher stage (p<.001), higher grade (p<.001), invasive carcinoma NST (p<.001), ER-negative (p<.001), PR-negative (p<.001), and HER2-positive (p=.001) tumours receiving chemotherapy.

Kaplan-Meier survival curves showing all-cause and breast cancer-specific survival for the overall analysis cohort and comorbidity subgroups are shown in **Figure 29**. Overall, in Cox proportional hazards regression, chemotherapy treatment was associated with a reduction in all-cause mortality (ATE HR 0.77, 95% CI 0.62-0.95, p=.02) (**Table 37**). This finding was mirrored in patients without comorbidity (C3 category 0: ATE HR 0.74, 95% CI 0.58-0.94, p=.02), but not for patients with any degree of comorbidity as measured by C3 category. Within the SMR-weighted sample, patients with metabolic disorders also experienced a reduction in the hazard of mortality (ATT HR 0.36, 95% CI 0.14-0.89, p=.03), although this did not quite reach statistical significance in the IPT-weighted sample. Conversely, for patients with cardiac arrhythmia, treatment with chemotherapy increased the hazard of death (ATE HR 3.19, 95% CI 1.23-8.27, p=.02).

Table 35. Propensity Score-weighted Competing Risks Regression for Breast Cancer Mortality: Treatment Effects of Adjuvant Radiotherapy by Comorbidity Status

	ATT		*ATE*	
	sHR (95% CI)	**P value**	**sHR (95% CI)**	**P value**
Overall	0.57 (0.44-0.72)	<.001	0.58 (0.46-0.73)	<.001
C3 category				
0 (≤0)	0.56 (0.42-0.73)	<.001	0.56 (0.43-0.73)	<.001
1 (0.1-2.00)	0.61 (0.31-1.20)	.15	0.62 (0.33-1.15)	.13
2 (>2.00)	0.64 (0.33-1.23)	.17	0.77 (0.43-1.36)	.37
Condition				
Cardiac arrhythmia	0.31 (0.08-1.22)	.09	0.36 (0.10-1.25)	.11
COPD/asthma	0.51 (0.19-1.37)	.31	0.61 (0.24-1.58)	.31
Diabetes	0.40 (0.14-1.11)	.08	0.49 (0.19-1.27)	.14
Hypertension	0.42 (0.22-0.79)	.01	0.48 (0.27-0.87)	.02
Metabolic disorder	0.38 (0.14-1.06)	.07	0.46 (0.17-1.22)	.12

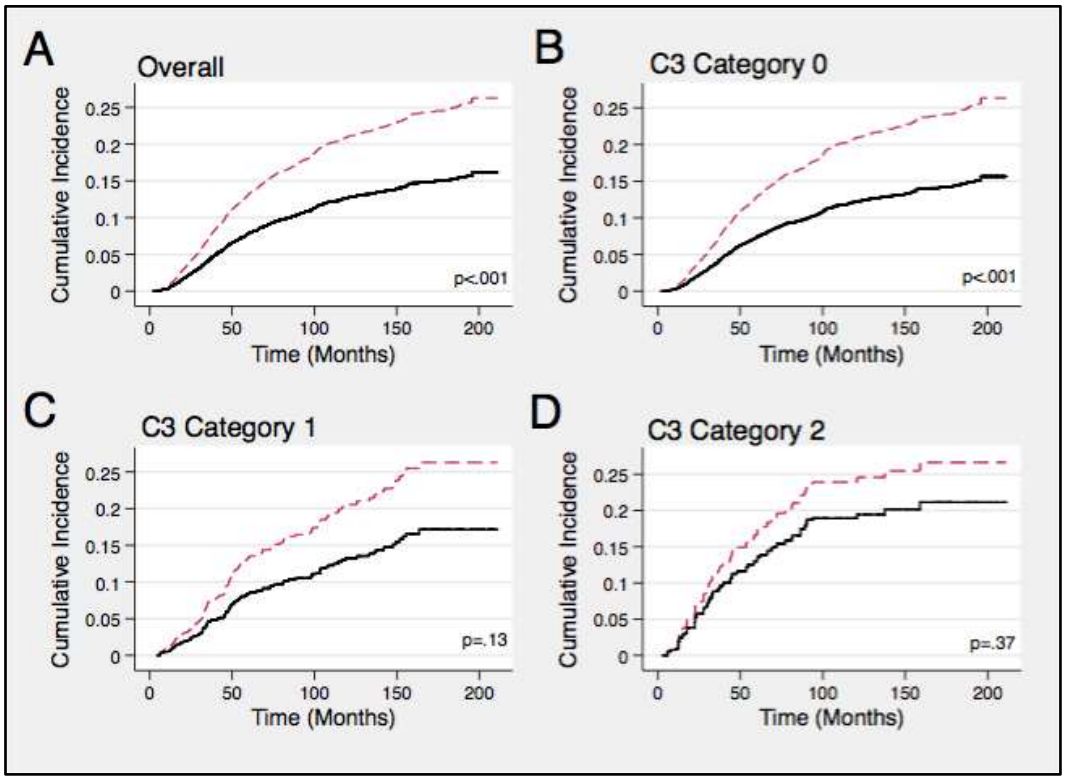


Figure 28. IPT-weighted Cumulative Incidence Function Curves for Breast Cancer Mortality by Adjuvant Radiotherapy Status: Overall and C3 Categories

Table 36. Descriptive Statistics by Adjuvant Chemotherapy Status (Weighted Sample)

Characteristic	Overall	Treated (%)	P value
Total	**3445**	**2022 (58.7)**	
C3 category			
0 (≤0)	2918	1764 (60.5)	
1 (0.01-2.00)	398	209 (52.5)	
2 (>2)	129	49 (38.0)	
Median (IQR) [range]	0 (0) [-0.03-10.5]	0 (0) [-0.03-7.99]	<.001
Cardiac arrhythmia	54	22 (40.7)	.01
COPD/asthma	61	27 (44.3)	.02
Diabetes	108	41 (38.0)	<.001
Hypertension	155	69 (44.5)	<.001
Metabolic disorder	83	37 (44.6)	.01
Age at diagnosis			
≤49	1175	903 (76.9)	
50-59	1129	663 (58.7)	
60-69	880	392 (44.5)	
≥70	261	64 (24.5)	
Median (IQR) [range]	54 (15) [23-75]	51 (15) [23-75]	<.001
Ethnicity			
European	2257	1325 (58.7)	.38
Māori	377	228 (60.5)	
Pacific Peoples	278	150 (54.0)	
Asian	321	198 (61.7)	
Other ethnic groups	181	106 (58.6)	
Missing	31	15 (48.4)	
Treatment facility			
Public	2008	1136 (56.6)	.002
Private	1435	885 (61.7)	
Missing	2	1 (50.0)	
NZDep2013 quintile			
1	796	469 (58.9)	.32
2	651	395 (60.7)	
3	633	383 (60.5)	
4	593	343 (57.8)	
5	758	423 (55.8)	
Missing	14	9 (64.3)	
Residence			
Urban	3189	1866 (58.5)	.25
Rural	251	153 (61.0)	
Missing	5	3 (60.0)	
Region			
Auckland	2774	1644 (59.3)	.09
Waikato	671	378 (56.3)	
Mode of detection			
Screen-detected	1246	531 (42.6)	<.001
Non-screen-detected	2199	1491 (67.8)	
Stage			
I	1279	478 (37.4)	<.001
II	1400	955 (68.2)	
III	758	589 (77.7)	
Missing	8	0 (0)	
Grade			
1	140	58 (41.4)	<.001
2	1576	693 (44.0)	
3	1698	1260 (74.2)	
Missing	31	11 (35.5)	
Histopathological type			
Invasive carcinoma NST	2926	1784 (61.0)	<.001
Lobular	375	160 (42.7)	
Other	140	74 (52.9)	
Missing	4	4 (100)	

Table 36 continued. Descriptive Statistics by Adjuvant Chemotherapy Status (Weighted Sample)

Characteristic	Overall	Treated (%)	P value
Focality/centricity			
Unifocal & unicentric	2807	1624 (57.9)	.02
Multifocal &/or multicentric	633	394 (62.2)	
Missing	5	4 (80.0)	
ER status			
Negative	1557	1139 (73.2)	<.001
Positive	1881	880 (46.8)	
Missing	7	3 (42.9)	
PR status			
Negative	1933	1296 (67.0)	<.001
Positive	1488	715 (48.1)	
Missing	24	11 (45.8)	
HER2 status			
Negative	2118	1277 (60.3)	.001
Positive	566	383 (67.7)	
Missing	761	362 (47.6)	
Year			
2000-2003	971	511 (52.6)	.11
2004-2007	714	490 (68.6)	
2008-2011	726	511 (70.4)	
2012-2015	1034	510 (49.3)	
Axillary surgery			
No	9	1 (11.1)	.01
Yes	3436	2021 (58.8)	
Radiotherapy			
No	1119	534 (47.7)	<.001
Yes	2326	1488 (64.0)	
HER2-directed therapy			
No	3227	1811 (56.1)	<.001
Yes	218	211 (96.8)	
Endocrine therapy			
No	1701	1131 (66.5)	<.001
Yes	1744	891 (51.1)	

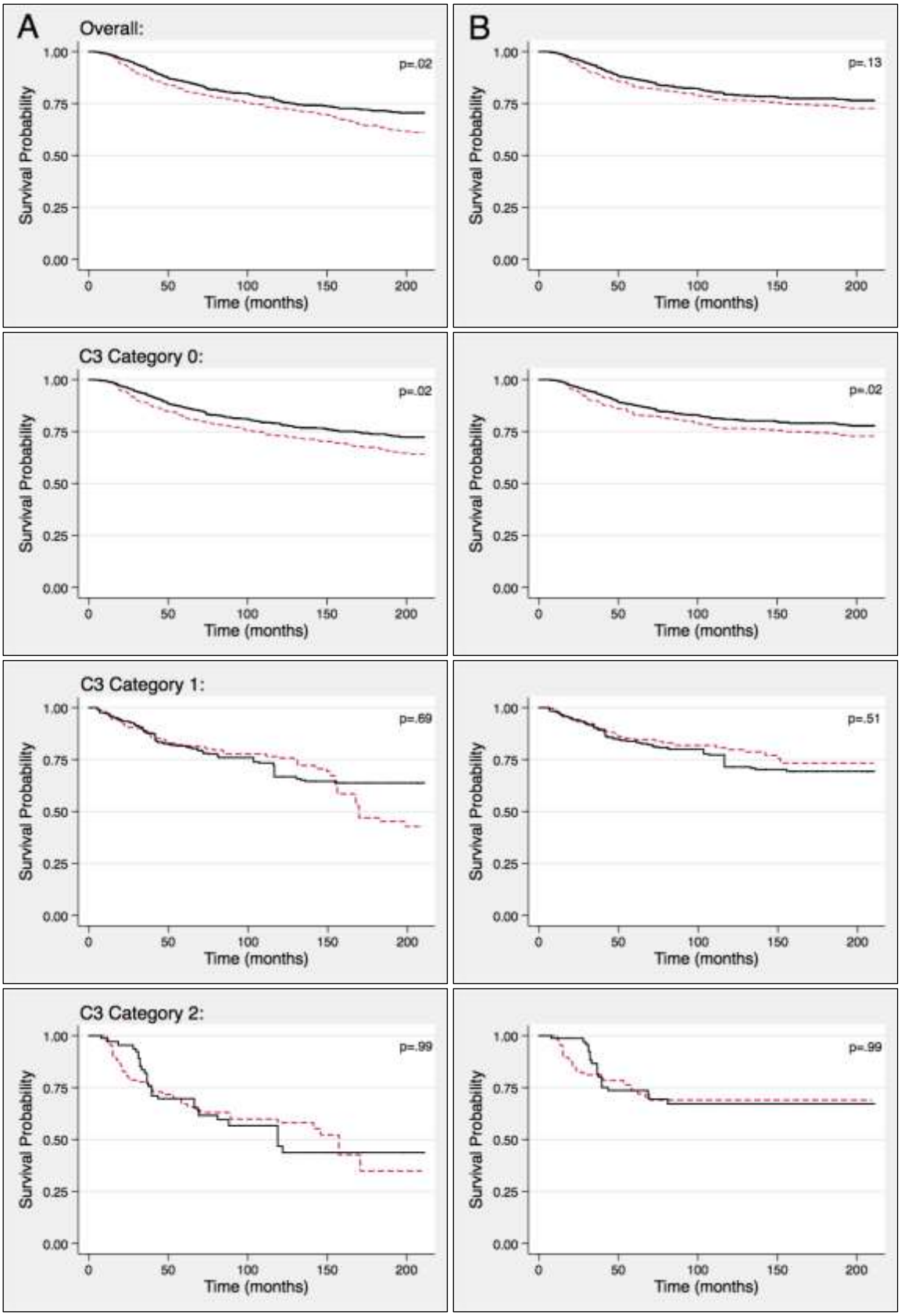


Figure 29. IPT-weighted Kaplan-Meier Survival Curves by Adjuvant Chemotherapy Status: Overall and C3 Categories

(A) All-cause survival (B) Breast cancer-specific survival

No treatment Treatment

Table 37. Propensity Score-weighted Cox Regression for All-cause and Breast Cancer-specific Mortality: Treatment Effects of Adjuvant Chemotherapy by Comorbidity Status

	All-cause Mortality				Breast Cancer-specific Mortality			
	ATT		*ATE*		*ATT*		*ATE*	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Overall	0.71 (0.56-0.91)	.01	0.77 (0.62-0.95)	.02	0.74 (0.56-0.98)	.03	0.82 (0.64-1.06)	.13
C3 category								
0 (≤0)	0.67 (0.51-0.89)	.01	0.74 (0.58-0.94)	.02	0.68 (0.50-0.93)	.01	0.77 (0.58-1.02)	.07
1 (0.1-2.00)	0.99* (0.59-1.67)	.96	0.91 (0.56-1.47)	.69	1.37 (0.71-2.62)	.35	1.21 (0.69-2.11)	.51
2 (>2.00)	0.85 (0.32-2.28)	.75	1.00 (0.52-1.89)	.99	0.73 (0.21-2.60)	.66	0.97 (0.42-2.23)	.94
Condition								
Cardiac arrhythmia	4.04 (1.04-15.7)	.04	3.19 (1.23-8.27)	.02	-	-	-	-
COPD/asthma	0.63 (0.26-1.53)	.31	0.42 (0.15-1.14)	.09	1.15 (0.28-4.71)	.84	0.54 (0.16-1.83)	.32
Diabetes	0.82 (0.40-1.69)	.60	0.79 (0.40-1.58)	.51	1.26 (0.49-3.28)	.63	1.08 (0.48-2.40)	.86
Hypertension	0.71 (0.32-1.56)	.39	1.09 (0.64-1.84)	.75	0.70 (0.24-1.99)	.50	1.11 (0.57-2.18)	.75
Metabolic disorder	0.36 (0.14-0.89)	.03	0.47 (0.23-1.02)	.06	0.29 (0.09-0.93)	.04	0.41 (0.15-1.11)	.08

* Time dependent covariate, average effect presented.
- Estimates withheld where events per variable numbered <10.

Chemotherapy was also associated with a reduction in the hazard of breast cancer-specific death, overall and for patients without comorbidity, though in the SMR-weighted sample only (overall: ATT HR 0.74, 95% CI 0.56-0.98, p=.03; C3 category 0: ATT HR 0.68, 95% CI 0.50-0.93, p=.01). Sensitivity analysis using conventional multivariate regression also demonstrated an overall breast cancer-specific mortality benefit from chemotherapy (aHR 0.66, 95% CI 0.53-0.83, p<.001), however sensitivity analyses using untrimmed weights did not (ATT 0.71, 95% CI 0.49-1.04) (**Appendix C**, **Figure 36a-b**). As with all-cause survival, chemotherapy had no significant impact on breast-cancer mortality for those with comorbidity, excepting patients with metabolic disorders, who experienced a mortality reduction in the SMR-weighted sample only (ATT HR 0.29, 95% CI 0.09-0.93, p=.04).

Similar results were obtained with competing risks regression. Treatment effect estimates are shown in **Table 38** with cumulative incidence function curves displayed in **Figure 30**. A breast cancer-specific survival benefit for the overall cohort and C3 category 0 was seen in the SMR-weighted sample only (overall: ATT sHR 0.75, 95% CI 0.56-0.98, p=.04; C3 category 0: ATT sHR 0.69, 95% CI 0.51-0.93, p=.02). There was also evidence of benefit in the SMR-weighted sample for patients with metabolic disorders (ATT sHR 0.28, 95% CI 0.09-0.89, p=.03). There was no evidence of heterogeneity in treatment effect in any of the survival models assessed.

7.3.4. Endocrine Therapy

There was good overlap in the propensity score distributions between groups who did and did not receive endocrine therapy (**Appendix B**, **Figure 34d**). Loss to off-support was 1.69%, with 194 patients above and 17 patients below support truncated. Truncated patients were less comorbid than patients remaining in the analysis (off-support: median C3 score 0, range -0.03-4.62; on-support: median C3 score 0, range -0.03-13.1; p<.001). Some extreme initial weights were observed (SMR: mean 0.89, SD 2.62, range 0.02-79.5; IPT: mean 1.11, SD 2.65, range 0.26-79.8), which were trimmed to produce SMR-weights with a mean of 0.74 (SD 0.58, range 0.04-5.00) and IPT-weights with a mean of 0.96 (SD 0.73, range 0.28-5.63). Reasonable covariate balance was achieved, with the largest differences noted for PR (0.21) and geographic region (0.21) in the SMR-weighted sample (**Appendix B**, **Figure 35d**).

Descriptive statistics by treatment status for the weighted sample are shown in **Table 39**. Overall, 7795 (76.0%) of participants received endocrine therapy, with marginally fewer comorbid patients treated (72.9% of C3 category 2 and 76.6% of C3 category 1 vs 76.6% of C3 category 0; p=.004). Higher proportions of patients with higher stage (p<.001), higher grade, multifocal/multicentric (p<.001), and HER2-positive (p<.001) tumours received endocrine therapy. Endocrine treatment was also more frequently received by patients who were also treated with radiotherapy (p<.001), chemotherapy (p<.001), and HER2-directed therapy (p<.001), but not breast surgery (p<.001).

Table 38. Propensity Score-weighted Competing Risks Regression for Breast Cancer Mortality: Treatment Effects of Adjuvant Chemotherapy by Comorbidity Status

	ATT		*ATE*	
	sHR (95% CI)	**P value**	**sHR (95% CI)**	**P value**
Overall	0.75 (0.56-0.98)	.04	0.83 (0.65-1.07)	.15
C3 index category				
0 (≤0)	0.69 (0.51-0.93)	.02	0.78 (0.59-1.03)	.08
1 (0.1-2.00)	1.37 (0.71-2.62)	.35	1.22 (0.70-2.13)	.48
2 (>2.00)	0.74 (0.21-2.57)	.63	0.97 (0.42-2.23)	.94
Condition				
Cardiac arrhythmia	-	-	-	-
COPD/asthma	1.19 (0.30-4.80)	.81	0.59 (0.18-1.99)	.40
Diabetes	1.33 (0.51-3.48)	.56	1.11 (0.50-2.48)	.79
Hypertension	0.69 (0.24-1.94)	.48	1.11 (0.57-2.18)	.76
Metabolic disorder	0.28 (0.09-0.89)	.03	0.40 (0.15-1.09)	.07

- Estimates withheld where events per variable numbered <10.

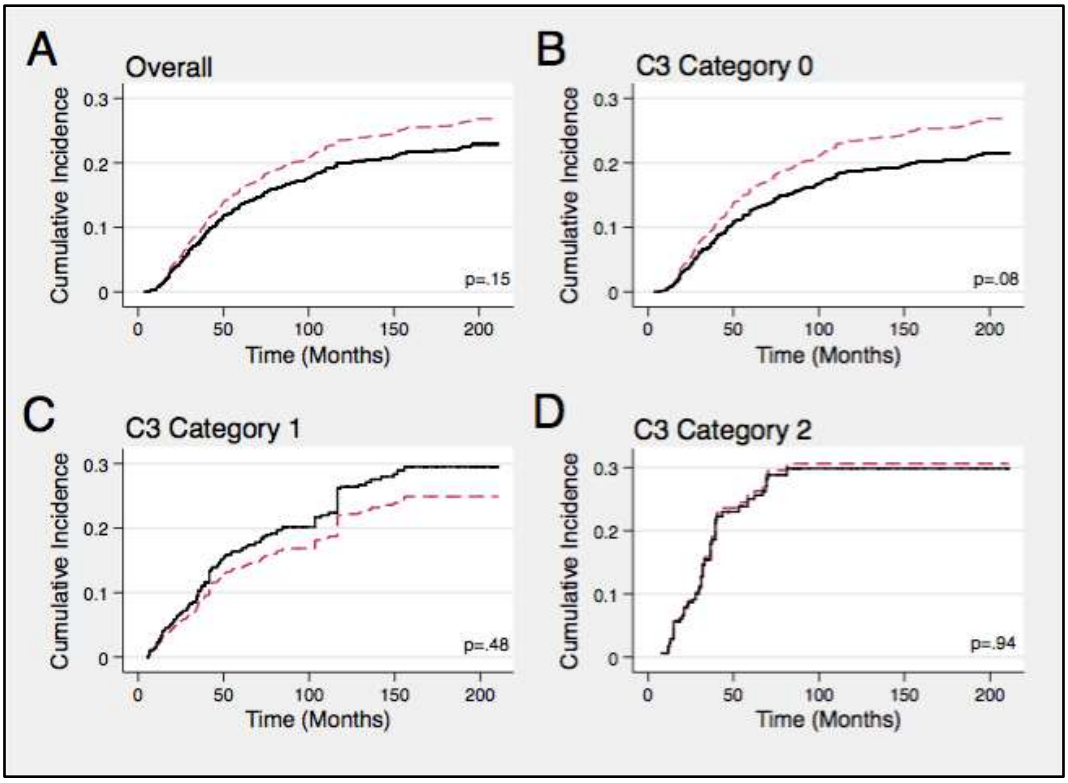


Figure 30. IPT-weighted Cumulative Incidence Function Curves for Breast Cancer Mortality by Adjuvant Chemotherapy Status: Overall and C3 Categories

Table 39. Descriptive Statistics by Endocrine Therapy Status (Weighted Sample)

Characteristic	Overall	Treated (%)	P value
Total	**10 254**	**7795 (76.0)**	
C3 category			
0 (≤0)	8101	6205 (76.6)	
1 (0.01-2.00)	1385	1030 (74.4)	
2 (>2)	768	560 (72.9)	
Median (IQR) [range]	0 (0) [-0.03-13.1]	0 (0) [-0.03-13.1]	.004
Cardiac arrhythmia	330	241 (73.0)	.11
COPD/asthma	270	197 (73.0)	.13
Diabetes	438	337 (76.9)	.35
Hypertension	799	583 (73.0)	.02
Metabolic disorder	386	291 (75.4)	.40
Age at diagnosis			
≤49	2780	2269	
50-59	2804	2088	
60-69	2488	1798	
≥70	2182	1640	
Median (IQR) [range]	58 (19) [21-104]	57 (19) [21-104]	<.001
Ethnicity			
European	6916	5205 (75.3)	<.001
Māori	1120	909 (81.2)	
Pacific Peoples	706	548 (77.6)	
Asian	853	655 (76.8)	
Other ethnic groups	587	444 (75.6)	
Missing	72	34 (47.2)	
Treatment facility			
Public	6452	4931 (76.4)	.11
Private	3798	2861 (75.3)	
Missing	4	3 (75.0)	
NZDep2013 quintile			
1	2323	1710 (73.6)	<.001
2	1880	1368 (72.8)	
3	2000	1529 (76.5)	
4	1857	1501 (80.8)	
5	2168	1676 (77.3)	
Missing	26	11 (42.3)	
Residence			
Urban	9526	7204 (75.6)	<.001
Rural	720	587 (81.5)	
Missing	8	4 (50.0)	
Region			
Auckland	8083	5779 (71.5)	<.001
Waikato	2171	2016 (92.9)	
Mode of detection			
Screen-detected	4529	3038 (67.1)	<.001
Non-screen-detected	5725	4757 (83.1)	
Stage			
I	4834	2939 (60.8)	<.001
II	3667	3362 (91.7)	
III	1342	1246 (92.8)	
Missing	411	248 (60.3)	
Grade			
1	2978	1547 (51.9)	<.001
2	5230	4442 (84.9)	
3	1865	1670 (89.5)	
Missing	181	136 (75.1)	
Histopathological type			
Invasive carcinoma NST	8256	6305 (76.4)	<.001
Lobular	1353	1160 (85.7)	
Other	589	277 (47.0)	
Missing	56	53 (94.6)	

Table 39 continued. Descriptive Statistics by Endocrine Therapy Status (Weighted Sample)

Characteristic	Overall	Treated (%)	P value
Focality/centricity			
Unifocal & unicentric	8261	6117 (74.0)	<.001
Multifocal &/or multicentric	1894	1595 (84.2)	
Missing	99	83 (83.8)	
ER status			
Negative	148	94 (63.5)	<.001
Positive	10104	7700 (76.2)	
Missing	2	1 (50.0)	
PR status			
Negative	1751	1342 (76.6)	.25
Positive	8443	6403 (75.8)	
Missing	60	50 (83.3)	
HER2 status			
Negative	7306	5497 (75.2)	<.001
Positive	1006	881 (87.6)	
Missing	1942	1417 (73.0)	
Year			
2000-2003	2014	1532 (76.1)	.12
2004-2007	2360	1873 (79.4)	
2008-2011	2920	2141 (73.3)	
2012-2015	2960	2249 (76.0)	
Breast surgery			
No	393	334 (85.0)	<.001
Yes	9861	7461 (75.7)	
Axillary surgery			
No	685	473 (69.1)	<.001
Yes	9569	7322 (76.5)	
Radiotherapy			
No	3802	2750 (72.3)	<.001
Yes	6452	5045 (78.2)	
Chemotherapy			
No	7521	5220 (69.4)	<.001
Yes	2733	2575 (94.2)	
HER2-directed therapy			
No	7521	5220 (69.4)	<.001
Yes	2733	2575 (94.2)	

Figure 31 shows Kaplan-Meier survival curves for all-cause and breast cancer-specific death by C3 category. Overall, and for patients without comorbidity, endocrine therapy was associated with a significantly reduced hazard of all-cause death (overall: ATE HR 0.68, 95% CI 0.49-0.71, p<.001; C3 category 0: ATE HR 0.59, 95% CI 0.49-0.71, p<.001) (**Table 40**). No significant differences in all-cause mortality were found for patients with any degree of comorbidity using propensity score methods. Sensitivity analysis using multivariate regression however, revealed a treatment effect for endocrine therapy in patients with comorbidity, producing adjusted HRs of 0.71 (95% CI 0.53-0.95, p=.02) and 0.76 (95 CI 0.58-0.99, p=.04) for C3 categories 1 and 2 respectively (**Appendix C**, **Figure 37c-d**).

Endocrine therapy reduced the hazard of breast cancer-specific death for the overall sample (ATE HR 0.56, 95% CI 0.45-0.70, p<.001), as well as patients without comorbidity (ATE HR 0.55, 95% CI 0.43-0.71, p<.001) or with a low level of comorbidity (C3 category 1: ATE HR 0.48, 95% CI 0.29-0.79, p=.004). Similarly, in competing risks regression, endocrine therapy was associated with a reduction in mortality amongst C3 category 0 and 1 patients, as well as overall (ATE sHR 0.57, 95% CI 0.47-0.72, p<.001) (**Table 41**, **Figure 32**).

There was evidence of heterogeneity in treatment effect by comorbidity. For all-cause mortality, the ratio of HRs between C3 categories 2 and 0 was 1.64 in the IPT-weighted sample (95% CI 1.19-2.27, p=.003). The Wald test for overall interaction was also statistically significant; p=.01. A similar pattern was noted for breast cancer mortality, in both the Cox (ATE ratio of HRs 2.09, 95% CI 1.10-3.98, p=.02) and competing risks (ATT ratio of sHRs 2.38 95% CI 1.18-4.78, p=.02) models, although the Wald tests for overall interaction were insignificant (p=.50 and p=.30 respectively).

7.4. Conclusions

This chapter has examined the survival benefits of breast and axillary surgery, adjuvant radiotherapy, adjuvant chemotherapy, and endocrine therapy in relation to comorbidity burden and 5 individual conditions. Propensity score methodology was used to control for a large number of variables with the potential to incur confounding by indication. The impact of the analytic methods employed was explored in a range of sensitivity analyses. Treatment had a variable effect on survival, depending on the modality assessed, the treatment effect under examination, and the type and level of comorbidity. The following chapter will provide additional detail on how the results, and those of the other studies of this thesis, may be interpreted, along with a discussion of their accuracy and potential implications.

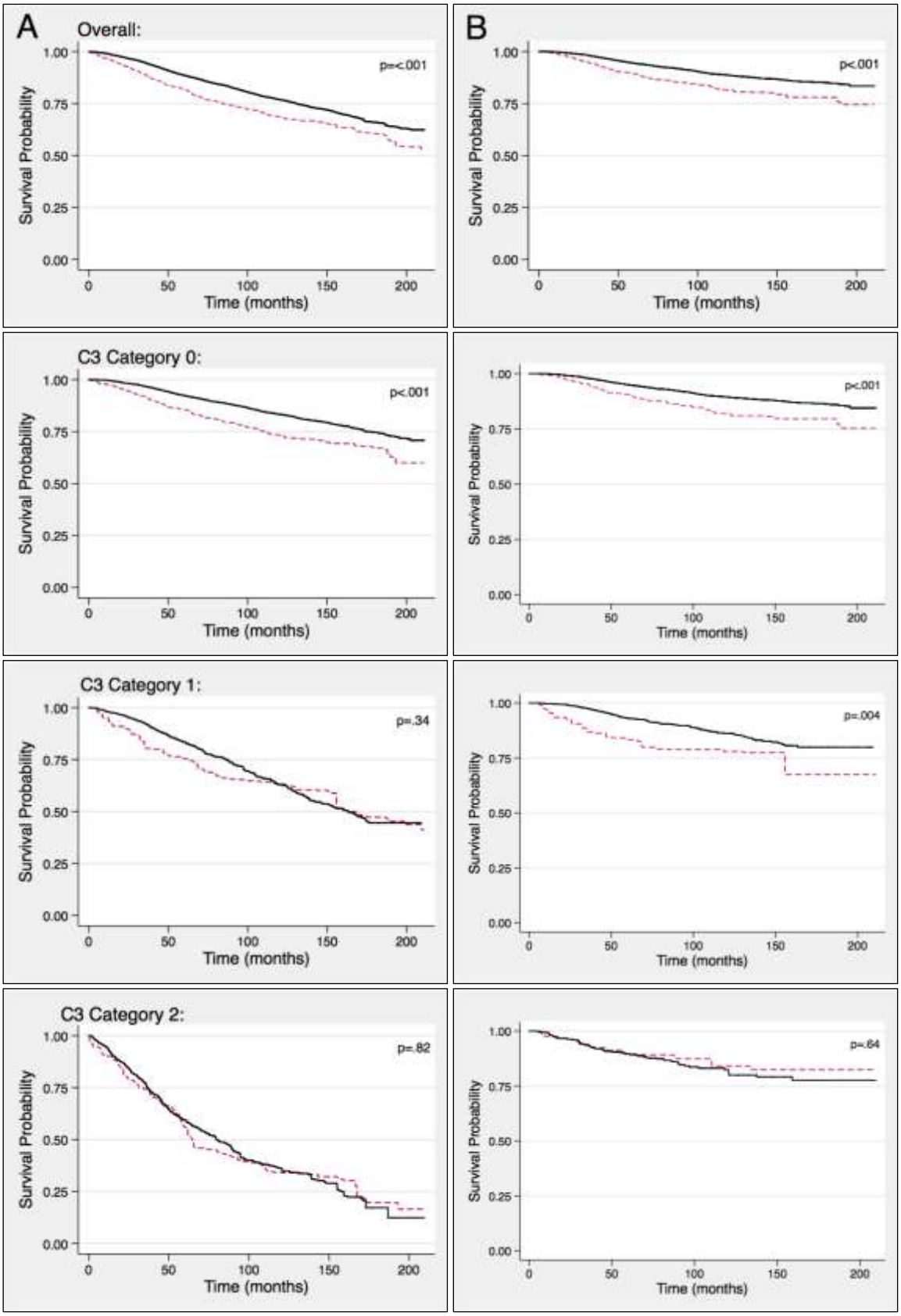


Figure 31. IPT-weighted Kaplan-Meier Survival Curves by Endocrine Therapy Status: Overall and C3 Categories

(A) All-cause survival (B) Breast cancer-specific survival

Table 40. Propensity Score-weighted Cox Regression for All-cause and Breast Cancer-specific Mortality: Treatment Effects of Endocrine Therapy by Comorbidity Status

	All-cause Mortality				Breast Cancer-specific Mortality			
	ATT		*ATE*		*ATT*		*ATE*	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Overall	0.63[a] (0.53-0.74)	<.001	0.68[a] (0.59-0.79)	<.001	0.52 (0.42-0.65)	<.001	0.56 (0.45-0.70)	<.001
C3 category								
0 (≤0)	0.56[a] (0.45-0.68)	<.001	0.59[a] (0.49-0.71)	<.001	0.51 (0.40-0.66)	<.001	0.55 (0.43-0.71)	<.001
1 (0.1-2.00)	0.75[a] (0.51-1.11)	.16	0.84[a] (0.59-1.20)	.34	0.45 (0.27-0.76)	.003	0.48 (0.29-0.79)	.004
2 (>2.00)	0.87 (0.65-1.17)	.37	0.97 (0.74-1.26)	.82	1.17 (0.62-2.25)	.63	1.15 (0.64-2.09)	.64
Condition								
Cardiac arrhythmia	0.67 (0.44-1.04)	.07	0.80 (0.55-1.18)	.27	1.21 (0.38-3.89)	.75	1.26 (0.44-3.65)	.67
COPD/asthma	1.40 (0.72-2.72)	.32	1.34 (0.77-2.32)	.29	0.89[a] (0.30-2.66)	.83	0.84[a] (0.31-2.28)	.73
Diabetes	0.74 (0.45-1.24)	.26	0.93 (0.58-1.48)	.75	1.08 (0.41-2.82)	.88	1.12 (0.46-2.71)	.80
Hypertension	0.82 (0.61-1.09)	.17	0.96 (0.73-1.25)	.75	0.70 (0.37-1.31)	.26	0.75 (0.40-1.39)	.36
Metabolic disorder	0.92 (0.56-1.54)	.76	1.08 (0.69-1.68)	.74	1.37 (0.51-3.66)	.53	1.48 (0.61-3.60)	.39

[a] Time dependent covariate, average effect presented.

Table 41. Propensity Score-weighted Competing Risks Regression for Breast Cancer Mortality: Treatment Effects of Endocrine Therapy by Comorbidity Status

	ATT		*ATE*	
	sHR (95% CI)	**P value**	**sHR (95% CI)**	**P value**
Overall	0.54 (0.43-0.68)	<.001	0.57 (0.47-0.72)	<.001
C3 index category				
0 (≤0)	0.53 (0.41-0.69)	<.001	0.70 (0.44-0.73)	<.001
1 (0.1-2.00)	0.45 (0.27-0.75)	.002	0.47 (0.28-0.78)	.003
2 (>2.00)	1.26 (0.66-2.41)	.49	1.21 (0.66-2.19)	.54
Condition				
Cardiac arrhythmia	1.53 (0.47-4.96)	.48	1.47 (0.50-4.30)	.48
COPD/asthma	0.76 (0.27-2.19)	.62	0.73 (0.28-1.92)	.53
Diabetes	1.23 (0.46-3.30)	.69	1.19 (0.48-2.92)	.71
Hypertension	0.75 (0.38-1.49)	.42	0.76 (0.39-1.47)	.41
Metabolic disorder	1.44 (0.53-3.95)	.47	1.50 (0.60-3.71)	.38

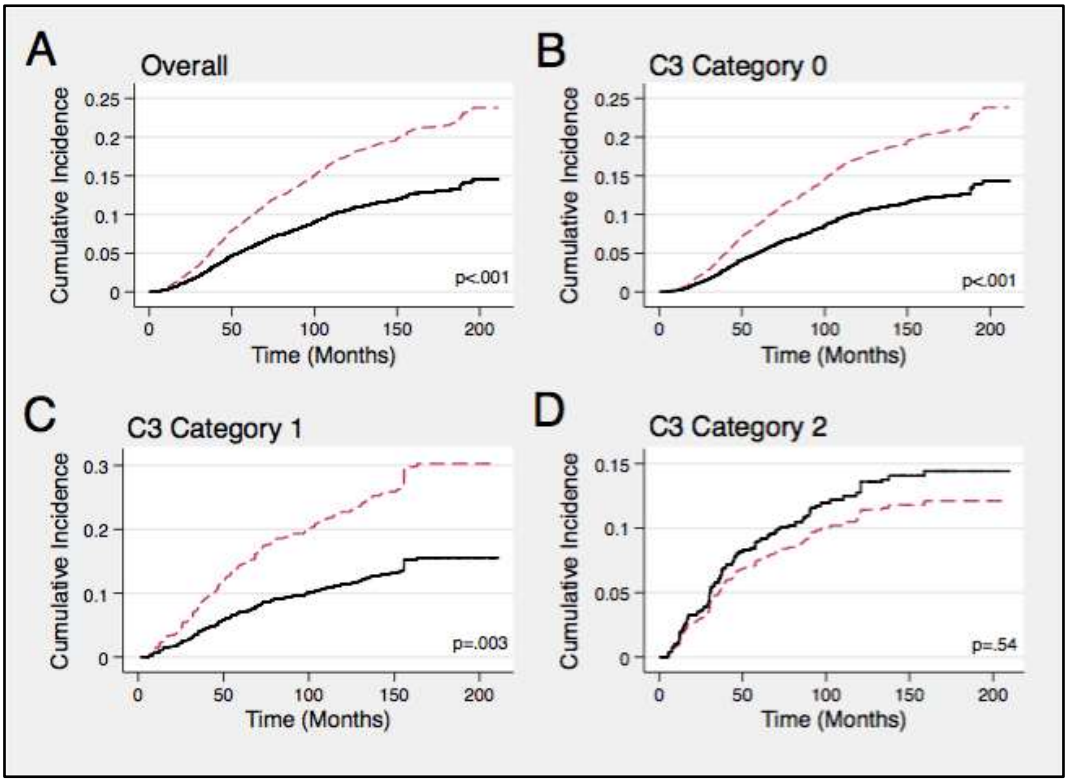


Figure 32. IPT-weighted Cumulative Incidence Function Curves for Breast Cancer Mortality by Endocrine Therapy Status: Overall and C3 Categories

Chapter 8. Discussion

The good physician treats the disease; the great physician treats the patient who has the disease.

—William Osler, 19th century physician-scientist

8.1. Introduction

The final chapter of this thesis discusses the results of the 3 studies conducted. Firstly, a summary of the key findings is given, followed by a discussion of how they may be interpreted and integrated with existing knowledge.

The accuracy of the results is then considered, with an examination of the strengths and weaknesses of the methodology used in relation to study validity and precision.

The thesis concludes with an exploration of the potential implications of the findings and suggested directions for further research.

8.2. Summary of Key Results

- Comorbidity is common amongst patients with breast cancer, affecting over a fifth of the study cohort; with the most common conditions being hypertension, diabetes, cardiac conditions, metabolic disorders, and respiratory diseases.
- Comorbidity is associated with poorer age- and stage-adjusted all-cause survival, with a greater impact on competing cause than breast cancer-specific mortality.
- Comorbidity is linked with other drivers of cancer inequities; with advancing age, minority ethnicity, socioeconomic deprivation, and residence within the Auckland region associated with the presence and/or severity of comorbidity amongst patients with breast cancer.
- Comorbidity has an adverse impact on the diagnosis of breast cancer, reducing the likelihood of presenting with a screen-detected tumour and increasing the risks of having unknown or more advanced stage at diagnosis.
- Comorbidity reduces the likelihood of receiving all modalities of breast cancer treatment in accordance with standard guidelines.
- There is heterogeneity in the impact of comorbidity on the receipt of treatment by tumour stage and grade.
- Comorbidity has variable impacts on the quality of breast cancer treatment; increasing the risk of inadequate surgical margins following BCS and receiving a substandard number

chemotherapy cycles, but reducing the likelihood of suboptimal adherence to endocrine therapy.

- Patients with comorbidity are more likely to experience long delays to primary surgical treatment, but not adjuvant therapy.
- While comorbid patients who are treated with breast and axillary surgery experience significant proportional reductions in the hazards of all-cause and breast cancer death, breast cancer-specific benefits reduce with increasing comorbidity severity.
- Patients with a low level of comorbidity who are treated with adjuvant radiotherapy have significantly lower all-cause (but not breast cancer-specific) mortality. Patients with cardiac arrhythmias and hypertension also experience mortality benefits (both overall and breast cancer-specific) with radiation treatment.
- Comorbid patients derive no benefit from treatment with adjuvant chemotherapy, while treated patients with cardiac arrhythmias experience increased all-cause mortality.
- Endocrine therapy results in a relative reduction in breast cancer-specific but not all-cause mortality for patients with a low level of comorbidity.

8.3. Interpretation of Findings

8.3.1. Characteristics of the Study Cohort

As no age restrictions were imposed on eligibility, a wide age range was observed, with a distribution largely as expected for a breast cancer cohort. The median age at diagnosis was 57 years, slightly younger than US estimates (median age from 2018 SEER cancer statistics: 62 years).[153] The ethnic composition of the cohort was slightly more diverse than the national average, with more Māori and Pacific peoples.[288] The majority of cancers were diagnosed following a symptomatic presentation, reflecting the wide age distribution of the cohort. The absolute numbers of breast cancers diagnosed per calendar year rose steadily over time, likely due to concomitant increases in population size.[285] Within this cohort of incident non-metastatic cancers, tumour histology was predominantly favourable; with the majority being early stage, low grade, hormone receptor-positive, and HER2-negative.

8.3.2. Comorbidity Burden amongst Patients with Breast Cancer

8.3.2.1. Prevalence of Comorbidity

Comorbidity was common in this cohort of New Zealand women with breast cancer, with 21.5% of patients possessing at least 1 major comorbid condition. As seen in other settings (**Table 2**), the most common individual conditions affecting study participants were hypertension, diabetes, cardiac conditions, metabolic disorders, and respiratory diseases. However, as prevalence estimates of comorbidity may vary widely due to differences in study population and methodology,

it is difficult to compare the findings to existing literature. In general, the prevalence of comorbidity in this cohort was lower than that reported by others (**Table 2**); likely due to the predominance of studies utilising the US SEER-Medicare linked database, which restricts participants to those aged 65 years and over.[711] Due to the strong correlation between comorbidity and age, the inclusion of younger patients in the current cohort will dilute the prevalence of comorbidity. Sarfati et al[116] provide the most similar cohort for comparison, utilising the NMDS to ascertain comorbidity (as measured by the C3 index) in breast cancer patients identified from the NZCR. In that study, 12.7% of participants were noted to have some form of major comorbidity. The greater prevalence of comorbidity in the current study may be due to sociodemographic differences between the study cohort and the overall New Zealand population, with minority ethnicity and deprivation associated with greater levels of chronic disease.[310]

8.3.2.2. Overall Impact of Comorbidity on Mortality

This study adds to the considerable body of evidence that comorbidity adversely affects survival amongst patients with breast cancer.[28,29] The general trend of a relatively greater impact on non-breast cancer than breast cancer-specific mortality was replicated, with an approximate 20% increase in the age- and stage-adjusted hazard of death for breast cancer-specific mortality with any degree of comorbidity, and a 50% increase in all-cause mortality; similar to the review findings of Hong et al.[29] These relationships were near-linear, with progressive risk of death with increasing C3 score.

Dementia, alcohol abuse, CHF, and renal disease had the greatest deleterious impact on all-cause survival, incurring around 3 times the hazard of death. All of the conditions studied (with the exception of intestinal disorders) had an adverse effect on overall survival, even minor conditions which may have less of an intuitive impact (such as sleep, eye, and inner ear disorders). While such conditions may have an independent effect on survival, it is more likely that some of the apparent effect is mediated through clustering with other, more severe conditions which have common pathophysiologic mechanisms. For example, sleep disorders such as obstructive sleep apnoea are often associated with concurrent obesity and respiratory disease. Untangling the cumulative effect of multiple comorbidities is an unwieldly task, requiring adjustment for combinations of conditions within mortality models; something which was not possible in this study due to the relatively small numbers of deaths within each condition.

8.3.2.2. Factors Associated with the Presence of Comorbidity

Several factors were associated with the presence and burden of comorbidity in the study cohort. As expected, advancing age was strongly associated with both the presence and severity of comorbidity, with minimal change in estimates following adjustment for other factors. The relationship between age and the presence of at least 1 major comorbid condition was nonlinear, with a steep increase in the likelihood of comorbidity from approximately 70 years.

Ethnicity was also strongly related to comorbidity, with Māori and Pacific women more likely to possess at least 1 major comorbidity (53% and 35% higher adjusted risk respectively) and experience a greater number of conditions than Europeans. This was also expected, as it is known that long term conditions disproportionately impact Māori and Pacific peoples.[310] Furthermore, as Māori are more likely than non-Māori to be hospitalised with the same disease,[309] comorbidity was more likely to be picked up amongst Māori in this cohort, given the use of hospital discharge data to ascertain the presence of comorbidity.

A social gradient in the prevalence of comorbidity was also noted, with progressively higher risk with increasing NZDep2013 quintile. While this trend was not replicated in the negative binomial model analysing the number of apparent conditions, in the logistic inflation model, increasing deprivation was associated with lower likelihood of a zero comorbidity count. Thus, while socioeconomic position impacts the likelihood of having some degree of comorbidity, it does not appear to drive a higher level of comorbidity burden amongst those with at least 1 condition.

Patients resident in the Auckland region were more likely to have comorbidity and a greater number of conditions than patients from the Waikato. Unexpectedly, this effect was not fully explained by sociodemographic differences, persisting despite adjustment for age, ethnicity, measures of deprivation, and urban/rural residential status. As it is difficult to ascribe such an effect to anything other than the known differences in population structure,[289-291] some degree of residual confounding in these covariates must exist.

No differences by residential status were noted; with rural patients no more or less likely to possess coexistent comorbidity than their urban counterparts. It should be noted, however, that relatively few patients in the cohort actually lived in a rural setting (7.01%), meaning the absence of a detectable association may reflect lack of power rather than true equality in health status.

8.3.3. Impacts of Comorbidity on Breast Cancer Diagnosis

In this cohort, comorbidity burden had a detrimental impact on breast cancer diagnosis. Consistent with other studies,[356,357] comorbidity was associated with greater likelihood of presenting with more advanced stage at diagnosis. Unique to this study was the modelling of stage as an ordinal variable, rather than dichotomising stage as early/late (where early stage may mean localised or non-metastatic; while late may mean regional or metastatic, depending on study methodology) as others have done.[26,132,352,353,355,356,358,359,361] Greater detail was provided by Gurney et al,[357] who used multinomial logistic regression to model the odds of regional, distant, and unknown stage of disease in comparison to localised disease. Using a generalised ordered regression model in the current study however, enabled the retention of information contained in the categorical ordering of stage; thus it could be determined that comorbidity burden was related to higher disease stage in a linear dose-response fashion, a finding not previously described.

A separate analytic model was used to evaluate the relationship between comorbidity and unknown (vs known) stage of disease. This showed that comorbidity severity was associated with greater risk of unknown stage, a finding which also echoed the literature.[357,396,399,712] In this cohort, the proportion of patients with missing stage information was 4.07%, lower than that reported by Gurney et al[396] (10%) and Seneviratne et al[399] (12.3%), who used NZCR data to perform similar analyses. This low proportion is an advantage of using breast cancer registry data rather than data from the NZCR, which has been previously criticised for inaccurate or missing staging.[399,713-715] This also indicates that comorbidity is an important factor influencing the likelihood of missing stage in this cohort (compared to others with higher rates of missing stage data), as a substantial level of comorbidity was required to preclude the performance of staging investigations.[396]

A trend was also noted amongst women of screening age where the likelihood of presenting with a screen-detected tumour (vs diagnosis following a symptomatic presentation) reduced with increasing burden of comorbidity in linear fashion. This is a unique method of evaluating the impact of comorbidity on screening for breast cancer, with other studies focussing on screening uptake or recommendation for screening, rather than mode of detection.[352,361,363,371-382] Despite this difference, the premise is similar, with the majority of the literature reporting a negative impact on breast cancer screening with the presence of comorbidity.[371,372,376]

Put together, an overall adverse effect of comorbidity on breast cancer diagnosis was found. This is in keeping with the so-called competing demands, death from other causes, and/or physiological hypotheses rather than a surveillance effect,[26] although it is difficult to speculate from the data the relative contributions of each of these mechanisms. As others have suggested,[336,350] it is likely that the type of comorbidity plays a role in the balance of these factors; for instance, hypertension was associated with an increased likelihood of screen-detection, which may relate to increased opportunities for prevention due to more frequent contact with primary care.[12,26,132,363] While this did not translate to a positive impact on stage at diagnosis, this may reflect a lack of power rather than a true absence of effect in this small subgroup of participants.

8.3.4. Impacts of Comorbidity on Standards of Treatment

8.3.4.1. Receipt of Treatment

Overall, comorbidity had a deleterious effect on receipt of treatment for breast cancer, with a reduction in the likelihood of receiving all 5 treatment modalities in accordance with guideline recommendations. This fits with the existing literature, with consistent reports of reduced treatment in the presence of comorbidity. An exception to this general trend is endocrine therapy, with evidence suggesting that comorbid patients are equally[61,114,122,401] or more likely[120,403,406] to receive endocrine therapy than their non-comorbid counterparts. In this respect, the current study is unique; with results showing a linear increase in the likelihood of endocrine non-concordance

with comorbidity burden. This unexpected result may be explained by the exclusion of 173 patients with unknown hormone receptor status from the analysis cohort. As comorbid patients are less likely to receive full diagnostic investigations, it would be reasonable to assume that comorbid patients represent a greater proportion of those with missing receptor status. Indeed, in descriptive analysis a significant relationship was observed between C3 score and missing ER ($p<.001$) and PR status ($p<.001$), which may have resulted in selection bias, shifting the association between comorbidity and endocrine non-concordance away from the null.

Evidence for effect modification of the association between comorbidity and non-receipt of treatment by tumour stage and/or grade was noted for breast surgery, axillary surgery, chemotherapy, and endocrine therapy. The evidence for this with respect to chemotherapy and endocrine therapy was particularly notable. With rising comorbidity severity, there was a greater risk of non-treatment amongst patients with higher stage (chemotherapy) and grade (chemotherapy and endocrine therapy) disease, compared to patients with lower stage/grade disease. This extends the work of Greenfield et al,[6] who noted less vigorous treatment for patients with higher levels of comorbidity who had more advanced stage of disease.

8.3.4.2. Quality of Treatment

Overall, amongst patients who received treatment for breast cancer, comorbidity had a variable impact on the quality of that treatment, depending on the modality assessed.

There was no association between comorbidity and quality of breast surgery when quality was defined as mastectomy or BCS with a negative margin. It is likely that this equivalence resulted from choice of surgical technique, with a greater proportion of comorbid patients undergoing mastectomy as opposed to BCS. The literature on this is mixed, with some studies reporting more mastectomies amongst patients with comorbidity,[406,421,422] while others have found the inverse,[9,130] or no difference.[50,122,401,423] In this cohort, where adjuvant radiotherapy was less likely to be received by comorbid, the finding that comorbid patients undergo mastectomy more frequently may represent a desire to avoid radiotherapy. Indeed, when the analysis was restricted to patients receiving BCS as their final surgery, an association between comorbidity burden and risk of an inadequate margin became apparent, reflecting a reluctance to perform re-excision under such circumstances, the consequence being greater acceptance of elevated recurrence risk.

Comorbidity was not associated with overall quality of axillary surgery. While some authors have noted a reduction in ALNDs for patients with comorbidity,[50,120,123,401,403] such studies compared ALND to no axillary surgery, rather than against a different technique. In this study, a greater proportion of comorbid patients underwent ALND than SLNB. It is likely that this relates to higher stage disease amongst comorbid patients, although a desire to perform a one-stage operation (with reluctance to perform further surgery in the case of a positive sentinel node) may play a role.

Most patients receiving adjuvant radiotherapy received appropriate doses of radiation, with over a third of those who did not receiving a hypofractionated regime which would be considered appropriate contemporary treatment. No differences in treatment quality were noted by level of comorbidity, indicating that radiotherapy was relatively well tolerated irrespective of comorbidity.

Comorbidity was strongly associated with completion of a substandard number of chemotherapy cycles. This is likely to reflect greater chemotherapy-associated toxicity, resulting in dose reductions or early discontinuation of treatment. While the literature suggests that comorbid patients are less likely to be treated with second and third generation regimens,[115,117,119,126,417-420] in this study, the use of anthracycline-containing regimes was not proportionally lower amongst patients with comorbidity.

Conversely, comorbidity was associated with a lower risk of suboptimal adherence to endocrine therapy. Thus, while patients with comorbidity were less likely to be commenced on endocrine therapy, for those who were, adherence was superior. The impact of comorbidity on adherence to endocrine therapy has not been well studied, with conflicting findings in the literature.[450,452] Contradictory forces may act to produce such inconsistencies. On the one hand, if endocrine therapy is the only tolerable treatment, a comorbid patient may have stronger motivation to persist than a healthier counterpart receiving full multimodality therapy. Greater frequency of contact with primary care may also play a role, providing more opportunities to encourage adherence. Opposing these mechanisms however is comorbidity-related polypharmacy, which may cause issues with drug interactions and tolerability, resulting in premature discontinuation of treatment.

8.3.4.3. Timeliness of Treatment

In this study, the primary threshold used to define delay was 31 days from diagnosis, in keeping with the national FCT target.[198,300] Disappointingly, this was reached by only 61.8% of patients undergoing primary surgery, with comorbid patients no less likely to be impacted. While the prognostic impact of surgical delay longer than 31 days is unknown, worse survival has certainly been demonstrated with delays beyond 60 days.[424,425] Although there were far fewer patients experiencing delay when the threshold was set at 90 days (1.87%), comorbidity was significantly associated with delays of this length, something which was not demonstrated by Seneviratne et al[427] in a local study using the same threshold. While delays to surgery beyond 31 days may be explained by resource constraints affecting the entire cohort, delays beyond 90 days are likely to reflect challenges unique to comorbidity, such as a requirement to investigate and optimise medical comorbidities prior to surgery and anaesthesia.

Delay to adjuvant therapy was also analysed in accordance with national targets (6 weeks[198]), with an additional sensitivity analyses performed in acknowledgement of the evidence purporting worse survival following delays of >12 weeks.[238,256,257] Once again, a substantial proportion of the

cohort failed to receive adjuvant therapy within a 6-week time frame (76.7%), which was largely attributable to difficulties in timely access to radiotherapy during the study period. Overall, comorbidity was not associated with delays to adjuvant radiotherapy or chemotherapy/HER2-directed therapy using either threshold. From this it may be concluded that comorbid patients who are selected to undergo adjuvant treatment are no more likely to experience postoperative complications which impact on start times for adjuvant therapy.

8.3.5. Effects of Treatment on Survival in Relation to Comorbidity

Surgical treatment had a substantial impact on survival, incurring a 50% proportional reduction in all-cause mortality and a 60% proportional reduction in breast cancer mortality in the weighted overall analysis cohort. Surgery resulted in all-cause mortality benefits within all strata of comorbidity severity, but breast cancer-specific benefits were only seen amongst patients with zero and low levels of comorbidity. Treatment effect heterogeneity in breast cancer mortality due to comorbidity was affirmed by the results of subgroup analysis, which showed that patients without comorbidity who received surgery had 2.5-times lower mortality than surgical patients with the highest level of comorbidity severity.

Adjuvant radiotherapy also had a considerable impact on survival, resulting in an approximate 45% proportional reduction in both all-cause and breast cancer-specific mortality in the overall sample. All-cause mortality benefits were also seen for patients with a low level of comorbidity, with a trend towards benefit in the highest severity comorbidity strata. Breast cancer-specific treatment effects were absent for patients with general comorbidity, other than patients with cardiac arrhythmias and hypertension. The observed effect size for the overall analysis cohort was greater than expected. Based on the 2005 EBCTCG Overview, which reported a 5.3% absolute difference in overall survival at 15 years with the addition of radiotherapy,[208] a treatment effect in the realm of a 15% proportional mortality reduction was expected. The EBCTCG estimate is likely to be conservative by today's standards however, with improvements in radiation techniques since the 1980s[716,717] offsetting the increased risk of death from other causes (particularly cardiovascular disease) observed in the earlier trials of radiotherapy.[228,229]

Within this cohort of patients with a minimum indication for adjuvant chemotherapy, treatment was more likely to be received by patients with worse prognostic tumour characteristics. Overall, chemotherapy resulted in a 23% proportional reduction in all-cause mortality. A 26% proportional reduction in breast cancer mortality was seen in the SMR-weighted sample, with no significant treatment effect observed in the IPT-weighted sample. This means that a breast cancer-specific treatment benefit was only seen in the sample weighted to balance the baseline characteristics of patients who ultimately received treatment (ie, the ATT), not the covariate distribution of the entire sample. Similar results were noted for patients without comorbidity, but no benefits were seen for patients with any degree of comorbidity (other than metabolic disorders). Patients with cardiac

arrhythmia who were treated with chemotherapy actually had an increased risk of death, with approximately 3-times higher all-cause mortality. This may reflect an increase in the incidence of cardiotoxicity amongst such patients, a known risk of treatment with anthracyclines and trastuzumab, which is more common in the setting of pre-existing cardiac disease.[342,440,441,444]

Endocrine therapy also resulted in mortality benefits for the cohort, with an overall 32% reduction in all-cause mortality, and a 44% reduction in breast cancer-specific death. Patients with a low level of comorbidity experienced a reduction in breast cancer-specific but not all-cause mortality with endocrine treatment. There was heterogeneity in treatment effect due to comorbidity, with reduced proportional benefits at higher levels of comorbidity severity.

8.3. Accuracy of Findings

The accuracy of an estimate in epidemiological studies may be described in terms of validity and precision.[636] Errors in the estimation process are traditionally classified as either systematic (affecting validity) or random (affecting precision). Validity may be examined in terms of the inferences drawn as they pertain to members of the study population (internal validity) and to people outside that population (external validity). Most violations of internal validity can be classified as selection bias, information bias, and confounding. External validity may be thought of in terms of scientific and statistical generalisability. The following section provides an evaluation of the strengths and weaknesses of this thesis as they relate to validity and precision.

8.3.1. Internal Validity

8.3.1.1. Selection Bias

Selection bias encompasses a variety of biases which may result from the procedure by which individuals are selected.[718] The common tenet is that the association between exposure and disease is different between those who participated, and those who were theoretically eligible but did.[636] Potential sources of selection bias in this study include sample selection bias, selection bias due to treatment received, missing data bias, and bias due to informative censoring.

Sample Selection Bias

Sampling bias exists when a non-random sample of the underlying source population is selected, due to the systematic exclusion of a subset of individuals with a particular attribute. In this study, potential participants were identified from breast cancer registers. Studies from the early 2000s using data from the Auckland register estimate its coverage rate at 80-85%.[521,719] Subsequent ethical approval to remove the requirement for individual consent (with backdating of nonconsenting cases) has increased the capture rate in both regions. The Auckland register

identifies local cases from the NZCR, while the Waikato register audits its completeness against the NZCR. Mandatory reporting of all new cancers to the NZCR[720] has meant reasonably complete register coverage. A study assessing the completeness of NZCR coverage for paediatric cancers reported an ascertainment rate of 97%,[713] while in similar study of lung cancers, ascertainment was 88.3%.[714] As pathology laboratories are the primary source of data for registration, underreporting is likely to be greater for cancers with lower rates of pathological diagnosis. As the capture rate for breast cancer (usually easily accessible for biopsy) is likely to be higher than for lung cancer, it can be assumed that >88% of total cases are captured. However, the small subset of patients with clinically evident breast cancers who do not receive a pathological diagnosis, and are hence not reported to the NZCR, are likely to be systematically different from the majority who are. Comorbidity and/or advanced age are likely to be major reasons for this decision. Such patients are also unlikely to receive full cancer treatment, and thus poorer survival is expected. Under these circumstances, inclusion on the NZCR, breast cancer registers, and ultimately participation in this study will influenced by comorbidity, with the potential to incur selection bias.

A pathological diagnosis of breast cancer, either by FNA or tissue biopsy, was a required inclusion criterion for this study. This was designed to limit participation to those with invasive cancer specific to the breast parenchyma. In situ disease and cancer originating from other tissues were excluded due to their very different natural histories and clinical management. Again, it was expected that patients with a presumptive but non-confirmed diagnosis of breast cancer would be disproportionately affected by comorbidity. While this only resulted in the exclusion of 13 patients, it is probable that more exist, but are managed by primary care without coming into contact with specialist breast cancer services.

As it is not possible to distinguish invasive from in situ disease on the basis of FNA alone,[3] and cytological classification of histological type is challenging, the inclusion of patients diagnosed by cytology may have resulted in some misclassified cases of isolated DCIS or non-breast tumours (although this risk was mitigated to some extent by the additional requirement for an otherwise positive triple assessment in FNA-diagnosed cases). Such patients were included however, as it was presumed that individuals receiving a lone cytological diagnosis would be systematically different (on the basis of comorbidity and age) from those with biopsy-proven cancers. Indeed, the 129 patients who were included without tissue diagnosis were found to be older (median age: 83 years) and more comorbid (median C3 score: 0.69) than the remainder of the study population.

Selection Bias due to Treatment Received

For analyses which investigated surgical quality/timeliness and adjuvant therapy, selection was conditioned on the receipt of breast surgery. Systematic differences were noted between the 4.25% of the cohort who did not receive surgery and the remainder who did, with a higher likelihood of comorbidity, advanced age, Pacific ethnicity, and public treatment. In particular,

59.2% of patients who did not receive breast surgery had some degree of comorbidity, with the likelihood of non-concordance increasing with comorbidity severity in a dose-dependent manner. In consequence, the effects of comorbidity on adjuvant treatment were likely to have been underestimated. Likewise, the ability to detect heterogeneity in adjuvant treatment effects by comorbidity was also probably reduced.

Treatment analyses, as part of their selection criteria, also required detail on tumour characteristics in order to ascertain minimum indication for treatment. Where such data was missing, individuals were excluded. As comorbid patients are more likely to have missing data on tumour characteristics due to incomplete diagnostic procedures and surgical treatment, it is likely that such patients were differentially excluded, further understating the impacts of comorbidity on treatment non-concordance and treatment-mediated survival.

Missing Data Bias

In addition to a loss of information, reduction in statistical power, and increased chance of type II errors, missing data may introduce selection bias, depending on the amount and mechanism of missingness.[616] It is rare that a dataset is perfectly complete, particularly one of the size used in this study. While there is no established cut-off at which inferences become biased, missingness rates of <5-10% have been posited as inconsequential.[721,722] In this study, the overall proportion of missingness was moderate (23.7%), with the majority driven by missing HER2 status (due to non-routine testing prior to 2007). Missingness in all other main variables was <5%. Analyses which did not include HER2 were not therefore substantially affected by missing data.

In addition to the amount of data missing, the pattern and mechanisms of missingness are important to validity. When data is MCAR (and the proportion of missingness is small; <5%), case deletion strategies can produce valid inferences, due to the assumption that discarded cases represent a random subsample of the original data.[616] In this study, the data could not be proven MCAR, with missing data due to item nonresponse related to the incomplete recording of data fields in the breast cancer registers. In particular, missing data on tumour characteristics was highly correlated with comorbidity, likely due to incomplete diagnostic work up in such patients. The use of complete case analysis was therefore inappropriate, incurring selection bias due to the presence of systematic differences between individuals with complete and incomplete data.

While several techniques for handling missing data exist,[613] multiple imputation is a commonly used flexible approach, which maintains maximum efficiency by retaining information from all cases. Under MAR conditions, it produces unbiased estimates and SEs, by acknowledging the uncertainty associated with the imputed values.[628] In general, proving conclusively that data is MAR and not MNAR is untestable, as it requires knowledge of the values of missing variables themselves.[612] However, given that good correlates of incomplete variables and their missingness mechanisms could be identified from the dataset, MAR was considered a plausible assumption,

justifying the use of imputation. The plausibility of the MAR assumption was further increased by the inclusion of auxiliary variables in imputation models.[628] While different thresholds for the inclusion of auxiliary variables have been proposed,[612,625,723] a relatively low cut-off of $r>0.15$[625] was set in order to avoid bias due to the omission of an important correlate of missingness.[624]

The decision to use multiple imputation required consideration of the potential for valuable information recovery versus the introduction of bias from a poorly fitting imputation model.[724] Multiple imputation is most useful when missingness is in confounding variables rather than the exposure or outcome variables, as was the case in this study. In order to explore the sensitivity of conclusions to the effects of missing data, and to ascertain the effectiveness of multiple imputation in recovering information, sensitivity analyses using complete cases were also performed (data not presented). In Studies 1 and 2, where the proportion of missingness in the main effects models was negligible (<5%), point estimates and confidence limits for multiply imputed and complete cases were essentially the same. In Study 2 however, where interaction terms between C3 and tumour variables (which had a greater proportion of missing data; up to 40%) were introduced to models in order to investigate effect-measure modification, multiple imputation played a greater role in information recovery, although this did not result in any important changes in statistical inferences when compared with complete case analysis.

Multiple imputation was also used to account for missing data in the vector of covariates contributing the propensity score estimation models in Study 3. The literature on how to deal with missing data on covariates in the context of propensity score analysis is sparse, although several approaches have been discussed.[669,670,725-727] A popular simple strategy is the missingness pattern approach,[728] however this has been shown to be biased,[726] particularly when using an IPT-weighted estimator to estimate marginal treatment effects.[672] Other principled approaches include pattern mixture models,[728] general location models,[729] multiple imputation,[730] and multiple imputation in combination with the missingness pattern method.[727] Of these, multiple imputation provides the least biased solution under a MAR mechanism.[672,725,727] While different authors debate the relative worth of the across (pooling propensity scores) and within approaches (pooling treatment effects) to multiple imputation,[670-672] studies of sufficient size to ensure positivity, and which include the outcome variable in the imputation model, advocate the superiority of the within approach in eliminating the greatest amount of selection (and confounding) bias, particularly in the context of IPT-weighting.[671,672]

Informative Censoring

An implicit concept in survival analysis is that, had the study had been prolonged, eventually the outcome of interest would be experienced by all.[658] The assumption is made of non-informative censoring; ie, that those no longer in the study (due to censoring or dropout) have the same future risk of the event of interest as those remaining. Clearly, when the failure event of interest is breast cancer survival, those who die from non-cancer causes are no longer at risk of death from breast

cancer. The conventional survival framework disregards the presence of competing risks, with death from other causes treated as non-informative and censored at that time point. This can result in selection bias, with upwardly biased estimates of the risk of the event of interest.[731,732] The magnitude of this bias depends on the proportion of deaths due to the competing cause.[732] As patients with comorbidity have a higher risk of death from other causes, failure to account for competing risks will upwardly bias estimates of breast cancer-specific mortality [732].

In Study 3, breast cancer mortality was therefore also analysed using Fine and Gray competing risks regression, which takes account of the marginal probabilities of each competing event.[659] While sHRs from competing risks regression and HRs from Cox regression have different interpretations, no substantive differences in statistical inferences were observed, indicating there was unlikely to be any major selection bias due to informative censoring.

8.3.1.2. Information Bias

Information bias relates to the misclassification (mismeasurement) of study variables. Errors that depend on the values of other variables is called differential misclassification, while errors that do not are non-differential.[636] The direction and magnitude of bias depends on the distribution of error for a variable, with non-differential misclassification biasing estimates towards the null and differential misclassification potentially acting in either direction.

Misclassification of Guideline-concordant Treatment

Defining guideline-concordance was a complex exercise. Despite extensive efforts to review all potential resources of relevance, misclassification of the construct is inevitable, given the multitude of guidelines in existence, all of which are based on expert consensus. Guidelines are not intended to be prescriptive for every patient, as good quality evidence of therapeutic efficiency does not exist for all subpopulations. While arguments could be made for the selection of different guidelines to those utilised in this thesis, what was ultimately required was some standard against which to judge received treatment, which was relevant to standard practice in New Zealand during the time course of the study, and detailed enough to enable application.

Accepting the inevitability of misclassification error, of crucial importance is whether the distribution of this error is differential; as it pertains to comorbidity. It is well known that patients with concurrent comorbidity are less likely to receive definitive cancer treatment. It is reasonable to assume that this applies particularly to situations where evidence is emerging and not yet standard, or where guidelines are nonconcrete in their recommendations. For instance, where a guideline is worded ‘treatment *may* be considered’, rather than ‘treatment *should* be given.’ As such, only minimum treatment standards for which there existed a strong guideline recommendation were selected for evaluation in this thesis, in order to minimise any potential differential misclassification by comorbidity.

For simplicity, guideline concordance was dichotomised (concordant/non-concordant). When operationalised as a binary outcome variable (as in Study 2), non-differential and nondependent misclassification will bias different absolute estimates of effect towards the null.[81] Ratio measures of effect will be unbiased however, when specificity is perfect (ie, nobody is classified as being non-concordant when they are concordant). Setting a high threshold for the classification of non-concordance (by evaluating only minimum standards for treatment) also acted to maximise specificity. Data on treatment receipt was assumed to be reasonably complete, with data obtained from the registers based on case note review (with annual quality assurance processes in place) and supplemented by cross-linkage with the Pharms DM (for HER2-directed and endocrine therapies). When acting as an exposure variable (as in Study 3); independent non-differential misclassification of guideline-concordance will also bias estimates of effect towards the null.[636] One would therefore expect the observed treatment effects to have been larger had such misclassification been absent. Misclassification of this type may also impact upon effect modification in an unpredictable manner, by either introducing or masking the appearance of treatment effect heterogeneity by comorbidity.

Misclassification of Comorbidity

A discussed in Chapter 2, comorbidity is a multifaceted construct. Its complexity and heterogeneity mean that only an estimate of the concept may ever be measured. There will always be some misclassification of comorbidity, with the impact of this dependent on whether this is differential or non-differential, and how it is operationalised as a variable.

Comorbidity as an Outcome Variable

In Study 1, the focus was on the prevalence and causes of comorbidity as measured by the C3 index. A major strength of the C3 index relative to other comorbidity indices is the extensive process involved in selecting the conditions for inclusion. While the resulting index of 42 conditions is comprehensive, it is possible that not all *important* conditions are included, as their low prevalence may have precluded the calculation of a useful weighting coefficient.

The practical advantages of using administrative data to identify comorbidity in a cohort of this size cannot be understated. However, major limitations stem from its unrelated primary purpose as administrative rather than research-related. Data quality varies by condition, with bias towards more severe disease, primary diagnoses, in-hospital complications, and those which attract higher levels of funding.[14,78,81,149,733] This affects the sensitivity of measurement, with under-ascertainment of comorbidity compared with medical record review.[144,145,150] A study assessing the quality of comorbidity data held by the NMDS in a colon cancer cohort found that while more comorbidity was identified by clinical note review, some conditions, most notably diabetes and renal failure, were identified more frequently from administrative data.[144] Agreement between the sources improved with a longer lookback period, with kappa coefficients varying between 0.32-

0.75 at 8 years. As the current study utilised a 5-year lookback period, at least moderate correlation with clinical note review can be assumed.

Other data sources for identifying comorbidity deserve consideration. Data from the NMDS was only available for 48.4% of the cohort, with the remainder having no hospital admissions within the 5-year period preceding their breast cancer diagnosis. A more useful alternative source could be the primary care sector, where patient attendance is be more frequent. While this would be a valuable avenue for future work, currently, national-level primary care data is not available. In the New Zealand Burden of Disease Study, conditions were identified from a number of data sources including the Laboratory Claims Collection, Mental Health Information National Collection, National Non-admitted Patient Collection, and Pharms DM.[734] Such an approach was not considered here, not only because of the inconsistency with validated C3 methodology, but due to the difficulties associated with data interpretation. For instance, the laboratory dataset provides only data on the fact of a test (not the result) and the Pharms DM contains only information on the dispensing of a drug (not the indication, for which there may be several), while the Non-admitted Collection does not provide ICD-10 codes.

As discussed above, the impact of outcome misclassification depends on its operationalisation as a dichotomous variable or not.[81] In the study evaluating baseline factors associated with the presence of comorbidity in the cohort, comorbidity was defined as the presence of at least 1 of the 42 C3 conditions. This division into patients with no comorbid disease versus those with at least 1 major condition makes intuitive sense, especially given the largely unknown nature of how multiple comorbidities cumulate to determine outcomes when evaluated as an exposure variable.[72,138] A higher threshold would reduce the sensitivity of the comorbidity measure, which was undesirable given that over three-quarters of the cohort possessed no conditions at all. The magnitude of potential misclassification by dichotomisation was explored in a sensitivity analysis, which employed comorbidity as a count variable. While a direct comparison of coefficients between the 2 models is inappropriate due to their differential methods of analysis, no substantial differences in inference were observed. Expanding the operationalisation to a count also enabled an examination of which sociodemographic factors drive a higher degree of severity-related risk.

Comorbidity as an Exposure Variable

In Study 2, comorbidity was analysed as an exposure variable, primarily using continuous C3 index score. The impact of misclassification in this setting is less predictable, even if the misclassification is non-differential and independent.[81] When errors in the classification of comorbidity are correlated with errors in classification of the outcome, the effect estimate can be severely positively biased away from the null.[735] However, as the data sources for the ascertainment of comorbidity (NMDS) and outcome variables (stage at diagnosis, mode of cancer detection, and non-concordant treatment; as ascertained from the breast cancer registers) in the current study were different, such error is unlikely.[81]

To minimise misclassification error when comorbidity acts as the primary exposure variable, an index with high validity should be selected. Content and face validity "…relate to the degree to which a measure actually evaluates the construct that it purports to measure."[13(p925)] This is a qualitative assessment, relating in this context to the relevance of the measure to breast cancer, whether all important conditions have been included, and the criteria by which they have been selected. Following an extensive narrative review of measurement approaches to comorbidity in breast cancer populations (**Table 1**), the C3 index was considered to possess the highest validity in the context of this thesis. Its development in a population of New Zealand patients with cancer gives it a high level of content and face validity. The iterative process of selection undertaken ensures that the conditions included are relevant to life expectancy in cancer patients. Assigning weighting coefficients based on 1-year non-cancer mortality avoids the influence of cancer-related factors, particularly stage.[32] While the ideal measure would be weighted to reflect each of the outcomes to be assessed, in reality, no such indices exist. In theory, within-study indices could be developed; modelling specific outcomes as a function of comorbid conditions and their interaction terms, with regression coefficients applied as subsequent weights.[75] However, evidence from Sarfati et al[32] suggests that the weights applied are relatively less important than the inclusion of all relevant conditions. Other weighting methods were trialled in the development of the C3 index, including estimates from models based on all-cause mortality, producing similar results.

Criterion validity refers to how an index correlates with another measure of the construct under study (*concurrent validity*) and the extent to which it is able to predict future outcomes (*predictive validity*).[13] Concurrent validity between C3 and the CCI has been evaluated, producing correlation coefficients within the range 0.61-0.78.[32] In their 2012 review, Sarfati et al[13] found some evidence to support the predictive ability of all comorbidity indices, with the CIRS,[103] CCI,[88] ICED,[56] Elixhauser,[149] NCI,[97] and ACE-27[83] demonstrating particularly good prediction in the context of cancer outcomes. The predictive validity of C3 was tested against the CCI and NCI, with modest improvements in prediction of non-cancer and all-cause mortality.[32]

Comorbidity as an Effect-modifying Variable

In the final study of this thesis, comorbidity was treated as a potential effect-modifier of the relationship between treatment and survival. When comorbidity as a modifying variable is subject to misclassification, true effect-measure modification may either be masked or falsely appear.[81] The risk of this bias was reduced by the aforementioned efforts to select a comorbidity index with the least amount of measurement error (ie, the highest validity).

Misclassification of Covariates

If covariates are mismeasured, there will be imperfect adjustment and residual confounding. Bias will occur in the direction of the confounding by the misclassified variable.[636] If confounding is strong, and the exposure-outcome relation weak, misleading results may be produced, even if the misclassified confounder is independent and non-differential.

Age

Compared with their use on a continuous scale, categorisation of variables may result in residual confounding due to the necessary coarseness of grouping.[649,651] For instance, in a study which evaluated control of confounding by categorisation, classifying a continuous confounder into 6 categories removed only 92% of bias.[736] While multiple categories result in more accurate modelling and greater control of confounding, numerous degrees of freedom are required within models, resulting in estimates with reduced precision and power.[649] In this study, given the strong confounding influence of age on the relationships between comorbidity, treatment, and survival, maximum control of confounding was desired. Age was therefore modelled on a continuous scale, using 3-knot RCS functions which have been shown to remove the majority of residual confounding.[651,652]

Ethnicity

While the definition of ethnicity stipulates that a person can belong to more than 1 ethnic group, it does not require that people indicate the group with which they identify the most.[600] Two main approaches for dealing with multiple ethnicity responses are documented, each with their own limitations. In total response (overlapping) output, each respondent is counted within each of the groups they identify.[601] This creates issues with statistical interpretation, as group comparisons may include overlapping data. In prioritised output (the method employed in this thesis) an individual is allocated to a single group according to prioritisation tables.[601] This ensures that where there is some need to assign a single category, ethnic groups of smaller size but higher priority policy importance are not swamped, maximising explanatory power. While this approach is widely used in the health and disability sector and is statistically advantageous, it is however somewhat inconsistent with the concept of self-identified ethnicity.

Another key element of the ethnicity framework is that ethnicity may change over time (ethnic mobility).[600] Ever-Māori adjusted estimates were used in this study which account for whether any previous health contacts have been recorded as Māori. This method reduces the likelihood of undercounting Māori[156] and provides an ethnicity distribution close to the gold standard New Zealand Census Mortality Study,[156,284] but does carry the risk of over-counting Māori patients who have frequent contact with the health system.[156]

Socioeconomic Deprivation

Socioeconomic position was measured using an area level deprivation index, categorising deprivation into quintiles of NZDep2013 score. Despite the inherent problems of categorisation, it was expected that the majority of confounding would be removed with this approach as the study cohort was roughly evenly distributed across the 5 categories. Controlling for the overlapping construct of treatment facility (a proxy variable for insurance status and ultimately, deprivation) also meant that any potential independent confounding influence of the NZDep2013 variable was unlikely to be strong.

Using an aggregate measure of deprivation derived from geographic area of residence rather than individual measures can have limitations; with dilution of effects due to social heterogeneity, which may cause non-differential misclassification.[530] However, the NZDep2013 is based on meshblocks (the smallest geographic units defined by Statistics New Zealand, containing a median of 81 people in 2013[603]),[602] which are considerably smaller than the small area units used by deprivation indices in other countries (such as the English Indices of Deprivation 2015, which are based on lower layer super output areas containing an average of 1500 people[737]). Major heterogeneity in the current study is therefore considered unlikely, with any measurement error likely to be smaller than in studies from other countries basing their results on larger area units.

Stage

Tumour stage was classified according to the AJCC TNM system,[609] with pathological stage used in preference to clinical stage, which was applied under the circumstances of neoadjuvant treatment, missing pathological stage, or non-receipt of surgery. Pathological stage, derived from post-surgical histopathology reports is more accurate than clinical stage, which is based on imaging and subjective clinical examination. Some misclassification is therefore expected, which is likely to be differential by comorbidity, since patients with comorbidity are less likely to receive surgical treatment. Furthermore, the clinical staging assigned to patients who received neoadjuvant therapy is likely to be more accurate than that assigned to non-surgical candidates, since clinical stage is an important factor determining the utility of neoadjuvant therapy.

Tissue Biomarker Status

Individual tissue biomarker status (ER, PR, and HER2 status) and tumour grade was used in substitute to intrinsic molecular subtype, as gene-expression profiling technology is not currently widely utilised in New Zealand. Clinicopathological surrogate definitions[579] of these subtypes were not employed either, due to a lack of routine Ki-67 testing. However, as these biomarkers all have some individual contribution to both treatment decisions and prognosis, their inclusion as separate variables is unlikely to have contributed to a significant degree of residual confounding.

Misclassification of Mortality

Misclassification of death could occur at 2 levels; the first relates to the actuality of death and the second, to cause of death. Occurrence of death was derived by linking participants with the New Zealand Mortality Collection. While it is unlikely that an individual may be incorrectly classified as having died, deaths may be missed if subjects died outside of New Zealand. For this reason, mortality was cross-referenced with information held on the breast cancer registers, identifying a further 10 deaths.

Differential misclassification of cause of death by comorbidity may cause bias in resulting estimates of breast cancer-specific survival. If patients with comorbidity are more likely to be incorrectly classified as having died from non-cancer causes than those without comorbidity,

estimates of effect will be biased towards the null. Conversely, misclassification of non-cancer death as being due to breast cancer will cause upward bias of estimates. As patients with comorbidity are more likely to die from a non-breast cancer cause,[28,29] any misclassification in this direction will be disproportionate. Reassuringly however, it has been shown that estimates of breast cancer-specific mortality based on death certificate data are not substantially biased (compared to relative survival methods),[490,738] particularly amongst older patients with lower risk malignancy.[490] In countries with good death registration systems, it has been suggested than the sensitivity and specificity of cancer-specific death from death certificates is >90%.[494] The relative impact of misclassified cause of death on survival estimates is also lower in cancer populations with good prognosis.[494]

8.3.1.2. Confounding

In Studies 1 and 2, confounding was addressed by multivariate regression analysis using a modelling strategy which aimed to capture the underlying causal framework.[632] While traditional modelling strategies have focussed on predictive accuracy (with core goals of parsimony and goodness-of-fit), in an epidemiological setting, ignorance of this theoretical foundation may result in the exclusion of clinically important confounders in preference of weaker, or even non-confounders, which statistically explain more model variation.[739] Adjusting for all potential confounders has its own problems however, leading to issues with data sparsity and multicollinearity; particularly when the number of covariates is large relative to the sample size and number of events.[739]

Alternatives to conventional regression for control of confounding include G-methods, stratification-based methods, instrumental variable techniques, fixed effects models, and propensity score analysis. Propensity scores allow adjustment for an unlimited number of confounding variables, circumventing the restrictions imposed on regression methods when outcome events are rare. A simulation study comparing propensity scores against multivariable logistic regression with multiple confounders concluded that propensity scores performed better in situations of <8 outcomes per covariate.[740] Thus propensity scores were most valuable in the subgroup analyses of Study 3, where stratification of treatment effects by comorbidity resulted in small samples with relatively few deaths, precluding the use of traditional multivariable regression.

A further advantage of propensity score methods over regression approaches is the separation of study design from outcome analysis.[741] During the design stage, the propensity score is estimated and a balanced sample created without any reference to the outcome. This mimics the setting of a randomised trial, where treatment effects are estimated after the study has been conducted. Implementing propensity score methods in combination with multiple imputation does invoke a slight conflict with this however, as including the outcome variable in the imputation model has been shown to result in less bias.[671,672]

When propensity scores are balanced between treated and untreated subjects, treatment groups are said to be (conditionally) exchangeable.[665] Propensity scores were considered to be balanced when the standardised differences in covariate means were <0.25. While a 0.25 cut-off has been advocated as a guide,[669,742,743] based on the simulations of Cochran and Rubin,[744] there is no absolute criterion for assessing bias, with some authors proposing more stringent thresholds of 0.20[745] or even 0.10.[746] Balance is particularly crucial with respect to covariates which have a strong association with the outcome, where even tiny imbalance may translate into large bias and/or inefficiency in the resulting estimates.[747] Every effort was made, therefore, to achieve the tightest possible balance, particularly for covariates believed to have the strongest associations with survival; namely C3 index score, age, and cancer stage. While balance diagnostics in the setting of missing data is an area of ongoing research,[669] by using a within approach, it could be shown that the estimated propensity scores were able to balance covariates between treatment groups within each imputed dataset.[672]

Despite these endeavours, the minimal breast cancer-specific treatment benefits obtained by adjuvant chemotherapy may be explained by the presence of residual confounding. Initial univariate regression analyses revealed a significantly higher hazard of breast cancer death amongst patients who received treatment, which may be explained by differences in tumour characteristics (with higher proportions of treated patients possessing high stage, high grade, and HER2-positive tumours compared to patients who did not receive treatment). Whilst covariates were considered to be balanced using the aforementioned criteria, tighter balance would have resulted in better control of confounding and potentially, the appearance of more substantial beneficial treatment effects.

The ability to achieve strong exchangeability using propensity score methods is analogous to a marginally randomised experiment, where the randomisation process ensures that potential confounders, both measured and unmeasured, are equally distributed between treatment groups. Underpinning the reliability of propensity score methods (and regression-based approaches) is the strongly ignorable treatment assignment assumption, whereby it is assumed that all variables that affect treatment assignment and outcome have been measured and included in the propensity score prediction model.[665] While every attempt was made to include all relevant measureable confounders in the propensity score model, some potential unmeasured candidates require consideration.

Functional status in particular is likely to be important, as this has been shown to independently predict treatment receipt,[48-50] as well as all-cause and cancer-specific survival amongst patients with breast cancer.[48,51] A consequence of comorbidity may be a reduction in functional status, although individuals may have poor functional status without objective evidence of comorbidity. Unfortunately however, functional status could not be included in this study, as measures such as ECOG status are not widely recorded by the breast cancer registers, nor captured by the NMDS.

Modifiable health risk behaviours such as smoking, high alcohol intake, and raised BMI represent other potential sources of unmeasured and residual confounding. Smoking is associated with worse breast cancer survival, with a 2017 meta-analysis finding a 28% increase in breast cancer-specific mortality amongst current compared to never smokers.[748] While smoking information in the NMDS is available via the ICD-10 code Z72.0 (tobacco use), detailed information (ie, previous vs current smoker; amount smoked) is not available. Alcohol consumption is also associated with poorer breast cancer survival, with a dose-response relationship.[749] While alcohol abuse is captured by the C3 index, lesser consumption may still be a risk factor. Likewise, it has been shown that obesity contributes to poorer breast cancer survival; due, in part, to obesity-related changes in glucose metabolism and a reduction in the efficacy of aromatase inhibitors.[137] Although obesity is also a component of the C3 index, in a preliminary validation exercise, obesity was noted to be poorly captured by the NMDS (unweighted kappa statistic=0.05, p<.001) compared with registry data (which was unfortunately, incomplete).

Additional unmeasured tumour characteristics may also influence treatment assignment and prognosis. The potential for residual confounding by intrinsic molecular subtype and Ki-67 has been discussed. A high proportion of missing data on LVI (59.3% of the cohort) also precluded its inclusion as a covariate, although the impact of this is unlikely to be substantial, due to uncertainty regarding its independent prognostic value.[170,171]

Although ignorability can never be directly tested,[669] the sensitivity of results to the impact of an unmeasured confounder can be considered in terms of the likely direction and strength of the potential confounder. While the direction of confounding by unmeasured tumour biology is uncertain, the potential confounding influence of functional status and health risk behaviours is likely to be positive; ie, away from the null. Given the correlation between these factors and comorbidity, the potential for unmeasured confounding is likely to be greater within subgroups with comorbidity. While treatment effects were compared amongst patients with an objectively similar level of comorbidity, patients who ultimately received treatment may have had better performance status.

Although propensity score methods have several advantages over traditional regression approaches when estimating causal treatment effects, the 2 methods should be seen as complementary.[669] Systematic reviews comparing estimated effects from multivariate versus propensity score analyses have found only minor differences in inference between the 2 techniques,[750,751] with propensity score methods tending to yield estimates slightly closer to the null.[750] In the present study, where sensitivity analysis using multivariate methods was possible (ie, not limited by low event: covariate ratios), estimates were indeed further from the null (with the exception of the surgery analysis). This led to some changes in inference, for example the appearance of a breast cancer-specific benefit with chemotherapy; overall and in the C3 category 0 subgroup, and an all-cause mortality benefit from endocrine therapy in C3 categories 1 and 2.

Hybrid strategies, where in addition to the propensity score, important outcome predictors are simultaneously adjusted in a multivariate model have been described, which may remove more residual confounding if either the treatment (propensity score) or outcome (multivariate) model is misspecified.[752] However, as these do not result in parameter estimates of the ATE or ATT,[705] nor do they offer superiority in terms of bias or precision compared with standard multivariate regression,[752] such an approach was not considered. A further (though somewhat complex) approach could be the use of *doubly-robust* estimators such as the inverse-probability-weighted regression adjustment estimator, which possess the property of being asymptotically unbiased when only 1 of the treatment or outcome models is correctly specified.[753]

8.3.2. External Validity

Overall, this study had good internal validity; that is, the findings described are unlikely to be explained by selection, information, or confounding biases alone. The results can therefore be considered valid for the subjects included in the analyses of this study. An important next step is to consider the external validity of findings to a broader target population of interest. A modern perspective of external validity differentiates scientific from statistical generalisation.[636] Scientific generalisation pertains to the applicability of the generated causal hypotheses to a more general set of circumstances. Statistical generalisation relates to how statistically representative an analysis sample is to the broader source population. The following will discuss the generalisability of the current study in relation to these 2 concepts.

8.3.2.1. Scientific Generalisability

Study 1 describes the burden of comorbidity in a population of women from the Auckland and Waikato regions of New Zealand with non-metastatic breast cancer. Comorbidity was defined in terms of the constituent conditions of the C3 index, as identified by ICD-10-AM codes from national hospitalisation data. It would be straightforward to generalise the comorbidity prevalence findings to a broader population of New Zealand women with breast cancer (although estimates are likely to be affected by the known sociodemographic differences between the Auckland/Waikato regions and the national average). How the estimates may compare to an international breast cancer population would depend on the type and quality of the data sources used to ascertain comorbidity. Despite probable differences, given its foundation in ICD-10 coding procedures, the C3 index could be feasibly applied in other countries that follow such protocols.

Study 1 also identified sociodemographic factors associated with the presence of comorbidity amongst women with breast cancer. Several exposure variables were selected for investigation, which aimed to capture the concepts hypothesised to impact upon inequities in comorbidity burden. The applicability of findings to a broader population therefore depends upon their ability to accurately represent some general measure of these underlying constructs. For example, the

absence of an association between rurality and comorbidity may not be generalisable to other countries, due to definitional issues and limitations in the ability of the current urban/rural classification profile to accurately capture rural health service access.[549] Likewise, the impact of deprivation on comorbidity in other populations may be different depending on how it is measured and operationalised, as well as local health system context. Societal differences between countries may also limit the generalisability of conclusions pertaining to indigenous and minority ethnicities.

In Study 2, where the focus was the impact of comorbidity on guideline-non-concordant breast cancer treatment, external validity may be considered in terms of the relevance of the guidelines selected for assessment. Where possible, New Zealand guidelines were selected, to provide a standard against which to judge appropriate temporal treatment delivered within the public health system. No significant international differences in treatment standards are expected with this approach, as the New Zealand guidelines are based on the same available evidence-base, in conjunction with the recommendations of major international guidelines, such as the St Gallen Consensus. What cannot be standardised however (nor easily measured), are the interpretations and preferences of clinicians applying guidelines to individual patients, which may differ by culture and healthcare system. The relative thresholds for cancer treatment in comorbid patients may therefore vary internationally, depending upon general attitudes to treatment as well as resource availability. While this may affect the generalisability of the ratio measures of effect estimated by this study, due to the pervasiveness of the literature on this topic, it is still expected that a general hypothesis of an adverse impact of comorbidity on concordant cancer treatment could be generalised to a broader population of women internationally.

The issues discussed in this section continue to be relevant to the scientific generalisability of the findings of Study 3. In addition, as the final analysis samples of Study 3 differed from the original study cohort due to the use of propensity score methodology, the statistical generalisability of the resultant findings also require consideration.

8.3.2.2. Statistical Generalisability

An essential assumption in causal inference is that of positivity; where, for each treatment group, there are individuals within each cross-classified level of confounders.[718] In randomised trials, positivity is guaranteed by virtue of study design. In observational studies, which are susceptible to confounding by indication, non-positivity may occur when all participants with certain values of covariates are assigned to either treatment or control. Propensity score methods enable the explicit examination of the degree of overlap in the baseline vector of confounders between treatment groups. Propensity score matching, or restricting the weighted or stratified analysis to common support can enable positivity to hold. This is an advantage over standard parametric regression methods, which do not routinely check overlap and utilise the entire analysis sample.

When there is strong separation between treated and untreated groups (ie, there is minimal or no overlap in the probabilities of treatment), confounding is complete and estimation of treatment effects is impossible. When there is insufficient overlap, regression-based approaches perform poorly and provide misleading results, as they invoke heroic modelling assumptions based on extrapolation between 2 distinct populations.[742,754] Excluding individuals outside of common support enhances internal validity, however it must be noted that the generalisability of the resulting inferences is altered and should be interpreted with caution. Examination of the number of excluded individuals and their baseline characteristics can give an indication of the applicability of the resulting inferences to the broader population. In this study there was minimal loss to off-support for the surgery, radiotherapy, and endocrine therapy analyses (0.18-2.64%). The withdrawal rate for the chemotherapy analysis was higher (16.4%); however there were no differences between truncated and non-truncated patients with respect to level of comorbidity severity.

Statistical generalisation was also affected by the use of trimmed weights, which were employed to reduce the undue influence of patients who received apparently unusual treatments.[673,676] If there is treatment effect heterogeneity amongst such patients due to some unmeasured confounder, the resulting estimates may be unlike those which would be obtained from other propensity score approaches.[755,756] This has been demonstrated in 2 studies which show treatment effect heterogeneity due to unmeasured frailty. In the first, which evaluated post-stroke thrombolysis, mortality was the highest amongst patients who received thrombolytic therapy despite having the lowest propensity for treatment.[755] In the second, which investigated the effect of biologic therapy on mortality amongst patients with rheumatoid arthritis, mortality was highest in patients with the highest propensity scores but who did not receive treatment.[756] Subsequently, Stürmer et al[679] investigated the effect of weight trimming on bias due to unmeasured confounding by frailty, finding that trimming increasing proportions of those at the tails of the overlapping propensity score distributions lead to reductions in both bias and the variance of treatment effects. Trimming therefore improves the plausibility of exchangeability, which is likely to be particularly beneficial in this study, due to the potential for unmeasured confounding by comorbidity-related constructs such as frailty and functional status. Again, this represents a trade-off between internal and external validity, as trimming leads to a more focused inference that is no longer generalisable to the source population.

The distribution of study weights was assessed to determine the potential benefit of trimming. Well-behaved weights have a mean of 1.0 and a non-extreme range[680] (which in practice may be interpreted as between 0.1-10[682]). As some extreme initial weights were observed, trimming at the 1st and 99th centiles was performed, resulting in weights <10. Estimates obtained from untrimmed weights were generally closer to the null, resulting in some changes in statistical inference. For instance, analyses using untrimmed weights revealed no breast cancer-specific mortality benefit from chemotherapy in the overall analysis cohort.

8.3.3. Precision

Random error equates to a divergence of observations from some true population value due to chance alone, leading to a lack of precision in estimated measures of association. While epidemiological cohorts do not satisfy the typical definition of a random sample, they may still be thought of as a figurative sample of subjects from a broader conceptual population of interest.[636]

8.3.3.1. Sample Size

Sampling variability is related to sample size, with larger samples yielding more precise estimates of effect. Despite the reductions in sample size due to the trimming of off-support observations, the estimated required sample sizes were achieved for each of the treatment effects analyses overall. However, while a large number of patients were included in the overall study cohort, the distribution of comorbidity was severely skewed, such that few patients actually possessed severe levels of comorbidity. As a result, while sample size requirements were met within each stratum of comorbidity in the surgery analysis, there were inadequate numbers within comorbidity subgroups for the radiotherapy, chemotherapy, and endocrine therapy analyses. It is uncertain, therefore, whether the observed lack of statistically significant treatment effects within strata in these analyses relates to insufficient sample size or a true absence of effect.

The estimated sample size required to detect interaction was only achieved in the surgery analysis. Sample sizes were inflated by a factor of 4 with the intention of detecting interaction with the same power as the overall treatment effect. However, even this may not have been sufficient, as the required inflation factor varies with the size of the interaction effect relative to the overall treatment effect. For instance, Brookes et al[690] found that to detect subtle interaction effects in the range of 20-40% of the overall effect, the inflation factor must increase between 25-100 times. Nonetheless, an interaction effect due to comorbidity was noted for endocrine therapy with respect to all-cause mortality, and for surgery with respect to breast cancer mortality (if, as some argue, the nominal significance level against which to assess interaction is raised to p=.10, given the low power of the test[757]).

The achievable sample size in this study was limited by the number of cases recorded on the breast cancer registers of Auckland and Waikato. Two further New Zealand breast cancer registers are also in operation; Wellington, which commenced in 2009 and Christchurch, which began in 2010, with the 4 registers consolidating into a single national register in 2016.[758] The Wellington and Christchurch registers contain relatively fewer patients however (approximately 3151 for Wellington and 3265 for Christchurch, as of October 2019 [Rachel Shirley, system administrator; Breast Cancer Foundation National Register; oral communication, 31 October 2019]), and their recency precludes the usefulness of long term mortality data. International data sources were not considered, given the use of the NMDS to assign comorbidity (as well as issues with additional confounding relating to health system differences).

8.3.3.2. Variance Estimation with Propensity Score Methods

In observational settings, propensity scores are estimated from the data, rather than fixed (by virtue of study design, as with random treatment assignment in clinical trials). Failing to account for this uncertainty (by using naïve model-based variance estimators) results in incorrect quantification of precision.[674,675] The use of weights also induce within-subject correlation in outcomes, which violates the assumption of independence of observations required by naïve estimators.[686] In an IPT-weighted pseudo-population, the use of naïve estimators results in an underestimate of the variance, producing inappropriately narrow confidence intervals, leading to type I error.[759] The use of robust variance estimators has therefore been proposed,[686,687] which account for this lack of independence. Others advocate the use of bootstrapped SEs, arguing that robust estimators result in overly conservative estimates of the variance.[759] The bootstrap method is not suitable for small datasets however, as too few values are available to select from, resulting in failure of convergence.[760] Sensitivity analyses using bootstrapped estimators revealed that this was indeed the case in this study, particularly within smaller subgroups, with no actual changes in statistical inference compared with results from robust SEs.

Uncertainty in the estimates of treatment effect due to missing data also requires consideration. Using Rubin's rules for estimating the variance of combined treatment effects in combination with a variance estimator which accounts for the uncertainty in propensity score estimation has been shown to perform well in IPT-weighted settings.[672,761] This was a further reason for preferring a within approach to multiple imputation in this study, as the optimal method of variance estimation for an across approach remains unclear.[672] While traditional texts suggest that small numbers of *m* (3-5) are adequate to obtain valid statistical inference,[617,721] many authors now advocate a greater number of imputations in order to improve the precision of estimates.[628,762,763] Diagnostic procedures to evaluate sampling error due to imputations[617,623,628] in this study were performed, with 40 imputations providing the optimal balance between precision and computational efficiency.

8.4. Implications and Recommendations

This thesis has shown that comorbidity is reasonably common amongst patients with newly diagnosed breast cancer. It has also demonstrated that comorbidity is an important moderator of breast cancer outcomes. Thus, while comorbidity may provide significant challenges to those involved with cancer care, it is imperative that these are addressed, as efforts to improve outcomes for comorbid patients will have important impacts at both an individual and population level. This project has provided some unique insights into the relationships between comorbidity, effective cancer treatment, and disease outcomes. The implications of the findings and resulting recommendations for those affected by cancer (healthcare providers and patients) and policy organisations will be discussed in this current section, along with suggested directions for future research.

8.4.1. Healthcare Providers and Patients

This project has shown that patients with comorbidity have a higher risk of presenting with more advanced stage breast cancer, which may be partially explained by a lower likelihood of screen-detection. Primary care providers should be aware that comorbidity may represent a competing demand on their time. While women with limited life expectancy should be spared the potential harms associated with over-screening, frequent contact with primary care due to milder comorbidity provides an excellent opportunity to detect early signs of cancer and reinforce participation in screening.

This thesis supports the considerable body of evidence that patients with breast cancer and coexistent comorbidity are less likely to receive potentially curative cancer treatments. The literature suggests that both patients and physicians are concerned about the increased potential for toxicity and this is likely to be a major reason for withholding treatment. While Study 2 did not directly examine the incidence of treatment-related toxicity, it did show that the quality of surgery, radiotherapy, and endocrine therapy received by comorbid patients was at worst no different than their healthier counterparts, suggesting that treatment was just as well tolerated. Patients with comorbidity were less likely to complete a full course of chemotherapy however, indicating that chemotherapy-associated toxicity is a reasonable concern. That comorbid patients did not receive less second/third generation chemotherapy suggests that the group of objectively comorbid patients selected to commence chemotherapy were perhaps perceived as being a subjectively healthier cohort by clinicians. However, given the finding that comorbidity was ultimately associated with non-completion of chemotherapy, it is reasonable to conclude that objective measures of comorbidity are more accurate when assessing fitness for treatment.

Uncertainty regarding the efficacy of cancer treatment in the context of increased risk of competing causes of mortality is another concern resulting in under-recommendation of treatment for patients with comorbidity. Given the lack of randomised data on this issue, the overall survival impacts of withholding treatment for comorbid patients with breast cancer was previously unknown. This thesis has shown that despite lower net survival, patients with comorbidity still derive substantial proportional mortality benefits from treatment with surgery, adjuvant radiotherapy, and endocrine therapy (breast cancer-specific only) although unfortunately, the benefits of chemotherapy remain uncertain. This provides useful information for both physicians and patients when making decisions about whether to accept or forgo treatment.

8.4.2. Policy Organisations

Results from Study 1 identified strong links between comorbidity and other drivers of cancer inequities; particularly Māori and Pacific ethnicity, older age, and social deprivation. This has important policy implications. At a population level, efforts to better outcomes for patients with

comorbidity would also drive improvements amongst these other groups which also experience health disparities.

The routine collection of comorbidity data amongst cancer populations (such as in cancer registers) yields numerous benefits for healthcare planning and research. Methodological variations in the measurement of comorbidity however make monitoring estimates of its prevalence over time and across different populations difficult. There is a need to establish standardised methods of recording comorbidity data at a national (and ideally, international) level to enable comparability across different settings. This thesis provides further evidence of the utility and feasibility of the C3 index in measuring comorbidity within a cancer cohort in New Zealand. While this has been developed using New Zealand routine data sources, its foundation in the ICD-10 coding system make this a reasonable option internationally.

8.4.3. Researchers

There are 3 clear avenues for future research to extend the work presented here.

Qualitative research amongst patients and clinicians to disentangle the multiple mechanisms at play in the impact of comorbidity on breast cancer diagnosis and treatment.

While it is clear from this project that patients with comorbidity are more likely to present with higher stage disease, and less likely to receive minimum treatments for breast cancer, the reasons for these patterns remain unclear. In particular, the relative contributions of patient and clinician preference require exploration, which are likely to differ by culture and country. For example, it would be useful to ascertain whether the more advanced stage at diagnosis experienced by cancer patients with comorbidity is the result of a competing demand on the physician's time, or a conscious decision to avoid screening due to limited life expectancy. Comorbidity probably has a threshold, whereby a low burden increases the likelihood of screening and early diagnosis, while a high burden acts in the opposing direction. Individual conditions are also likely to have a differential impact on the net mechanisms at play. Diabetes in particular, while presenting many opportunities for health system contact, seems to have a biological interaction potentiating breast cancer, although this effect may be countered by the action of metformin.

Improving the evidence base from which to make treatment decisions for comorbid patients with breast cancer.

In the absence of randomised evidence, this thesis has attempted to quantify the survival benefits obtainable by breast cancer treatments in the context of comorbidity. However its findings are generally limited by low power to detect treatment effects amongst patients with higher levels of comorbidity. As an observational study, the results must also be interpreted in terms of how well

confounding was addressed, lest they be influenced by bias. These obstacles could be overcome by employing the gold standard method for estimation of causal treatment effects, the randomised controlled trial. Including comorbid patients in clinical trials or the creation of high quality experimental studies focussing specifically on this patient population would generate useful, directly applicable information about the efficacy of treatments. This would greatly enhance the evidence base from which patients, in consultation with their clinicians can make treatment decisions that are consistent with their values and preferences. Consideration should also be given to the most relevant end points to measure for patients with comorbidity. Due to competing risks of mortality, despite expected benefits in terms of cancer relapse, survival gains might not be so evident. Disease-free survival may therefore be a more appropriate outcome for trials conducted amongst those with comorbidity.

The relative weight that comorbid patients place on different considerations related to their treatment is likely to be different from their non-comorbid counterparts. Comorbid patients may prefer to choose treatment options that will maintain their quality of life rather than focusing solely on length of remission or survival. Often only very narrow outcomes are analysed in clinical trials (eg, disease-free and overall survival). Collecting data on expanded outcomes relevant to comorbid patients (particularly toxicity and patient reported outcomes such as quality of life and relief of symptoms relief) would enable affected individuals to make adequately informed decisions about their care.

Finding reliable and effective ways to include comorbid patients in clinical trials is a major challenge which requires attention. Reluctance to participate may be at the level of trial leaders, referring clinicians, or individual patients. Qualitative research to determine the barriers to recruitment could shed light on how these could be mitigated. For example, due to the additional costs and risk to pharmaceutical companies of including patients with comorbidity, financial and legal incentives could be provided. For instance, the US Institute of Medicine have suggested an amendment to patent law providing extensions for companies to conduct clinical trials in populations that more accurately reflect the age distribution and health risk profile of patients with cancer.[764]

Creation of treatment decision aids which incorporate an objective assessment of comorbidity.

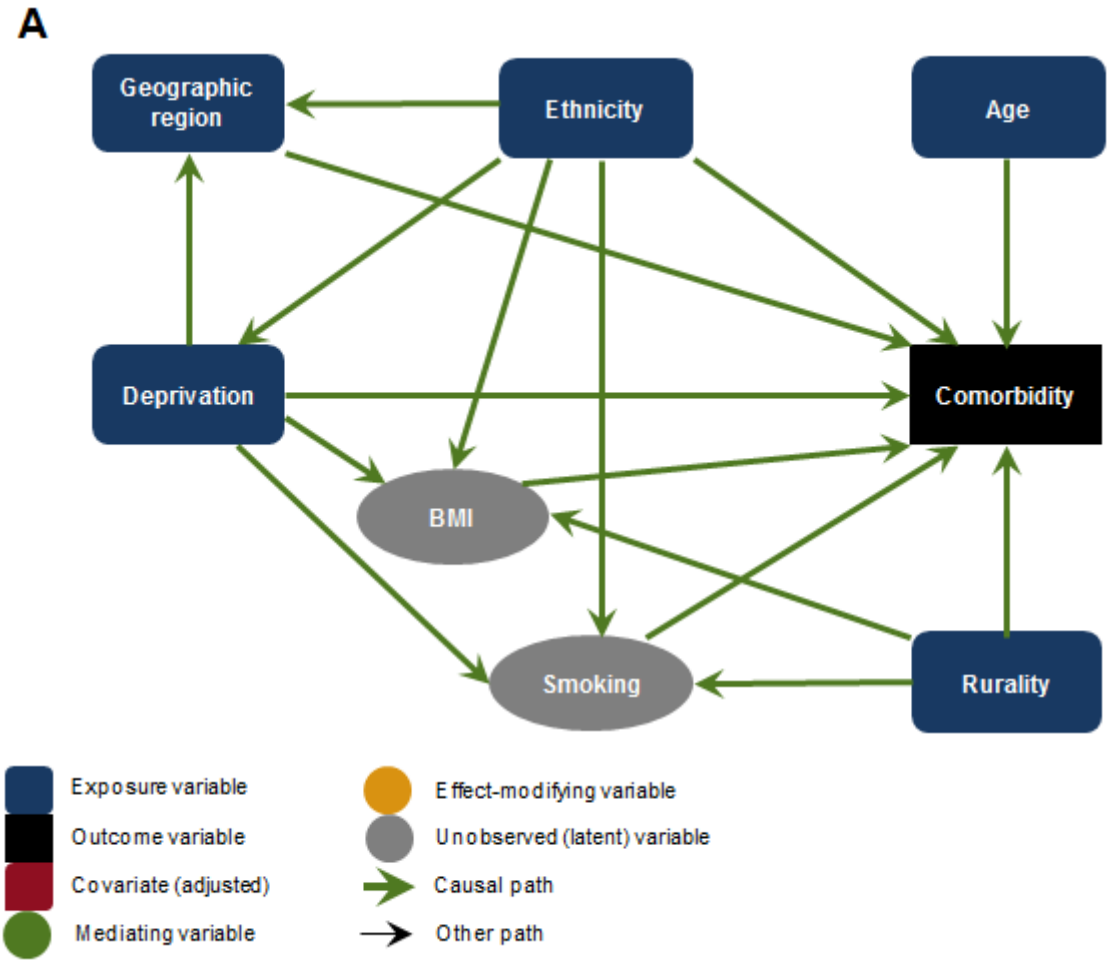
As we have seen, comorbidity imparts a strong negative impact on survival from breast cancer, both disease-specific and overall, which is independent of chronological age. Quality evidence estimating the projected benefits of treatments in the context of comorbidity and competing risks of mortality would permit the creation of algorithms to aid in treatment decision processes for patients and clinicians. The increasing focus on molecularly targeted medicine and personalised care is particularly relevant to patients with comorbidity, given the higher stakes in terms of the potential for harm by giving interventions destined to be ineffectual.

8.5. Concluding Remarks

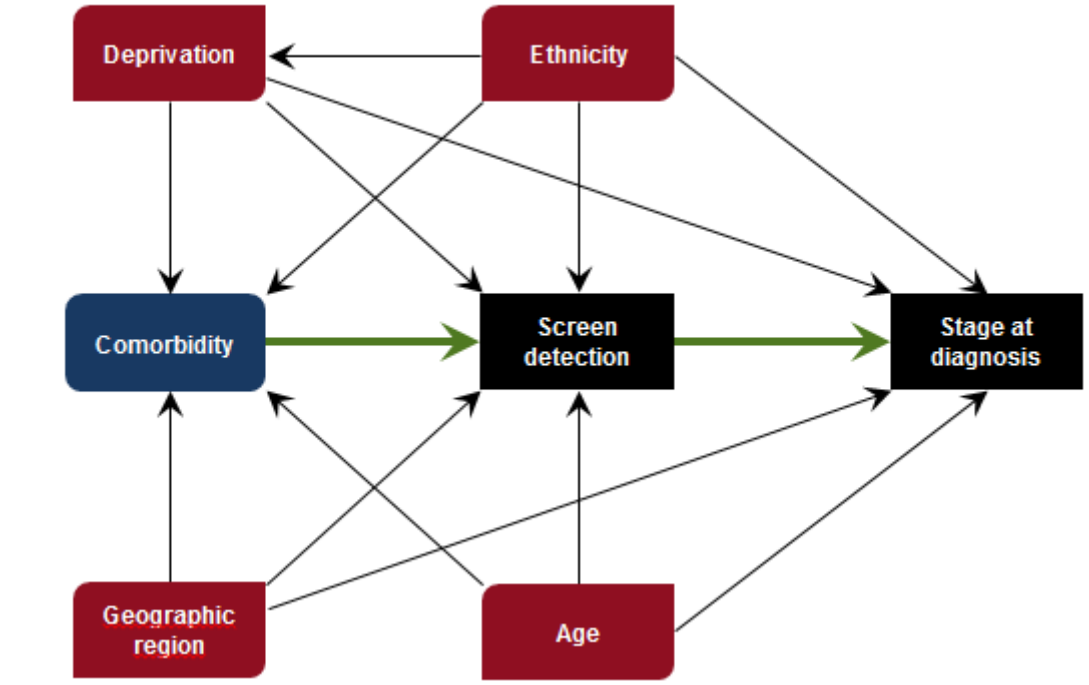
The overarching aim of this thesis was to evaluate the impact of coexistent comorbidity on breast cancer treatment and disease outcomes. The rationale for this aim was the lack of randomised evidence purporting the efficacy of cancer treatment amongst patients with comorbidity, who have high risk of competing cause mortality. Best practice treatment guidelines and prognostic decision aids extrapolate results from clinical trials projecting the expected benefits of treatments in relation to disease characteristics. However, without evidence that is directly generalisable to patients with comorbidity, such resources are of little use. This thesis has shown that comorbidity is relatively common amongst patients with breast cancer and has important implications for diagnosis, treatment, and ultimate survival. The findings suggest that withholding potentially curative surgical, radiation, and endocrine treatment from patients with comorbidity may be unnecessary and detrimental to their survival. However, due to increasing risk of competing cause mortality, the survival gains obtainable by treatment reduce with comorbidity severity. Thus, while reduced receipt of treatment is likely to be an important mediator of the inferior survival experienced by patients with comorbidity, there are additional mechanisms involved.

Appendix A

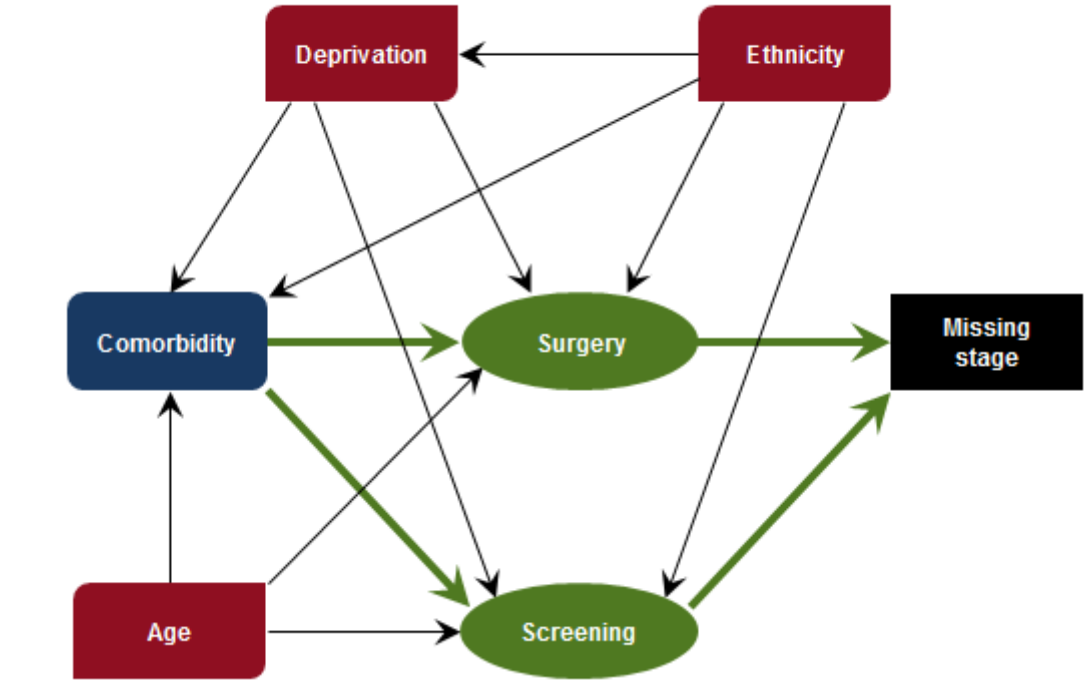
Directed Acyclic Graphs



B


Deprivation
Ethnicity
Comorbidity
Screen detection
Stage at diagnosis
Geographic region
Age

C


Deprivation
Ethnicity
Comorbidity
Surgery
Missing stage
Age
Screening

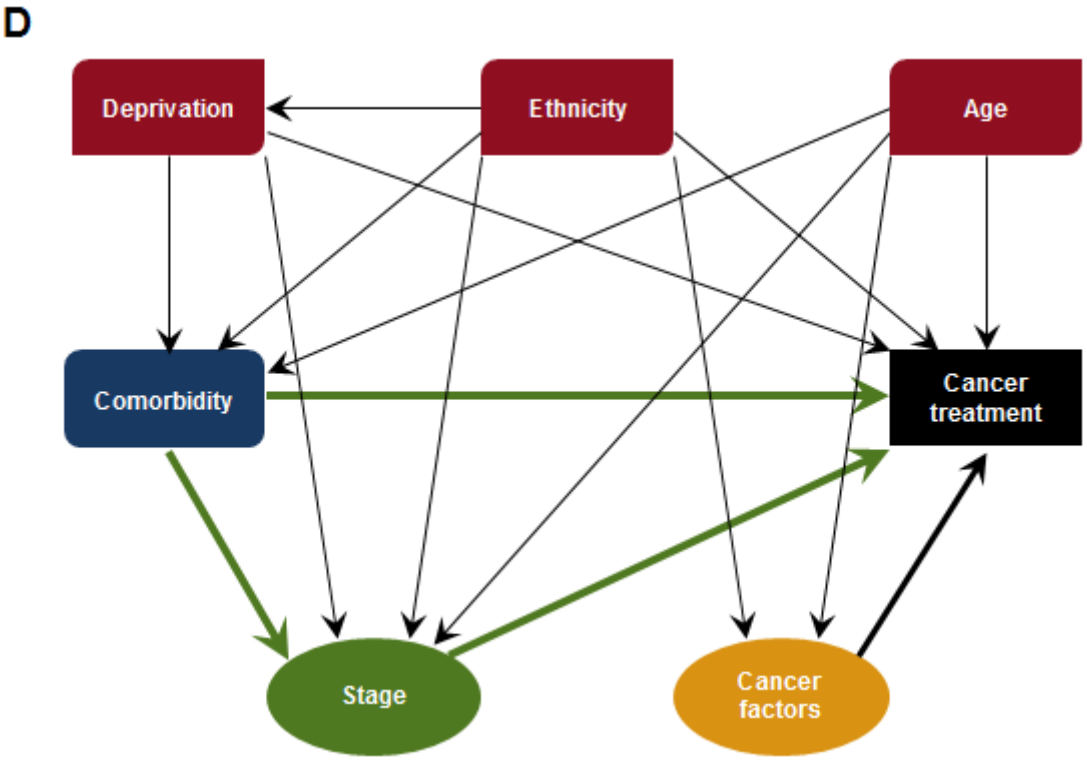


Figure 33. Directed Acyclic Graphs Depicting Presumed Relationships in Study Analyses
(A) Sociodemographic factors and comorbidity (B) Comorbidity, screening, and breast cancer stage at diagnosis (C) Comorbidity and missing breast cancer stage (D) Comorbidity and cancer treatment

Appendix B

Propensity Score Distributions and Balance

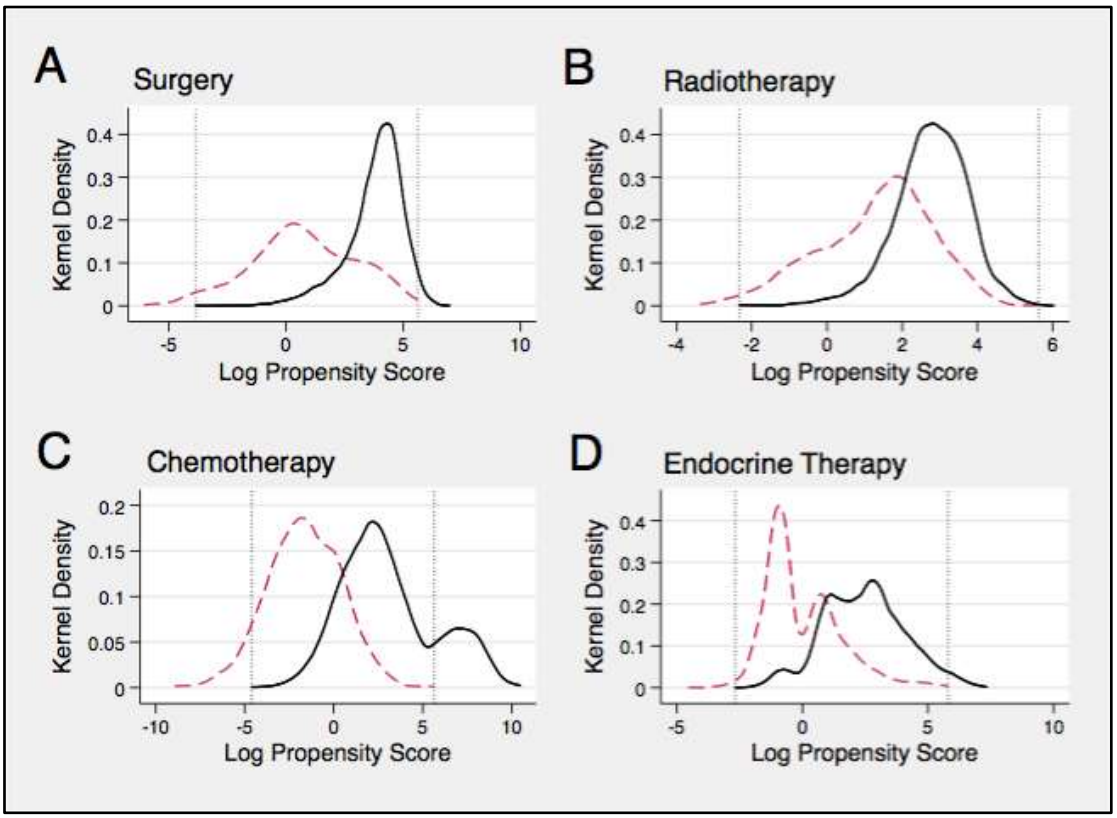


Figure 34. Distribution of Log Propensity Scores by Treatment Status

No treatment Treatment

Vertical dotted lines denote limits of common support.

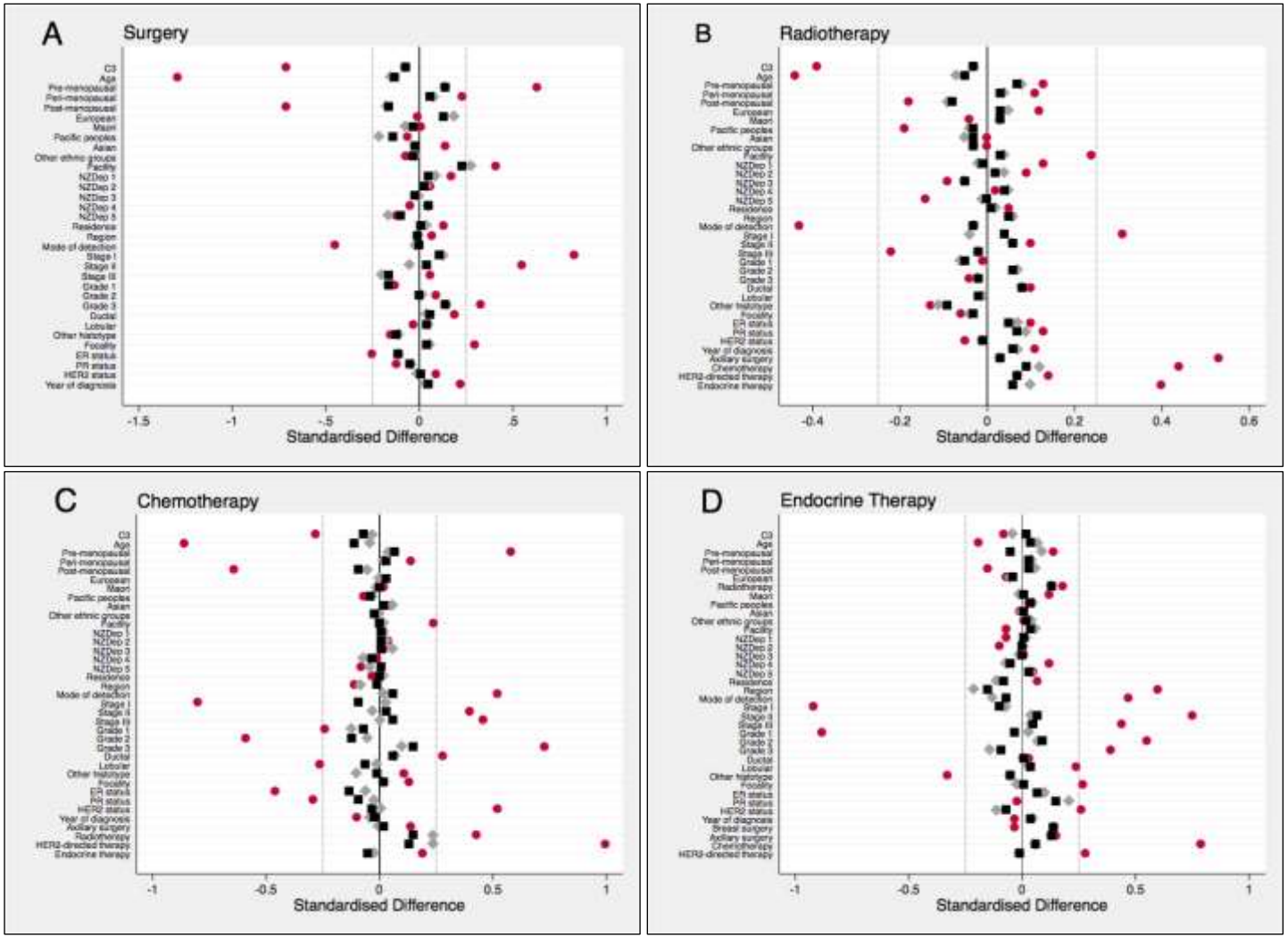


Figure 35. Standardised Differences between Treatment Groups: Raw and Trimmed IPT- and SMR-weighted Samples

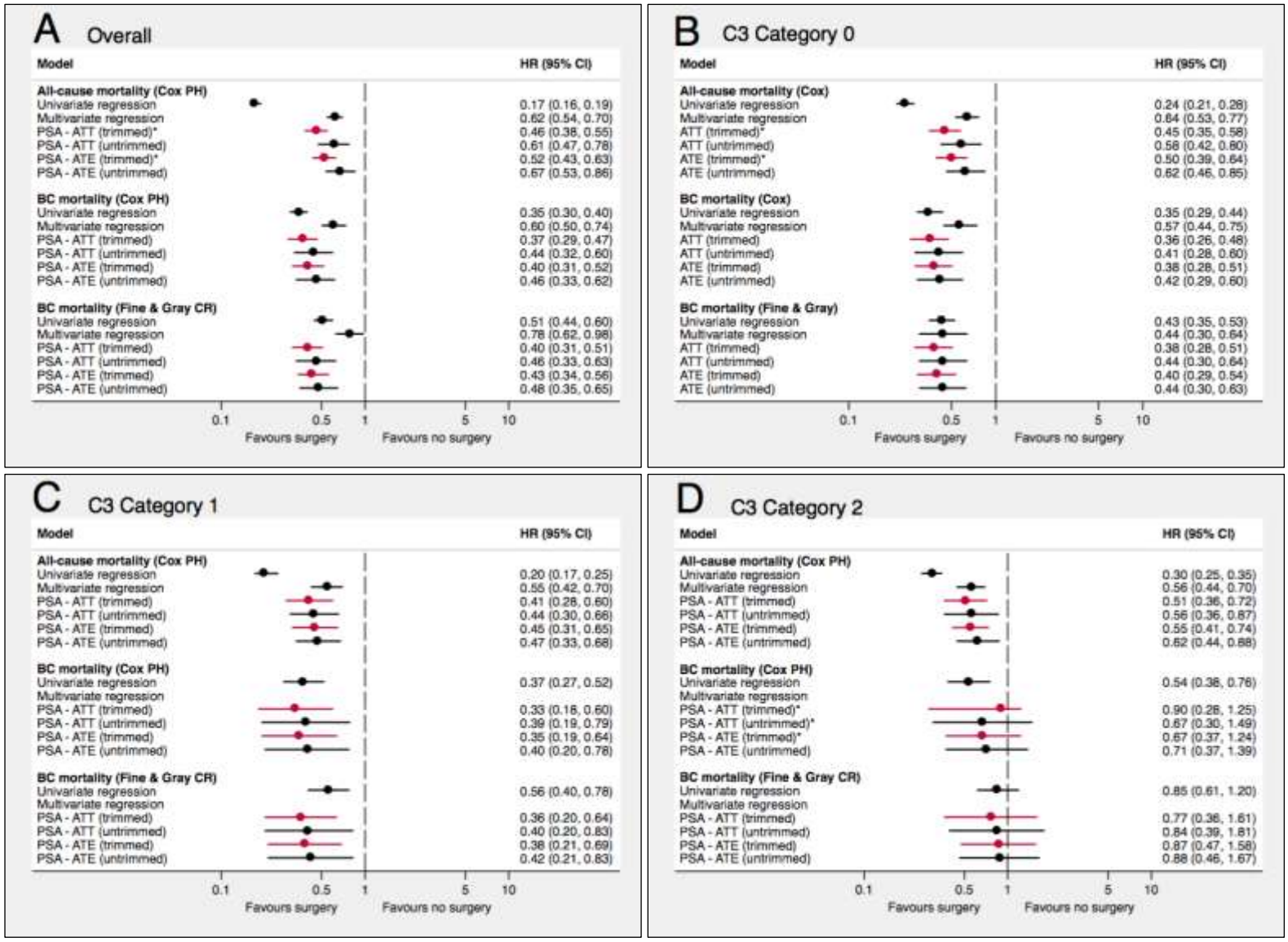
■ IPT-weighted ◆ SMR-weighted ● Raw

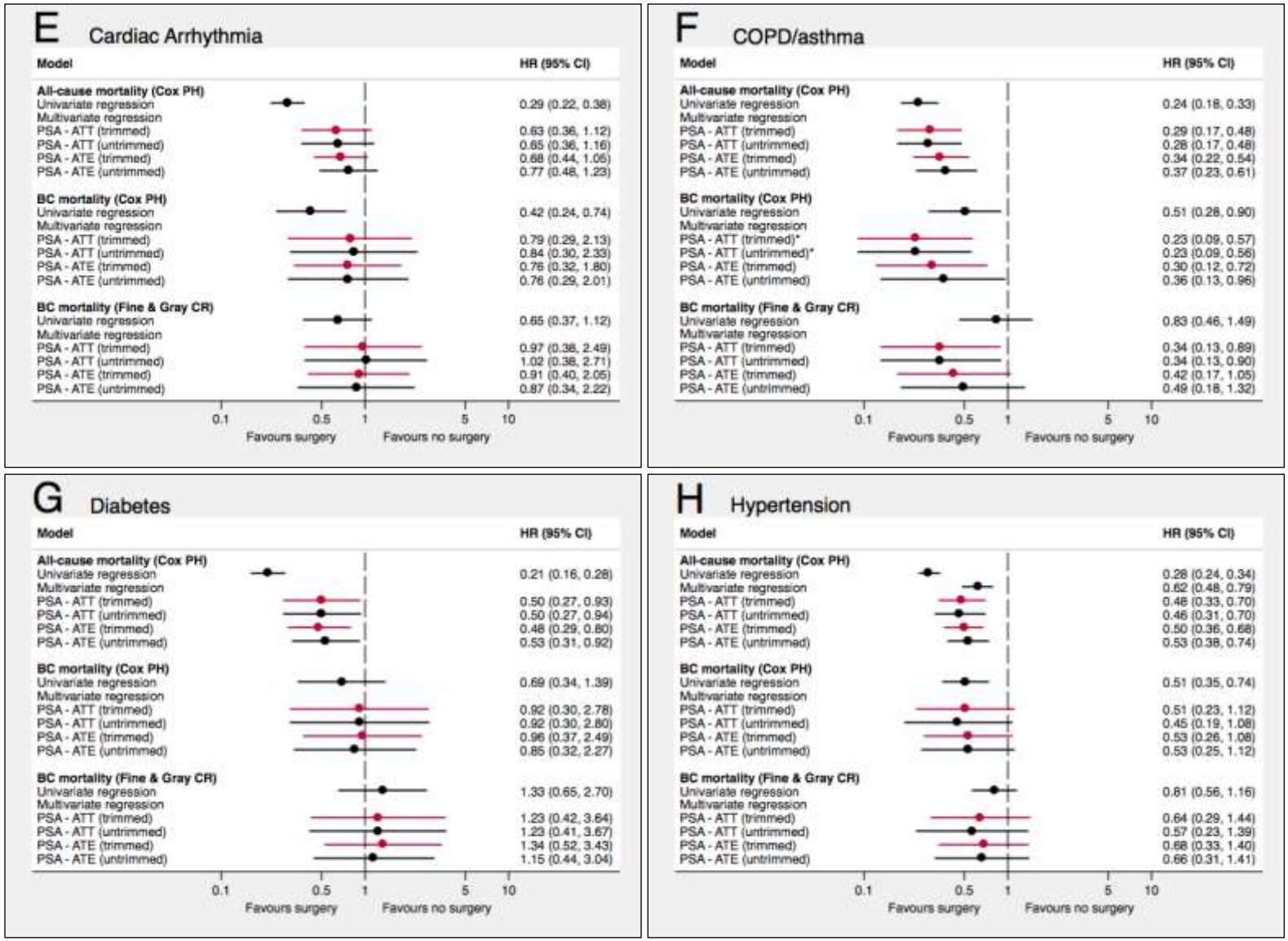
Vertical dotted lines indicate 0.25 threshold for adequate balance

Appendix C

Study 3 Sensitivity Analyses

Appendix C displays the results of the sensitivity analyses conducted as part of Study 3. The results are summarised in a series of forest plots, produced using the `forestplot` command.[765] For each treatment effects analysis, plots were produced for each comorbidity subgroup and the overall sample. For each mortality outcome (all-cause and breast cancer-specific mortality from Cox models, and breast cancer mortality from Fine and Gray competing risks models), results from conventional univariate and multivariate regression, as well as ATTs and ATEs derived from propensity score analysis using untrimmed weights are displayed. These sensitivity analyses are shown in black, while results from the main analyses reported in Chapter 7 (ATTs and ATEs using trimmed weights) are given in red, for ease of comparison. Multivariate models were adjusted for all variables included in the propensity score estimation model. The multivariate model for surgery also accounted for non-baseline treatment variables which were not included in the propensity score model. Time dependent covariates are denoted with an asterisk, with the average effect presented. The x axis displays HRs for Cox regression models and sHRs for competing risks models. Where events per variable numbered <10, estimates were withheld.


A Overall
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.17 (0.16, 0.19)
Multivariate regression 0.62 (0.54, 0.70)
PSA - ATT (trimmed)* 0.46 (0.38, 0.55)
PSA - ATT (untrimmed) 0.61 (0.47, 0.78)
PSA - ATE (trimmed)* 0.52 (0.43, 0.63)
PSA - ATE (untrimmed) 0.67 (0.53, 0.86)
BC mortality (Cox PH)
Univariate regression 0.35 (0.30, 0.40)
Multivariate regression 0.60 (0.50, 0.74)
PSA - ATT (trimmed) 0.37 (0.29, 0.47)
PSA - ATT (untrimmed) 0.44 (0.32, 0.60)
PSA - ATE (trimmed) 0.40 (0.31, 0.52)
PSA - ATE (untrimmed) 0.46 (0.33, 0.62)
BC mortality (Fine & Gray CR)
Univariate regression 0.51 (0.44, 0.60)
Multivariate regression 0.78 (0.62, 0.98)
PSA - ATT (trimmed) 0.40 (0.31, 0.51)
PSA - ATT (untrimmed) 0.46 (0.33, 0.63)
PSA - ATE (trimmed) 0.43 (0.34, 0.56)
PSA - ATE (untrimmed) 0.48 (0.35, 0.65)
0.1
0.5
1
5
10
Favours surgery
Favours no surgery
B C3 Category 0
Model
HR (95% CI)
All-cause mortality (Cox)
Univariate regression 0.24 (0.21, 0.28)
Multivariate regression 0.64 (0.53, 0.77)
ATT (trimmed)* 0.45 (0.35, 0.58)
ATT (untrimmed) 0.58 (0.42, 0.80)
ATE (trimmed)* 0.50 (0.39, 0.64)
ATE (untrimmed) 0.62 (0.46, 0.85)
BC mortality (Cox)
Univariate regression 0.35 (0.29, 0.44)
Multivariate regression 0.57 (0.44, 0.75)
ATT (trimmed) 0.36 (0.26, 0.48)
ATT (untrimmed) 0.41 (0.28, 0.60)
ATE (trimmed) 0.38 (0.28, 0.51)
ATE (untrimmed) 0.42 (0.29, 0.60)
BC mortality (Fine & Gray)
Univariate regression 0.43 (0.35, 0.53)
Multivariate regression 0.44 (0.30, 0.64)
ATT (trimmed) 0.38 (0.28, 0.51)
ATT (untrimmed) 0.44 (0.30, 0.64)
ATE (trimmed) 0.40 (0.29, 0.54)
ATE (untrimmed) 0.44 (0.30, 0.63)
0.1
0.5
1
5
10
Favours surgery
Favours no surgery
C C3 Category 1
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.20 (0.17, 0.25)
Multivariate regression 0.55 (0.42, 0.70)
PSA - ATT (trimmed) 0.41 (0.28, 0.60)
PSA - ATT (untrimmed) 0.44 (0.30, 0.66)
PSA - ATE (trimmed) 0.45 (0.31, 0.65)
PSA - ATE (untrimmed) 0.47 (0.33, 0.68)
BC mortality (Cox PH)
Univariate regression 0.37 (0.27, 0.52)
Multivariate regression
PSA - ATT (trimmed) 0.33 (0.18, 0.60)
PSA - ATT (untrimmed) 0.39 (0.19, 0.79)
PSA - ATE (trimmed) 0.35 (0.19, 0.64)
PSA - ATE (untrimmed) 0.40 (0.20, 0.78)
BC mortality (Fine & Gray CR)
Univariate regression 0.56 (0.40, 0.78)
Multivariate regression
PSA - ATT (trimmed) 0.36 (0.20, 0.64)
PSA - ATT (untrimmed) 0.40 (0.20, 0.83)
PSA - ATE (trimmed) 0.38 (0.21, 0.69)
PSA - ATE (untrimmed) 0.42 (0.21, 0.83)
0.1
0.5
1
5
10
Favours surgery
Favours no surgery
D C3 Category 2
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.30 (0.25, 0.35)
Multivariate regression 0.56 (0.44, 0.70)
PSA - ATT (trimmed) 0.51 (0.36, 0.72)
PSA - ATT (untrimmed) 0.56 (0.36, 0.87)
PSA - ATE (trimmed) 0.55 (0.41, 0.74)
PSA - ATE (untrimmed) 0.62 (0.44, 0.88)
BC mortality (Cox PH)
Univariate regression 0.54 (0.38, 0.76)
Multivariate regression
PSA - ATT (trimmed)* 0.90 (0.28, 1.25)
PSA - ATT (untrimmed)* 0.67 (0.30, 1.49)
PSA - ATE (trimmed)* 0.67 (0.37, 1.24)
PSA - ATE (untrimmed) 0.71 (0.37, 1.39)
BC mortality (Fine & Gray CR)
Univariate regression 0.85 (0.61, 1.20)
Multivariate regression
PSA - ATT (trimmed) 0.77 (0.36, 1.61)
PSA - ATT (untrimmed) 0.84 (0.39, 1.81)
PSA - ATE (trimmed) 0.87 (0.47, 1.58)
PSA - ATE (untrimmed) 0.88 (0.46, 1.67)
0.1
0.5
1
5
10
Favours surgery
Favours no surgery


E Cardiac Arrhythmia
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.29 (0.22, 0.38)
Multivariate regression
PSA - ATT (trimmed)
0.63 (0.36, 1.12)
PSA - ATT (untrimmed)
0.65 (0.36, 1.16)
PSA - ATE (trimmed)
0.68 (0.44, 1.06)
PSA - ATE (untrimmed)
0.77 (0.48, 1.23)
BC mortality (Cox PH)
Univariate regression
0.42 (0.24, 0.74)
Multivariate regression
PSA - ATT (trimmed)
0.79 (0.29, 2.13)
PSA - ATT (untrimmed)
0.84 (0.30, 2.33)
PSA - ATE (trimmed)
0.76 (0.32, 1.80)
PSA - ATE (untrimmed)
0.76 (0.29, 2.01)
BC mortality (Fine & Gray CR)
Univariate regression
0.65 (0.37, 1.12)
Multivariate regression
PSA - ATT (trimmed)
0.97 (0.38, 2.49)
PSA - ATT (untrimmed)
1.02 (0.38, 2.71)
PSA - ATE (trimmed)
0.91 (0.40, 2.05)
PSA - ATE (untrimmed)
0.87 (0.34, 2.22)
0.1
0.5
1
5
10
Favours surgery
Favours no surgery
F COPD/asthma
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.24 (0.18, 0.33)
Multivariate regression
PSA - ATT (trimmed)
0.29 (0.17, 0.48)
PSA - ATT (untrimmed)
0.28 (0.17, 0.48)
PSA - ATE (trimmed)
0.34 (0.22, 0.54)
PSA - ATE (untrimmed)
0.37 (0.23, 0.61)
BC mortality (Cox PH)
Univariate regression
0.51 (0.28, 0.90)
Multivariate regression
PSA - ATT (trimmed)*
0.23 (0.09, 0.57)
PSA - ATT (untrimmed)*
0.23 (0.09, 0.56)
PSA - ATE (trimmed)
0.30 (0.12, 0.72)
PSA - ATE (untrimmed)
0.36 (0.13, 0.96)
BC mortality (Fine & Gray CR)
Univariate regression
0.83 (0.46, 1.49)
Multivariate regression
PSA - ATT (trimmed)
0.34 (0.13, 0.89)
PSA - ATT (untrimmed)
0.34 (0.13, 0.90)
PSA - ATE (trimmed)
0.42 (0.17, 1.05)
PSA - ATE (untrimmed)
0.49 (0.18, 1.32)
0.1
0.5
1
5
10
Favours surgery
Favours no surgery
G Diabetes
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.21 (0.16, 0.28)
Multivariate regression
PSA - ATT (trimmed)
0.50 (0.27, 0.93)
PSA - ATT (untrimmed)
0.50 (0.27, 0.94)
PSA - ATE (trimmed)
0.48 (0.29, 0.80)
PSA - ATE (untrimmed)
0.53 (0.31, 0.92)
BC mortality (Cox PH)
Univariate regression
0.69 (0.34, 1.39)
Multivariate regression
PSA - ATT (trimmed)
0.92 (0.30, 2.78)
PSA - ATT (untrimmed)
0.92 (0.30, 2.80)
PSA - ATE (trimmed)
0.96 (0.37, 2.49)
PSA - ATE (untrimmed)
0.85 (0.32, 2.27)
BC mortality (Fine & Gray CR)
Univariate regression
1.33 (0.65, 2.70)
Multivariate regression
PSA - ATT (trimmed)
1.23 (0.42, 3.64)
PSA - ATT (untrimmed)
1.23 (0.41, 3.67)
PSA - ATE (trimmed)
1.34 (0.52, 3.43)
PSA - ATE (untrimmed)
1.15 (0.44, 3.04)
0.1
0.5
1
5
10
Favours surgery
Favours no surgery
H Hypertension
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.28 (0.24, 0.34)
Multivariate regression
0.62 (0.48, 0.79)
PSA - ATT (trimmed)
0.48 (0.33, 0.70)
PSA - ATT (untrimmed)
0.46 (0.31, 0.70)
PSA - ATE (trimmed)
0.50 (0.36, 0.68)
PSA - ATE (untrimmed)
0.53 (0.38, 0.74)
BC mortality (Cox PH)
Univariate regression
0.51 (0.35, 0.74)
Multivariate regression
PSA - ATT (trimmed)
0.51 (0.23, 1.12)
PSA - ATT (untrimmed)
0.45 (0.19, 1.08)
PSA - ATE (trimmed)
0.53 (0.26, 1.08)
PSA - ATE (untrimmed)
0.53 (0.25, 1.12)
BC mortality (Fine & Gray CR)
Univariate regression
0.81 (0.56, 1.16)
Multivariate regression
PSA - ATT (trimmed)
0.64 (0.29, 1.44)
PSA - ATT (untrimmed)
0.57 (0.23, 1.39)
PSA - ATE (trimmed)
0.68 (0.33, 1.40)
PSA - ATE (untrimmed)
0.66 (0.31, 1.41)
0.1
0.5
1
5
10
Favours surgery
Favours no surgery

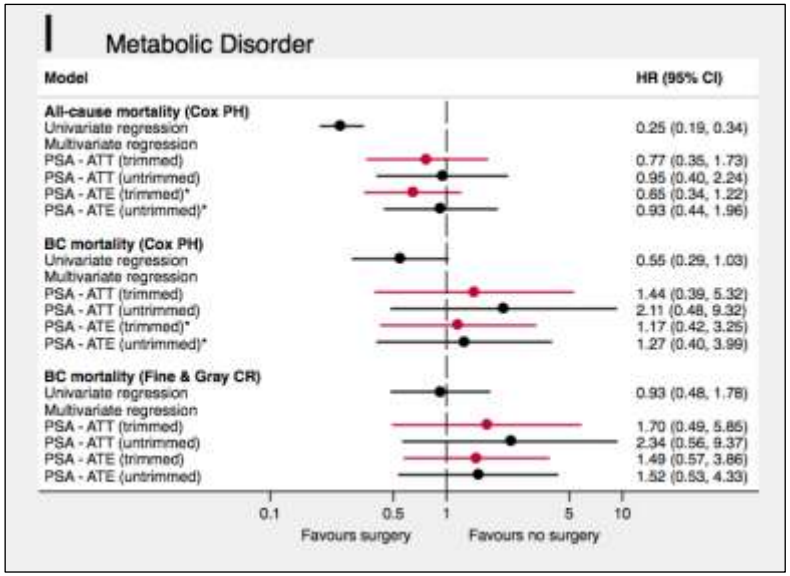
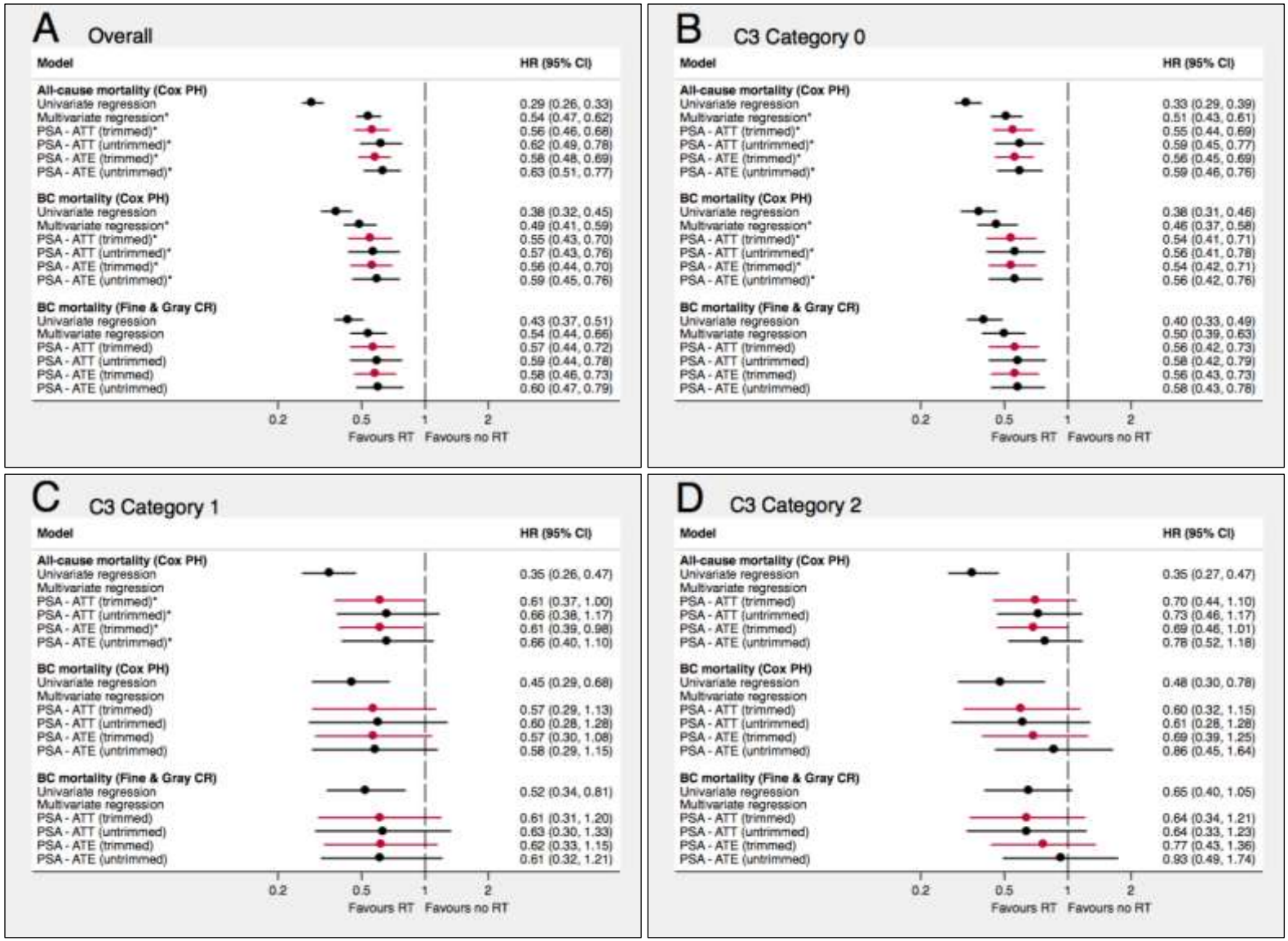
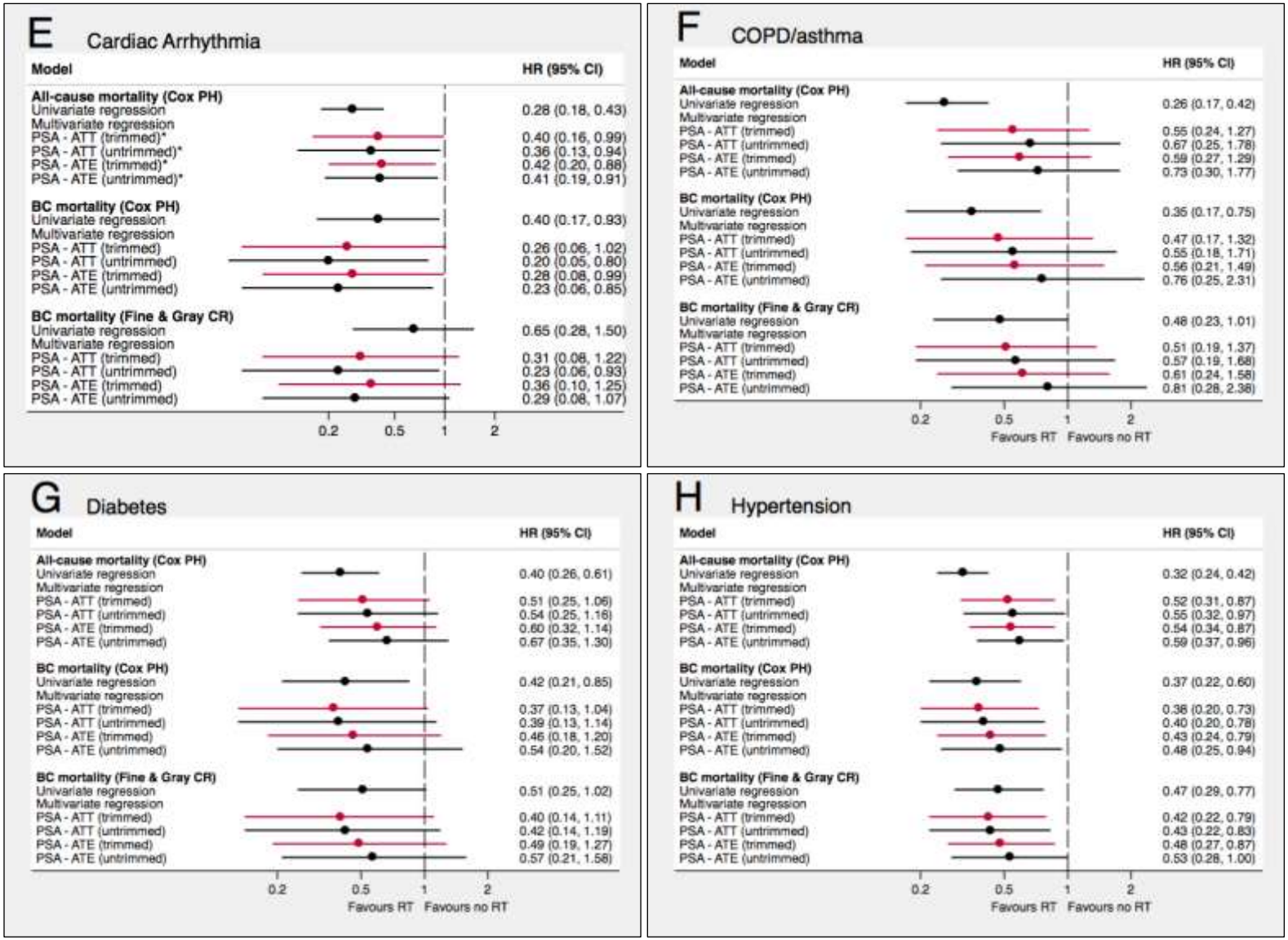


Figure 36. Forest Plots Showing Sensitivity Analyses for Treatment Effects of Surgery by Comorbidity Status

Abbreviations: BC, breast cancer; CR, competing risks; PH, proportional hazards; PSA, propensity score analysis.


A Overall
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.29 (0.26, 0.33)
Multivariate regression* 0.54 (0.47, 0.62)
PSA - ATT (trimmed)* 0.56 (0.46, 0.68)
PSA - ATT (untrimmed)* 0.62 (0.49, 0.78)
PSA - ATE (trimmed)* 0.58 (0.48, 0.69)
PSA - ATE (untrimmed)* 0.63 (0.51, 0.77)
BC mortality (Cox PH)
Univariate regression 0.38 (0.32, 0.45)
Multivariate regression* 0.49 (0.41, 0.59)
PSA - ATT (trimmed)* 0.55 (0.43, 0.70)
PSA - ATT (untrimmed)* 0.57 (0.43, 0.76)
PSA - ATE (trimmed)* 0.56 (0.44, 0.70)
PSA - ATE (untrimmed)* 0.59 (0.45, 0.76)
BC mortality (Fine & Gray CR)
Univariate regression 0.43 (0.37, 0.51)
Multivariate regression 0.54 (0.44, 0.66)
PSA - ATT (trimmed) 0.57 (0.44, 0.72)
PSA - ATT (untrimmed) 0.59 (0.44, 0.78)
PSA - ATE (trimmed) 0.58 (0.46, 0.73)
PSA - ATE (untrimmed) 0.60 (0.47, 0.79)
0.2
0.5
1
2
Favours RT
Favours no RT
B C3 Category 0
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.33 (0.29, 0.39)
Multivariate regression* 0.51 (0.43, 0.61)
PSA - ATT (trimmed)* 0.55 (0.44, 0.69)
PSA - ATT (untrimmed)* 0.59 (0.45, 0.77)
PSA - ATE (trimmed)* 0.56 (0.45, 0.69)
PSA - ATE (untrimmed)* 0.59 (0.46, 0.76)
BC mortality (Cox PH)
Univariate regression 0.38 (0.31, 0.46)
Multivariate regression* 0.46 (0.37, 0.58)
PSA - ATT (trimmed)* 0.54 (0.41, 0.71)
PSA - ATT (untrimmed)* 0.56 (0.41, 0.78)
PSA - ATE (trimmed)* 0.54 (0.42, 0.71)
PSA - ATE (untrimmed)* 0.56 (0.42, 0.76)
BC mortality (Fine & Gray CR)
Univariate regression 0.40 (0.33, 0.49)
Multivariate regression 0.50 (0.39, 0.63)
PSA - ATT (trimmed) 0.56 (0.42, 0.73)
PSA - ATT (untrimmed) 0.58 (0.42, 0.79)
PSA - ATE (trimmed) 0.56 (0.43, 0.73)
PSA - ATE (untrimmed) 0.58 (0.43, 0.78)
0.2
0.5
1
2
Favours RT
Favours no RT
C C3 Category 1
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.35 (0.26, 0.47)
Multivariate regression
PSA - ATT (trimmed)* 0.61 (0.37, 1.00)
PSA - ATT (untrimmed)* 0.66 (0.38, 1.17)
PSA - ATE (trimmed)* 0.61 (0.39, 0.98)
PSA - ATE (untrimmed)* 0.66 (0.40, 1.10)
BC mortality (Cox PH)
Univariate regression 0.45 (0.29, 0.68)
Multivariate regression
PSA - ATT (trimmed) 0.57 (0.29, 1.13)
PSA - ATT (untrimmed) 0.60 (0.28, 1.28)
PSA - ATE (trimmed) 0.57 (0.30, 1.08)
PSA - ATE (untrimmed) 0.58 (0.29, 1.15)
BC mortality (Fine & Gray CR)
Univariate regression 0.52 (0.34, 0.81)
Multivariate regression
PSA - ATT (trimmed) 0.61 (0.31, 1.20)
PSA - ATT (untrimmed) 0.63 (0.30, 1.33)
PSA - ATE (trimmed) 0.62 (0.33, 1.15)
PSA - ATE (untrimmed) 0.61 (0.32, 1.21)
0.2
0.5
1
2
Favours RT
Favours no RT
D C3 Category 2
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.35 (0.27, 0.47)
Multivariate regression
PSA - ATT (trimmed) 0.70 (0.44, 1.10)
PSA - ATT (untrimmed) 0.73 (0.46, 1.17)
PSA - ATE (trimmed) 0.69 (0.46, 1.01)
PSA - ATE (untrimmed) 0.78 (0.52, 1.18)
BC mortality (Cox PH)
Univariate regression 0.48 (0.30, 0.78)
Multivariate regression
PSA - ATT (trimmed) 0.60 (0.32, 1.15)
PSA - ATT (untrimmed) 0.61 (0.28, 1.28)
PSA - ATE (trimmed) 0.69 (0.39, 1.25)
PSA - ATE (untrimmed) 0.86 (0.45, 1.64)
BC mortality (Fine & Gray CR)
Univariate regression 0.65 (0.40, 1.05)
Multivariate regression
PSA - ATT (trimmed) 0.64 (0.34, 1.21)
PSA - ATT (untrimmed) 0.64 (0.33, 1.23)
PSA - ATE (trimmed) 0.77 (0.43, 1.36)
PSA - ATE (untrimmed) 0.93 (0.49, 1.74)
0.2
0.5
1
2
Favours RT
Favours no RT


E Cardiac Arrhythmia
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.28 (0.18, 0.43)
Multivariate regression
PSA - ATT (trimmed)*
0.40 (0.16, 0.99)
PSA - ATT (untrimmed)*
0.36 (0.13, 0.94)
PSA - ATE (trimmed)*
0.42 (0.20, 0.88)
PSA - ATE (untrimmed)*
0.41 (0.19, 0.91)
BC mortality (Cox PH)
Univariate regression
0.40 (0.17, 0.93)
Multivariate regression
PSA - ATT (trimmed)
0.26 (0.06, 1.02)
PSA - ATT (untrimmed)
0.20 (0.05, 0.80)
PSA - ATE (trimmed)
0.28 (0.08, 0.99)
PSA - ATE (untrimmed)
0.23 (0.06, 0.85)
BC mortality (Fine & Gray CR)
Univariate regression
0.65 (0.28, 1.50)
Multivariate regression
PSA - ATT (trimmed)
0.31 (0.08, 1.22)
PSA - ATT (untrimmed)
0.23 (0.06, 0.93)
PSA - ATE (trimmed)
0.36 (0.10, 1.25)
PSA - ATE (untrimmed)
0.29 (0.08, 1.07)
0.2
0.5
1
2
F COPD/asthma
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.26 (0.17, 0.42)
Multivariate regression
PSA - ATT (trimmed)
0.55 (0.24, 1.27)
PSA - ATT (untrimmed)
0.67 (0.25, 1.78)
PSA - ATE (trimmed)
0.59 (0.27, 1.29)
PSA - ATE (untrimmed)
0.73 (0.30, 1.77)
BC mortality (Cox PH)
Univariate regression
0.35 (0.17, 0.75)
Multivariate regression
PSA - ATT (trimmed)
0.47 (0.17, 1.32)
PSA - ATT (untrimmed)
0.55 (0.18, 1.71)
PSA - ATE (trimmed)
0.56 (0.21, 1.49)
PSA - ATE (untrimmed)
0.76 (0.25, 2.31)
BC mortality (Fine & Gray CR)
Univariate regression
0.48 (0.23, 1.01)
Multivariate regression
PSA - ATT (trimmed)
0.51 (0.19, 1.37)
PSA - ATT (untrimmed)
0.57 (0.19, 1.68)
PSA - ATE (trimmed)
0.61 (0.24, 1.58)
PSA - ATE (untrimmed)
0.81 (0.28, 2.36)
0.2
0.5
1
2
Favours RT
Favours no RT
G Diabetes
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.40 (0.26, 0.61)
Multivariate regression
PSA - ATT (trimmed)
0.51 (0.25, 1.06)
PSA - ATT (untrimmed)
0.54 (0.25, 1.16)
PSA - ATE (trimmed)
0.60 (0.32, 1.14)
PSA - ATE (untrimmed)
0.67 (0.35, 1.30)
BC mortality (Cox PH)
Univariate regression
0.42 (0.21, 0.85)
Multivariate regression
PSA - ATT (trimmed)
0.37 (0.13, 1.04)
PSA - ATT (untrimmed)
0.39 (0.13, 1.14)
PSA - ATE (trimmed)
0.46 (0.18, 1.20)
PSA - ATE (untrimmed)
0.54 (0.20, 1.52)
BC mortality (Fine & Gray CR)
Univariate regression
0.51 (0.25, 1.02)
Multivariate regression
PSA - ATT (trimmed)
0.40 (0.14, 1.11)
PSA - ATT (untrimmed)
0.42 (0.14, 1.19)
PSA - ATE (trimmed)
0.49 (0.19, 1.27)
PSA - ATE (untrimmed)
0.57 (0.21, 1.58)
0.2
0.5
1
2
Favours RT
Favours no RT
H Hypertension
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.32 (0.24, 0.42)
Multivariate regression
PSA - ATT (trimmed)
0.52 (0.31, 0.87)
PSA - ATT (untrimmed)
0.55 (0.32, 0.97)
PSA - ATE (trimmed)
0.54 (0.34, 0.87)
PSA - ATE (untrimmed)
0.59 (0.37, 0.96)
BC mortality (Cox PH)
Univariate regression
0.37 (0.22, 0.60)
Multivariate regression
PSA - ATT (trimmed)
0.38 (0.20, 0.73)
PSA - ATT (untrimmed)
0.40 (0.20, 0.78)
PSA - ATE (trimmed)
0.43 (0.24, 0.79)
PSA - ATE (untrimmed)
0.48 (0.25, 0.94)
BC mortality (Fine & Gray CR)
Univariate regression
0.47 (0.29, 0.77)
Multivariate regression
PSA - ATT (trimmed)
0.42 (0.22, 0.79)
PSA - ATT (untrimmed)
0.43 (0.22, 0.83)
PSA - ATE (trimmed)
0.48 (0.27, 0.87)
PSA - ATE (untrimmed)
0.53 (0.28, 1.00)
0.2
0.5
1
2
Favours RT
Favours no RT

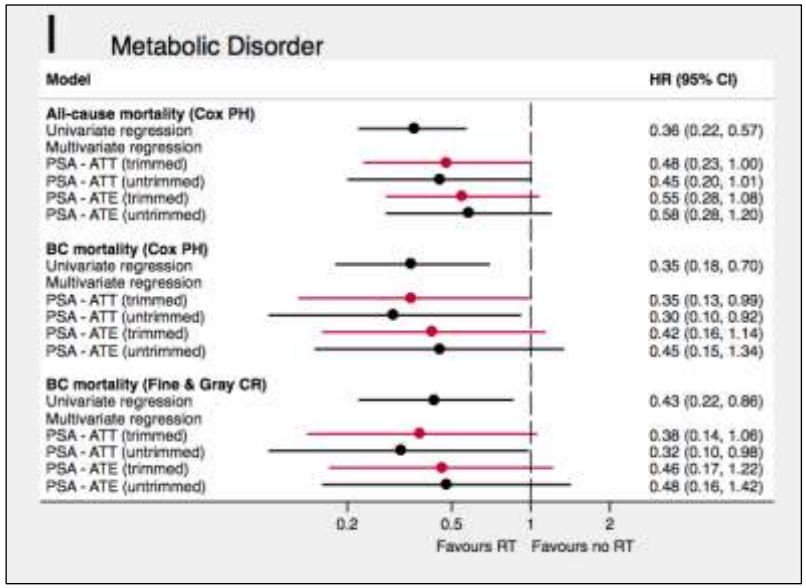
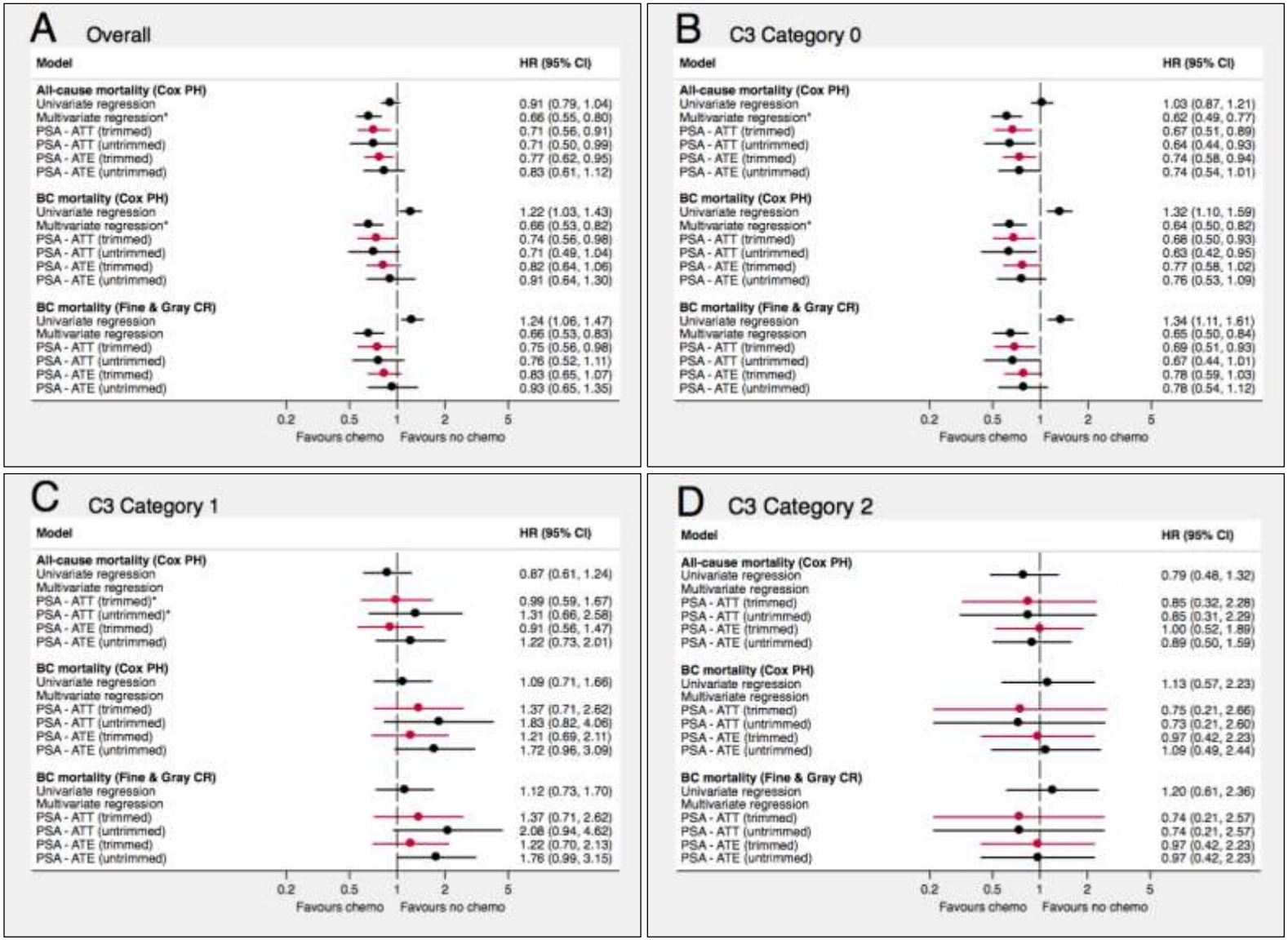
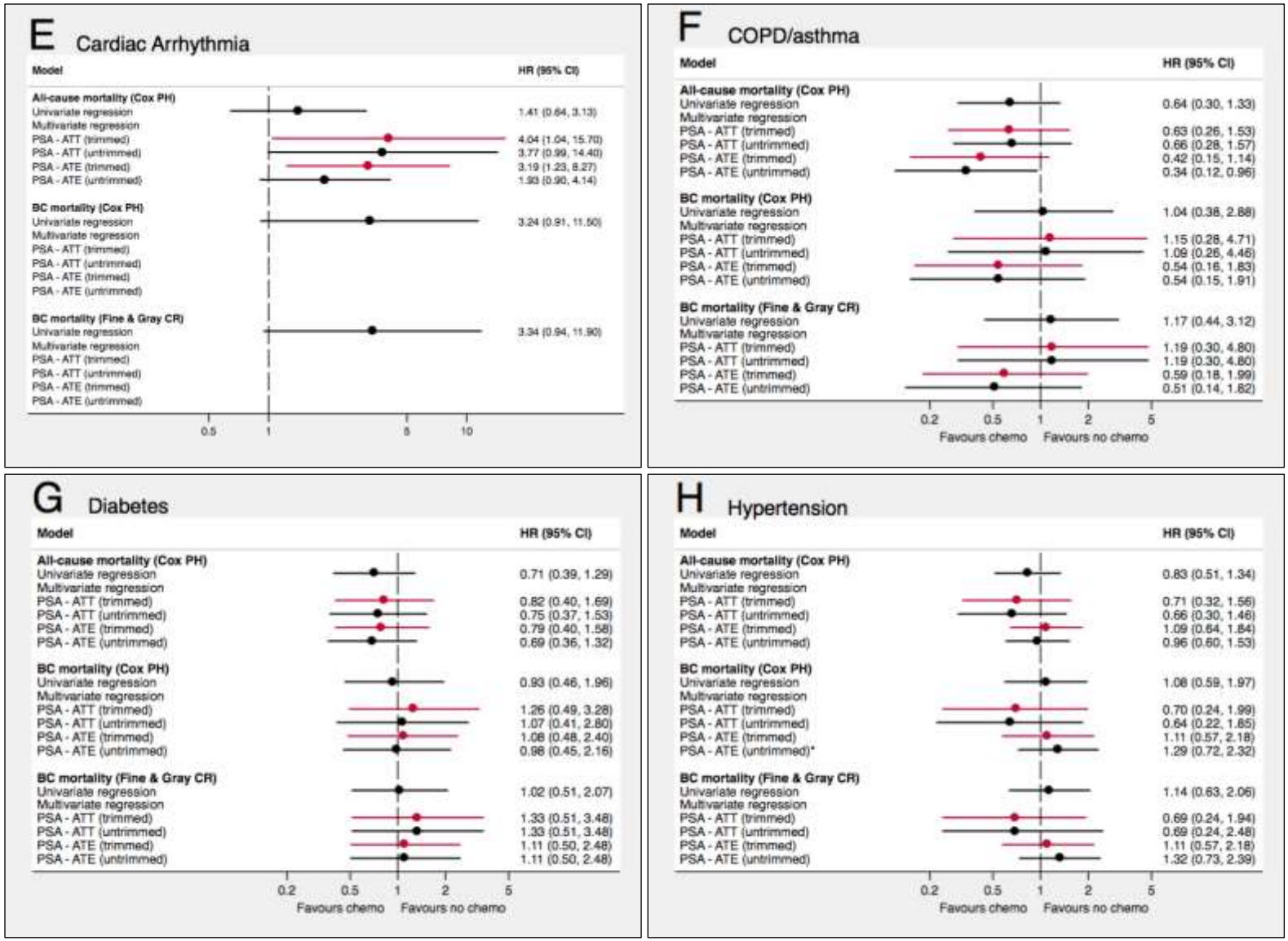


Figure 37. Forest Plots Showing Sensitivity Analyses for Treatment Effects of Adjuvant Radiotherapy by Comorbidity Status

Abbreviations: BC, breast cancer; CR, competing risks; PH, proportional hazards; PSA, propensity score analysis; RT, radiotherapy.


A Overall
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.91 (0.79, 1.04)
Multivariate regression* 0.66 (0.55, 0.80)
PSA - ATT (trimmed) 0.71 (0.56, 0.91)
PSA - ATT (untrimmed) 0.71 (0.50, 0.99)
PSA - ATE (trimmed) 0.77 (0.62, 0.95)
PSA - ATE (untrimmed) 0.83 (0.61, 1.12)
BC mortality (Cox PH)
Univariate regression 1.22 (1.03, 1.43)
Multivariate regression* 0.66 (0.53, 0.82)
PSA - ATT (trimmed) 0.74 (0.56, 0.98)
PSA - ATT (untrimmed) 0.71 (0.49, 1.04)
PSA - ATE (trimmed) 0.82 (0.64, 1.06)
PSA - ATE (untrimmed) 0.91 (0.64, 1.30)
BC mortality (Fine & Gray CR)
Univariate regression 1.24 (1.06, 1.47)
Multivariate regression 0.66 (0.53, 0.83)
PSA - ATT (trimmed) 0.75 (0.56, 0.98)
PSA - ATT (untrimmed) 0.76 (0.52, 1.11)
PSA - ATE (trimmed) 0.83 (0.65, 1.07)
PSA - ATE (untrimmed) 0.93 (0.65, 1.35)
0.2 0.5 1 2 5
Favours chemo Favours no chemo
B C3 Category 0
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 1.03 (0.87, 1.21)
Multivariate regression* 0.62 (0.49, 0.77)
PSA - ATT (trimmed) 0.67 (0.51, 0.89)
PSA - ATT (untrimmed) 0.64 (0.44, 0.93)
PSA - ATE (trimmed) 0.74 (0.58, 0.94)
PSA - ATE (untrimmed) 0.74 (0.54, 1.01)
BC mortality (Cox PH)
Univariate regression 1.32 (1.10, 1.59)
Multivariate regression* 0.64 (0.50, 0.82)
PSA - ATT (trimmed) 0.66 (0.50, 0.93)
PSA - ATT (untrimmed) 0.63 (0.42, 0.95)
PSA - ATE (trimmed) 0.77 (0.58, 1.02)
PSA - ATE (untrimmed) 0.76 (0.53, 1.09)
BC mortality (Fine & Gray CR)
Univariate regression 1.34 (1.11, 1.61)
Multivariate regression 0.65 (0.50, 0.84)
PSA - ATT (trimmed) 0.69 (0.51, 0.93)
PSA - ATT (untrimmed) 0.67 (0.44, 1.01)
PSA - ATE (trimmed) 0.78 (0.59, 1.03)
PSA - ATE (untrimmed) 0.78 (0.54, 1.12)
0.2 0.5 1 2 5
Favours chemo Favours no chemo
C C3 Category 1
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.87 (0.61, 1.24)
Multivariate regression
PSA - ATT (trimmed)* 0.99 (0.59, 1.67)
PSA - ATT (untrimmed)* 1.31 (0.66, 2.58)
PSA - ATE (trimmed) 0.91 (0.56, 1.47)
PSA - ATE (untrimmed) 1.22 (0.73, 2.01)
BC mortality (Cox PH)
Univariate regression 1.09 (0.71, 1.66)
Multivariate regression
PSA - ATT (trimmed) 1.37 (0.71, 2.62)
PSA - ATT (untrimmed) 1.83 (0.82, 4.06)
PSA - ATE (trimmed) 1.21 (0.69, 2.11)
PSA - ATE (untrimmed) 1.72 (0.96, 3.09)
BC mortality (Fine & Gray CR)
Univariate regression 1.12 (0.73, 1.70)
Multivariate regression
PSA - ATT (trimmed) 1.37 (0.71, 2.62)
PSA - ATT (untrimmed) 2.08 (0.94, 4.62)
PSA - ATE (trimmed) 1.22 (0.70, 2.13)
PSA - ATE (untrimmed) 1.76 (0.99, 3.15)
0.2 0.5 1 2 5
Favours chemo Favours no chemo
D C3 Category 2
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 0.79 (0.48, 1.32)
Multivariate regression
PSA - ATT (trimmed) 0.85 (0.32, 2.28)
PSA - ATT (untrimmed) 0.85 (0.31, 2.29)
PSA - ATE (trimmed) 1.00 (0.52, 1.89)
PSA - ATE (untrimmed) 0.89 (0.50, 1.59)
BC mortality (Cox PH)
Univariate regression 1.13 (0.57, 2.23)
Multivariate regression
PSA - ATT (trimmed) 0.75 (0.21, 2.66)
PSA - ATT (untrimmed) 0.73 (0.21, 2.60)
PSA - ATE (trimmed) 0.97 (0.42, 2.23)
PSA - ATE (untrimmed) 1.09 (0.49, 2.44)
BC mortality (Fine & Gray CR)
Univariate regression 1.20 (0.61, 2.36)
Multivariate regression
PSA - ATT (trimmed) 0.74 (0.21, 2.57)
PSA - ATT (untrimmed) 0.74 (0.21, 2.57)
PSA - ATE (trimmed) 0.97 (0.42, 2.23)
PSA - ATE (untrimmed) 0.97 (0.42, 2.23)
0.2 0.5 1 2 5
Favours chemo Favours no chemo


E Cardiac Arrhythmia
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
1.41 (0.64, 3.13)
Multivariate regression
PSA - ATT (trimmed)
4.04 (1.04, 15.70)
PSA - ATT (untrimmed)
3.77 (0.99, 14.40)
PSA - ATE (trimmed)
3.19 (1.23, 8.27)
PSA - ATE (untrimmed)
1.93 (0.90, 4.14)
BC mortality (Cox PH)
Univariate regression
3.24 (0.91, 11.50)
Multivariate regression
PSA - ATT (trimmed)
PSA - ATT (untrimmed)
PSA - ATE (trimmed)
PSA - ATE (untrimmed)
BC mortality (Fine & Gray CR)
Univariate regression
3.34 (0.94, 11.90)
Multivariate regression
PSA - ATT (trimmed)
PSA - ATT (untrimmed)
PSA - ATE (trimmed)
PSA - ATE (untrimmed)
0.5
1
5
10
F COPD/asthma
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.64 (0.30, 1.33)
Multivariate regression
PSA - ATT (trimmed)
0.63 (0.26, 1.53)
PSA - ATT (untrimmed)
0.66 (0.28, 1.57)
PSA - ATE (trimmed)
0.42 (0.15, 1.14)
PSA - ATE (untrimmed)
0.34 (0.12, 0.96)
BC mortality (Cox PH)
Univariate regression
1.04 (0.38, 2.88)
Multivariate regression
PSA - ATT (trimmed)
1.15 (0.28, 4.71)
PSA - ATT (untrimmed)
1.09 (0.26, 4.46)
PSA - ATE (trimmed)
0.54 (0.16, 1.83)
PSA - ATE (untrimmed)
0.54 (0.15, 1.91)
BC mortality (Fine & Gray CR)
Univariate regression
1.17 (0.44, 3.12)
Multivariate regression
PSA - ATT (trimmed)
1.19 (0.30, 4.80)
PSA - ATT (untrimmed)
1.19 (0.30, 4.80)
PSA - ATE (trimmed)
0.59 (0.18, 1.99)
PSA - ATE (untrimmed)
0.51 (0.14, 1.82)
0.2
0.5
1
2
5
Favours chemo
Favours no chemo
G Diabetes
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.71 (0.39, 1.29)
Multivariate regression
PSA - ATT (trimmed)
0.82 (0.40, 1.69)
PSA - ATT (untrimmed)
0.75 (0.37, 1.53)
PSA - ATE (trimmed)
0.79 (0.40, 1.58)
PSA - ATE (untrimmed)
0.69 (0.36, 1.32)
BC mortality (Cox PH)
Univariate regression
0.93 (0.46, 1.96)
Multivariate regression
PSA - ATT (trimmed)
1.26 (0.49, 3.28)
PSA - ATT (untrimmed)
1.07 (0.41, 2.80)
PSA - ATE (trimmed)
1.08 (0.48, 2.40)
PSA - ATE (untrimmed)
0.98 (0.45, 2.16)
BC mortality (Fine & Gray CR)
Univariate regression
1.02 (0.51, 2.07)
Multivariate regression
PSA - ATT (trimmed)
1.33 (0.51, 3.48)
PSA - ATT (untrimmed)
1.33 (0.51, 3.48)
PSA - ATE (trimmed)
1.11 (0.50, 2.48)
PSA - ATE (untrimmed)
1.11 (0.50, 2.48)
0.2
0.5
1
2
5
Favours chemo
Favours no chemo
H Hypertension
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
0.83 (0.51, 1.34)
Multivariate regression
PSA - ATT (trimmed)
0.71 (0.32, 1.56)
PSA - ATT (untrimmed)
0.66 (0.30, 1.46)
PSA - ATE (trimmed)
1.09 (0.64, 1.84)
PSA - ATE (untrimmed)
0.96 (0.60, 1.53)
BC mortality (Cox PH)
Univariate regression
1.08 (0.59, 1.97)
Multivariate regression
PSA - ATT (trimmed)
0.70 (0.24, 1.99)
PSA - ATT (untrimmed)
0.64 (0.22, 1.85)
PSA - ATE (trimmed)
1.11 (0.57, 2.18)
PSA - ATE (untrimmed)*
1.29 (0.72, 2.32)
BC mortality (Fine & Gray CR)
Univariate regression
1.14 (0.63, 2.06)
Multivariate regression
PSA - ATT (trimmed)
0.69 (0.24, 1.94)
PSA - ATT (untrimmed)
0.69 (0.24, 2.48)
PSA - ATE (trimmed)
1.11 (0.57, 2.18)
PSA - ATE (untrimmed)
1.32 (0.73, 2.39)
0.2
0.5
1
2
5
Favours chemo
Favours no chemo

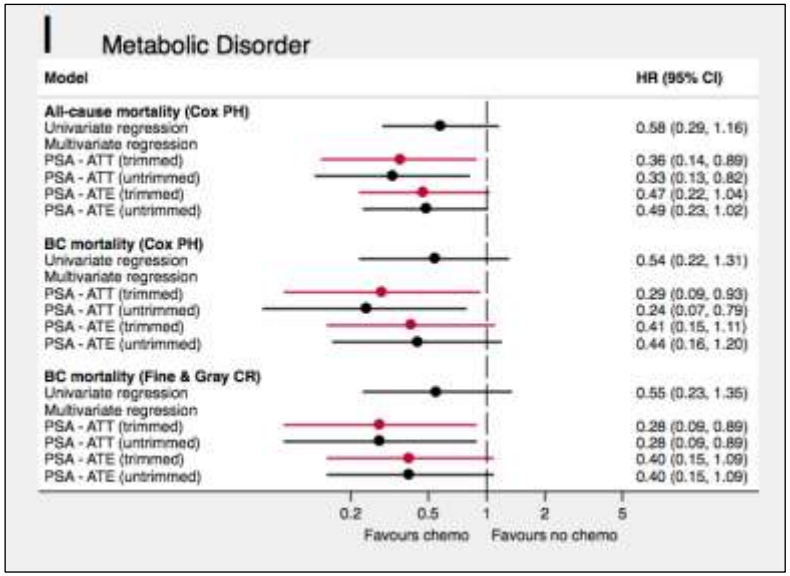
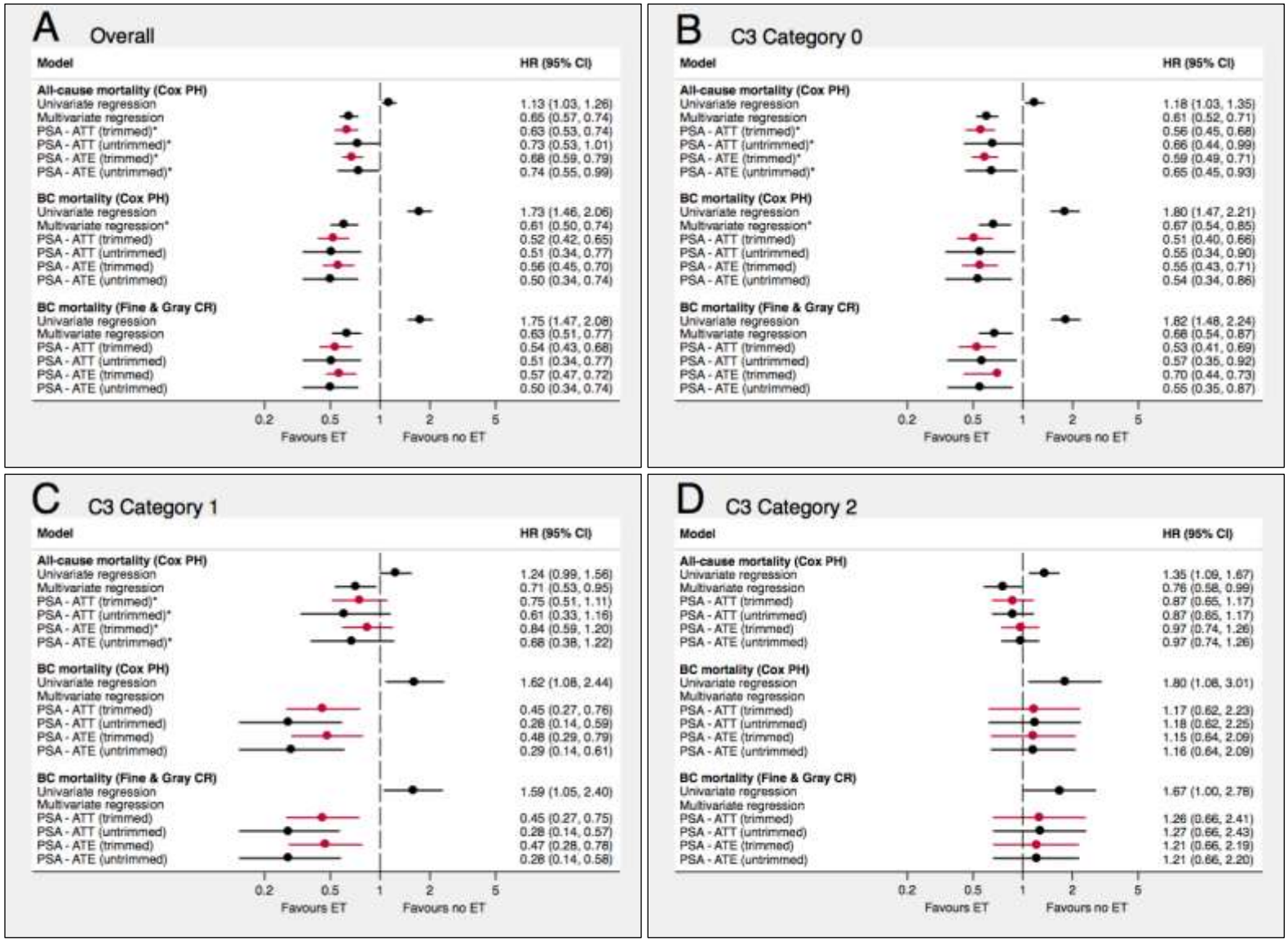
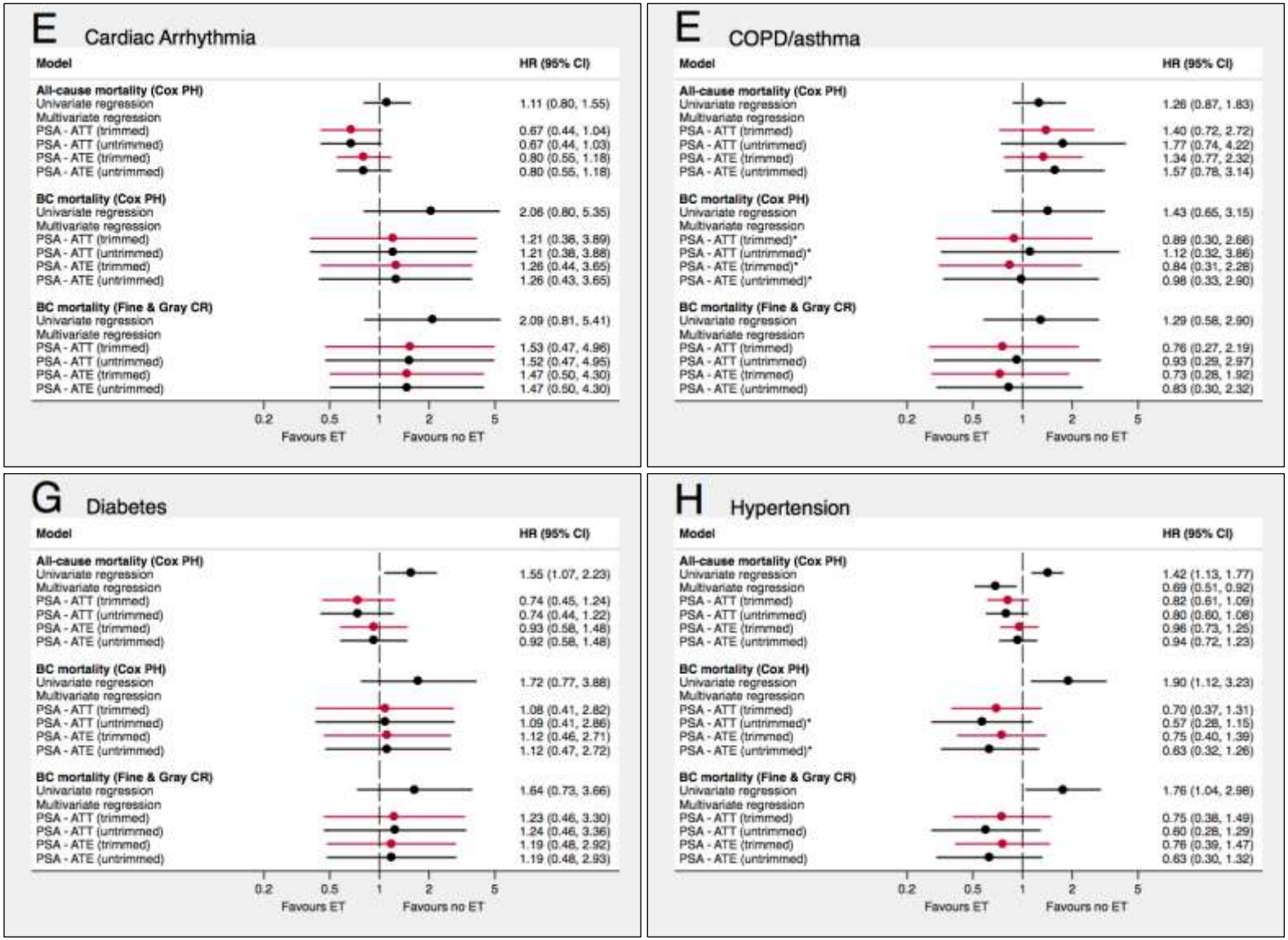


Figure 38. Forest Plots Showing Sensitivity Analyses for Treatment Effects of Adjuvant Chemotherapy by Comorbidity Status

Abbreviations: BC, breast cancer; chemo, chemotherapy; CR, competing risks; PH, proportional hazards; PSA, propensity score analysis.


A Overall
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 1.13 (1.03, 1.26)
Multivariate regression 0.65 (0.57, 0.74)
PSA - ATT (trimmed)* 0.63 (0.53, 0.74)
PSA - ATT (untrimmed)* 0.73 (0.53, 1.01)
PSA - ATE (trimmed)* 0.68 (0.59, 0.79)
PSA - ATE (untrimmed)* 0.74 (0.55, 0.99)
BC mortality (Cox PH)
Univariate regression 1.73 (1.46, 2.06)
Multivariate regression* 0.61 (0.50, 0.74)
PSA - ATT (trimmed) 0.52 (0.42, 0.65)
PSA - ATT (untrimmed) 0.51 (0.34, 0.77)
PSA - ATE (trimmed) 0.56 (0.45, 0.70)
PSA - ATE (untrimmed) 0.50 (0.34, 0.74)
BC mortality (Fine & Gray CR)
Univariate regression 1.75 (1.47, 2.08)
Multivariate regression 0.63 (0.51, 0.77)
PSA - ATT (trimmed) 0.54 (0.43, 0.68)
PSA - ATT (untrimmed) 0.51 (0.34, 0.77)
PSA - ATE (trimmed) 0.57 (0.47, 0.72)
PSA - ATE (untrimmed) 0.50 (0.34, 0.74)
0.2 0.5 1 2 5
Favours ET
Favours no ET
B C3 Category 0
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 1.18 (1.03, 1.35)
Multivariate regression 0.61 (0.52, 0.71)
PSA - ATT (trimmed)* 0.56 (0.45, 0.68)
PSA - ATT (untrimmed)* 0.66 (0.44, 0.99)
PSA - ATE (trimmed)* 0.59 (0.49, 0.71)
PSA - ATE (untrimmed)* 0.65 (0.45, 0.93)
BC mortality (Cox PH)
Univariate regression 1.80 (1.47, 2.21)
Multivariate regression* 0.67 (0.54, 0.85)
PSA - ATT (trimmed) 0.51 (0.40, 0.66)
PSA - ATT (untrimmed) 0.55 (0.34, 0.90)
PSA - ATE (trimmed) 0.55 (0.43, 0.71)
PSA - ATE (untrimmed) 0.54 (0.34, 0.86)
BC mortality (Fine & Gray CR)
Univariate regression 1.82 (1.48, 2.24)
Multivariate regression 0.68 (0.54, 0.87)
PSA - ATT (trimmed) 0.53 (0.41, 0.69)
PSA - ATT (untrimmed) 0.57 (0.35, 0.92)
PSA - ATE (trimmed) 0.70 (0.44, 0.73)
PSA - ATE (untrimmed) 0.55 (0.35, 0.87)
0.2 0.5 1 2 5
Favours ET
Favours no ET
C C3 Category 1
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 1.24 (0.99, 1.56)
Multivariate regression 0.71 (0.53, 0.95)
PSA - ATT (trimmed)* 0.75 (0.51, 1.11)
PSA - ATT (untrimmed)* 0.61 (0.33, 1.16)
PSA - ATE (trimmed)* 0.84 (0.59, 1.20)
PSA - ATE (untrimmed)* 0.68 (0.38, 1.22)
BC mortality (Cox PH)
Univariate regression 1.62 (1.08, 2.44)
Multivariate regression
PSA - ATT (trimmed) 0.45 (0.27, 0.76)
PSA - ATT (untrimmed) 0.28 (0.14, 0.59)
PSA - ATE (trimmed) 0.48 (0.29, 0.79)
PSA - ATE (untrimmed) 0.29 (0.14, 0.61)
BC mortality (Fine & Gray CR)
Univariate regression 1.59 (1.05, 2.40)
Multivariate regression
PSA - ATT (trimmed) 0.45 (0.27, 0.75)
PSA - ATT (untrimmed) 0.28 (0.14, 0.57)
PSA - ATE (trimmed) 0.47 (0.28, 0.78)
PSA - ATE (untrimmed) 0.28 (0.14, 0.58)
0.2 0.5 1 2 5
Favours ET
Favours no ET
D C3 Category 2
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression 1.35 (1.09, 1.67)
Multivariate regression 0.76 (0.58, 0.99)
PSA - ATT (trimmed) 0.87 (0.65, 1.17)
PSA - ATT (untrimmed) 0.87 (0.65, 1.17)
PSA - ATE (trimmed) 0.97 (0.74, 1.26)
PSA - ATE (untrimmed) 0.97 (0.74, 1.26)
BC mortality (Cox PH)
Univariate regression 1.80 (1.08, 3.01)
Multivariate regression
PSA - ATT (trimmed) 1.17 (0.62, 2.23)
PSA - ATT (untrimmed) 1.18 (0.62, 2.25)
PSA - ATE (trimmed) 1.15 (0.64, 2.09)
PSA - ATE (untrimmed) 1.16 (0.64, 2.09)
BC mortality (Fine & Gray CR)
Univariate regression 1.67 (1.00, 2.78)
Multivariate regression
PSA - ATT (trimmed) 1.26 (0.66, 2.41)
PSA - ATT (untrimmed) 1.27 (0.66, 2.43)
PSA - ATE (trimmed) 1.21 (0.66, 2.19)
PSA - ATE (untrimmed) 1.21 (0.66, 2.20)
0.2 0.5 1 2 5
Favours ET
Favours no ET


E Cardiac Arrhythmia
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
1.11 (0.80, 1.55)
Multivariate regression
PSA - ATT (trimmed)
0.67 (0.44, 1.04)
PSA - ATT (untrimmed)
0.67 (0.44, 1.03)
PSA - ATE (trimmed)
0.80 (0.55, 1.18)
PSA - ATE (untrimmed)
0.80 (0.55, 1.18)
BC mortality (Cox PH)
Univariate regression
2.06 (0.80, 5.35)
Multivariate regression
PSA - ATT (trimmed)
1.21 (0.38, 3.89)
PSA - ATT (untrimmed)
1.21 (0.38, 3.88)
PSA - ATE (trimmed)
1.26 (0.44, 3.65)
PSA - ATE (untrimmed)
1.26 (0.43, 3.65)
BC mortality (Fine & Gray CR)
Univariate regression
2.09 (0.81, 5.41)
Multivariate regression
PSA - ATT (trimmed)
1.53 (0.47, 4.96)
PSA - ATT (untrimmed)
1.52 (0.47, 4.95)
PSA - ATE (trimmed)
1.47 (0.50, 4.30)
PSA - ATE (untrimmed)
1.47 (0.50, 4.30)
0.2
0.5
1
2
5
Favours ET
Favours no ET
E COPD/asthma
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
1.26 (0.87, 1.83)
Multivariate regression
PSA - ATT (trimmed)
1.40 (0.72, 2.72)
PSA - ATT (untrimmed)
1.77 (0.74, 4.22)
PSA - ATE (trimmed)
1.34 (0.77, 2.32)
PSA - ATE (untrimmed)
1.57 (0.78, 3.14)
BC mortality (Cox PH)
Univariate regression
1.43 (0.65, 3.15)
Multivariate regression
PSA - ATT (trimmed)*
0.89 (0.30, 2.66)
PSA - ATT (untrimmed)*
1.12 (0.32, 3.86)
PSA - ATE (trimmed)*
0.84 (0.31, 2.28)
PSA - ATE (untrimmed)*
0.98 (0.33, 2.90)
BC mortality (Fine & Gray CR)
Univariate regression
1.29 (0.58, 2.90)
Multivariate regression
PSA - ATT (trimmed)
0.76 (0.27, 2.19)
PSA - ATT (untrimmed)
0.93 (0.29, 2.97)
PSA - ATE (trimmed)
0.73 (0.28, 1.92)
PSA - ATE (untrimmed)
0.83 (0.30, 2.32)
0.2
0.5
1
2
5
Favours ET
Favours no ET
G Diabetes
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
1.55 (1.07, 2.23)
Multivariate regression
PSA - ATT (trimmed)
0.74 (0.45, 1.24)
PSA - ATT (untrimmed)
0.74 (0.44, 1.22)
PSA - ATE (trimmed)
0.93 (0.58, 1.48)
PSA - ATE (untrimmed)
0.92 (0.58, 1.48)
BC mortality (Cox PH)
Univariate regression
1.72 (0.77, 3.88)
Multivariate regression
PSA - ATT (trimmed)
1.08 (0.41, 2.82)
PSA - ATT (untrimmed)
1.09 (0.41, 2.86)
PSA - ATE (trimmed)
1.12 (0.46, 2.71)
PSA - ATE (untrimmed)
1.12 (0.47, 2.72)
BC mortality (Fine & Gray CR)
Univariate regression
1.64 (0.73, 3.66)
Multivariate regression
PSA - ATT (trimmed)
1.23 (0.46, 3.30)
PSA - ATT (untrimmed)
1.24 (0.46, 3.36)
PSA - ATE (trimmed)
1.19 (0.48, 2.92)
PSA - ATE (untrimmed)
1.19 (0.48, 2.93)
0.2
0.5
1
2
5
Favours ET
Favours no ET
H Hypertension
Model
HR (95% CI)
All-cause mortality (Cox PH)
Univariate regression
1.42 (1.13, 1.77)
Multivariate regression
0.69 (0.51, 0.92)
PSA - ATT (trimmed)
0.82 (0.61, 1.09)
PSA - ATT (untrimmed)
0.80 (0.60, 1.08)
PSA - ATE (trimmed)
0.96 (0.73, 1.25)
PSA - ATE (untrimmed)
0.94 (0.72, 1.23)
BC mortality (Cox PH)
Univariate regression
1.90 (1.12, 3.23)
Multivariate regression
PSA - ATT (trimmed)
0.70 (0.37, 1.31)
PSA - ATT (untrimmed)*
0.57 (0.28, 1.15)
PSA - ATE (trimmed)
0.75 (0.40, 1.39)
PSA - ATE (untrimmed)*
0.63 (0.32, 1.26)
BC mortality (Fine & Gray CR)
Univariate regression
1.76 (1.04, 2.98)
Multivariate regression
PSA - ATT (trimmed)
0.75 (0.38, 1.49)
PSA - ATT (untrimmed)
0.60 (0.28, 1.29)
PSA - ATE (trimmed)
0.76 (0.39, 1.47)
PSA - ATE (untrimmed)
0.63 (0.30, 1.32)
0.2
0.5
1
2
5
Favours ET
Favours no ET

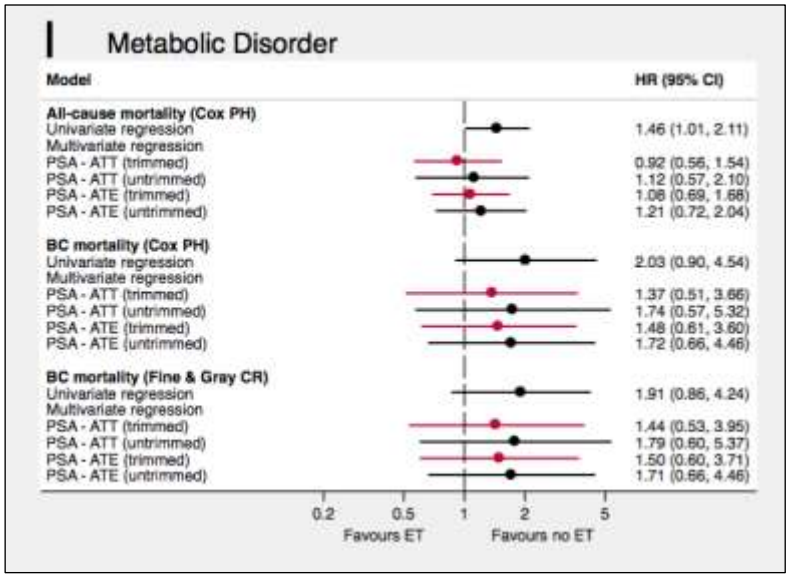


Figure 39. Forest Plots Showing Sensitivity Analyses for Treatment Effects of Endocrine Therapy by Comorbidity Status

Abbreviations: BC, breast cancer; CR, competing risks; ET, endocrine therapy; PH, proportional hazards; PSA, propensity score analysis.

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