Quality and Outcomes of Diabetes Care in Patients Diagnosed with Cancer

Robert Ian Griffiths, MS, ScD

A thesis submitted for the degree of

Doctor of Philosophy in Evidence-Based Health Care

Balliol College, Department of Continuing Education

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ABSTRACT

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Background and Rationale: Overlooking other medical conditions during cancer treatment and follow-up could result in excess morbidity and mortality, thereby undermining gains associated with early detection and improved treatment of cancer. ***Objective*****:** This thesis examined the quality and outcomes of diabetes care in patients diagnosed with cancer. ***Methods of Research*****:** The methods included a systematic review of the quality of diabetes care in cancer, and primary research on the quality—including diabetes control and the provision of services—and outcomes of diabetes care in breast, colorectal, or prostate cancer using the Clinical Practice Research Datalink. ***Results of the Systematic Review*****:** There were 15 studies from five countries, with 88 comparisons of quality measures between cancer patients and controls, including cholesterol and glycosylated haemoglobin (HbA1c) control, diabetes education, and eye examinations. Of these 88, 47 (53%; 95% Confidence Interval [CI], 43%-64%) were no different, 12 (14%; 95% CI, 6%-21%) were better, and 29 (33%; 95% CI, 23%-43%) were worse in cancer patients. ***Results of the Primary Research*****:** The primary research included 3,382 diabetic cancer patients and 11,135 matched, diabetic, non-cancer controls, who were followed from two years before, up to 10 years after, cancer or a matched date in controls. Cancer patients were less likely to meet 5/14 quality measures examined, including total cholesterol ≤5 mmol/L (adjusted odds ratio [OR], 0.82; 95% CI, 0.75-0.90) and HbA1c ≤59 mmol/mol (adjusted OR=0.77; 95% CI, 0.70-0.85). However, differences in actual levels were small, and lasted <1 year after diagnosis. Cancer patients were no less likely to meet quality measures for retinal screening, foot examination, or dietary review. Cancer was not associated with increased rates of microvascular or macrovascular complications, or diabetes-related mortality. ***Conclusions and Implications*****:** Overall, the findings indicate that diabetes is not overlooked in older breast, colorectal, or prostate cancer patients. Any short-term deficits in cholesterol and HbA1c control do not result in increased diabetes complications or excess diabetes-related mortality over the long-term.

I dedicate this thesis to Derrick Griffiths, my father

Born, February 12, 1927 in Darfield, Yorkshire, England

Died, July 2, 2011 in Delray Beach, Florida, United States

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I wish to thank my academic supervisors Dr. Clare Bankhead, University Research Lecturer, Nuffield Department of Primary Care Health Sciences (NDPCHS), University of Oxford, and Dr. Nancy Keating, Professor of Health Care Policy and Medicine, Harvard Medical School, for their guidance throughout the process of completing this thesis. I am grateful to Dr. Bankhead, especially for providing advice on the design, implementation, and presentation of the findings from the systematic review for this thesis, for sharing her knowledge of the data I used for the primary database research, and for helping me negotiate the administrative processes involved in completing the DPhil. I am indebted to Dr. Keating, especially for providing guidance on the design and implementation of the primary database research, for bringing a clinical perspective to all aspects of the thesis, including the methods of research and interpretation of the findings, and for encouraging me to pursue other lines of related research. Also, I wish to thank my former supervisor, José Valderas, Professor of Health Services and Policy Research, University of Exeter Medical School, for agreeing to supervise me when I first applied to Oxford, for seeing me through the early phases of my DPhil, and for continuing to provide input on the primary database research as a co-author on several related papers.

I am grateful to the Population Research Committee of Cancer Research UK (CRUK) for providing grant support for a study that resulted in the primary database research for this thesis, and also to the members (in addition to those acknowledged above) of the research team for that project, Drs. Nada Khan of the Royal Liverpool Hospital, Emily McFadden of the NDPCHS, Bernadette Lavery of the Thames Valley Cancer Strategic Clinical Network, and Richard Stevens of the NDPCHS, for their contributions to the design and implementation of the CRUK-funded project. Also, Sarah Stevens of the NDPCHS provided preliminary data for the primary database analyses. I wish to thank Professors Carl Heneghan and Rafael Perera of the NDPCHS, who were the assessors for both my Transfer of Status and Confirmation of Status examinations. I would also like to thank all of the staff of the NDPCHS for their support throughout the process.

It is almost 25 years since I completed a Doctor of Science degree in Health Policy and Management at the Johns Hopkins University, and I am grateful for all the friends and colleagues in the field of evidence-based health care I have come to know since then. Among them, Robert Herbert has been there since the beginning. I thank him for his enthusiastic and steadfast support of me during my time at Johns Hopkins, during the long intermission, and now, again, at the end of my time at the University of Oxford.

Finally, I wish to thank my family, especially Suzanne, for their patience, and for indulging me when I tried to reassure them that "all my means are sane, my motive and my object mad."[a]

[a] p. 205. Melville, H. (1851) *Moby-Dick: or, The Whale*. New York: Harper & Brothers.

STATEMENT OF CONTRIBUTIONS

This doctoral thesis is an independent and original work of which I am the sole author. Academic supervisors Clare Bankhead, University Research Lecturer, NDPCHS, University of Oxford, and Nancy Keating, Professor of Health Care Policy and Medicine, Harvard Medical School, contributed intellectual guidance on the overall thesis topic, research methods, and presentation of the findings. Both participated as co-authors on research papers resulting from this thesis

Other individuals, in alphabetical order below, have made contributions in the following ways:

Carl Heneghan, Professor of Evidence-Based Medicine, NDPCHS, University of Oxford, was an assessor for both my Transfer of Status and Confirmation of Status examinations, and provided input on the research methods, structure of the thesis, and presentation of the findings.

Nada Khan, Royal Liverpool Hospital, provided intellectual guidance on the overall thesis topic, research methods, and presentation of the findings, and participated as a co-author on research papers resulting from this thesis.

Bernadette Lavery, oncologist and Clinical Director, Thames Valley Cancer Strategic Clinical Network, provided intellectual guidance on the overall thesis topic and interpretation of the findings, and participated as a co-author on research papers resulting from this thesis.

Emily McFadden, Senior Statistical Epidemiologist, NDPCHS, University of Oxford, provided programming support and statistical advice on the primary research using the Clinical Practice Research Datalink (CPRD), and participated as a co-author on research papers resulting from this thesis.

Rafael Perera, Professor of Medical Statistics, NDPCHS, University of Oxford, was an assessor for both my Transfer of Status and Confirmation of Status Examinations, and provided input on the research methods, structure of the thesis, and presentation of the findings.

Claire Snyder, Associate Professor of Medicine, Johns Hopkins University School of Medicine, reviewed a draft protocol for the systematic review.

Richard Stevens, Associate Professor, NDPCHS, University of Oxford, provided statistical advice on the primary research using CPRD, and participated as a co-author on research papers resulting from this thesis.

Sarah Stevens, Statistician and Doctoral Student in Primary Care, NDPCHS, University of Oxford, provided a preliminary data set of patients for the primary research using CPRD.

José Valderas, Professor of Health Services and Policy Research, University of Exeter Medical School, my former supervisor, provided intellectual guidance on the overall thesis topic, research methods, and presentation of the findings, and participated as a co-author on research papers resulting from this thesis.

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
ACE-I	angiotensin-converting enzyme inhibitor
AHRQ	Agency for Healthcare Research and Quality
ARB	angiotensin receptor blocker
BC	breast cancer
BMI	body mass index
BNF	British National Formulary
CC	colorectal cancer
CI	confidence interval
COMBO	Group Health Cooperative Commonly Used Medications and Breast Cancer Outcomes
CPRD	Clinical Practice Research Datalink
CRUK	Cancer Research UK
ECR	Eindhoven Cancer Registry
ESBC	early-stage breast cancer
GLD	glucose-lowering drug
GP	general practitioner
HbA1c	glycosylated haemoglobin
HDL	high density lipoprotein
HES	Hospital Episode Statistics
HR	hazard ratio
ICD-10	International Classification of Diseases, 10th Revision
IMD	Index of Multiple Deprivation
ISAC	Independent Scientific Advisory Committee
KNHANES	Korea National Health and Nutrition Examination Survey
LDL	low density lipoprotein
MeSH	Medical Subject Headings
MPR	medication possession ratio

Abbreviation	Meaning
MV	multivariate
NA	not applicable
NCIN	National Cancer Intelligence Network
NDPCHS	Nuffield Department of Primary Care Health Sciences
NHS	National Health Service
ONS	Office for National Statistics
OR	odds ratio
PC	prostate cancer
PDC	proportion of days covered
PEO	patients, exposures, outcomes
PHARMO	PHARmacoMorbidity Database Network
PPPY	per patient per year
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOF	Quality and Outcomes Framework
RR	risk ratio
SBP	systolic blood pressure
SEER	Surveillance, Epidemiology, and End Results
TIA	transient ischaemic attack
UK	United Kingdom
UKPDS	UK Prospective Diabetes Study
US	United States

CHAPTER ONE

Introduction

I INTRODUCTION

1.1 BACKGROUND AND RATIONALE FOR THESIS TOPIC

Early detection and advances in therapy and supportive care have substantially improved the relative survival of many of the most common types of cancer.[1] Consequently, overall morbidity and mortality in cancer depend increasingly on the quality and outcomes of primary care for underlying conditions.[2] In response, Cancer Research UK (CRUK) and other organizations, such as Macmillan Cancer Support, have expressed concern that overlooking other medical conditions during cancer treatment and follow-up could result in excess morbidity and mortality, thereby undermining gains associated with early detection and improved treatment of cancer.[3,4]

Although cancer could have an adverse impact on many conditions, and vice-versa, the quality and outcomes of diabetes care in cancer deserve specific attention, for the following reasons. First, diabetes and cancer are common, especially in older people. Second, diabetes and some types of cancer, including breast and colorectal, co-occur at rates that are higher than expected by chance alone, which implies shared risk factors and, possibly, causal mechanisms.[5] Third, some types of cancer treatments, for instance, androgen deprivation therapy for prostate cancer, [6] appear to increase the risk of diabetes and related complications. Fourth, diabetes is associated with excess morbidity and mortality in cancer.[7]

There is broad consensus on what constitutes high quality diabetes care, with position statements[8] and clinical guidelines[9,10] that provide recommendations on key components—patient education, dietary advice, management of blood pressure and

blood glucose, prevention and treatment of complications—as well as programmes that provide incentives to deliver recommended care.[11] One overarching theme is that high quality diabetes care depends on a partnership between the patient and a team of healthcare professionals, which is best served through regular delivery of recommended diabetes services by healthcare professionals, plus ongoing participation in diabetes self-management activities by the patient. For example, achieving optimal glycaemic control may entail a combination of patient and provider actions, including regular glycosylated haemoglobin (HbA1c) testing, patient self-monitoring of blood glucose, medical nutritional therapy, physical activity, and pharmacologic therapy—including patient adherence to prescribed regimens. Consequently, there are several mechanisms by which cancer could adversely impact the quality and outcomes of diabetes care.

First, cancer could disrupt the regular delivery of diabetes services,[8-11] especially in primary care at times when cancer specialty care is most intensive, e.g., diagnosis and initial treatment. At the time that the topic for this thesis was developed, there had been several studies on the delivery of diabetes care in cancer patients, predominantly in the United States (US),[12-19] with inconsistent findings on the impact of cancer on the provision of medical services, laboratory testing, and control of blood pressure, cholesterol, and HbA1c. In a recent study of older (age ≥66 years at diagnosis) patients who had survived at least three years after breast, colorectal, or prostate cancer, which was based on US cancer registry data (Surveillance, Epidemiology, and End Results [SEER]) linked to public health insurance records (Medicare), Snyder and colleagues[12] found that breast and prostate cancer patients were more likely than matched non-cancer controls to have a physician visit every six months. Colorectal cancer patients

were less likely to have annual eye examinations and haemoglobin and fructosamine testing every six months.

Keating and colleagues[17] used clinical and administrative data from a large health care system in Northern California, US, to examine differences in nine measures of diabetes technical quality and clinical outcomes between diabetes patients with cancer and non-cancer controls. They found higher adjusted rates of HbA1c and urine microalbumin testing, and higher rates of HbA1c control, in cancer patients, but lower rates of low density lipoprotein (LDL) cholesterol control and statin use. Adjusted rates of LDL cholesterol testing, dilated retinal examinations, blood pressure control, and use of angiotensin-converting enzyme inhibitors (ACE-I) for hypertension were similar between cancer cases and controls.

Differences in the organization, delivery, and financing of primary care services between the US and the United Kingdom (UK), including historically poorer coverage of preventative services by public health insurers in the US, could, in this instance, undermine the generalizability of evidence on the quality and outcomes of diabetes care in cancer from the US to the UK. In the UK, evidence is limited to one study based on the UK General Practice Research Database[b] (2003–2006), in which long-term survivors of breast, colorectal, or prostate cancer were followed for blood pressure, cholesterol, and HbA1c monitoring and control beginning at least five years after cancer was diagnosed.[19] However, because this study was conducted in long-term survivors, and follow-up did not begin until at least five years after cancer diagnosis, the UK study did

[b] The precursor to the Clinical Practice Research Datalink, which was the database used for the primary research in this thesis on the quality and outcomes of diabetes care in patients diagnosed with cancer.

not assess differences in the quality of diabetes primary care during the first five years after cancer—a limitation acknowledged by the investigators, who called for research on the shorter-term consequences of cancer.[19] Also, the study did not include an assessment of other diabetes primary care services, such as retinal screening and foot examination, and it was conducted when the Quality and Outcomes Framework (QOF)—the annual reward and incentive programme detailing practice achievement results, which rewards practices for the provision of quality care and helps standardize improvement in the delivery of primary medical services—was first implemented.

Second, cancer could disrupt recommended patient self-management of diabetes.[8-11,20] In an exploratory study of 43 adults with diabetes and a solid tumor cancer, after eight weeks of chemotherapy patients performed significantly fewer diabetes self-management activities.[20] Some patients reported an overall negative impact of cancer on their ability to manage diet, exercise, medication, and blood glucose monitoring (self-management issues); some reported glycaemic issues—mainly hyperglycaemia—and an overall increase in symptoms (health issues); and some reported that they had been advised by their primary care provider not to worry about their diabetes while undergoing chemotherapy, that they had made the decision to "put their diabetes on the back-burner" during cancer treatment, or that, while they recognized the need to continue diabetes care, they could no longer accomplish it by themselves (prioritization issues).[20]

Third, cancer treatment could adversely impact the quality and outcomes of diabetes care. For instance, glucocorticoids "wreak havoc on post-prandial glycaemic control," and hyperglycaemia is a frequent complication of both tube feeding and total parenteral

nutrition.[21] In addition, several therapeutic agents are known to cause or exacerbate renal, cardiac, and neuropathic complications of diabetes.[6,21]

The overall impact of cancer on diabetes outcomes is likely to depend, in part, on whether changes in biological parameters, e.g., HbA1c, blood pressure, and lipids, resulting from the mechanisms described above, are of sufficient size and duration to increase the risk of diabetes complications. Evidence from the UK Prospective Diabetes Study (UKPDS) indicates that the risks of diabetic microvascular and macrovascular complications are strongly associated with long-term elevations in both HbA1c and systolic blood pressure.[22-25] For example, in UKPDS 35,[22] a prospective observational study to determine the relation between exposure to glycaemia over time and the risk of microvascular and macrovascular complications in patients newly diagnosed with type II diabetes, each 1% reduction in updated mean HbA1c[c] was associated with reductions in risk of 21% for any endpoint related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications. In UKPDS 36,[23] a companion study to UKPDS 35,[22] each 10mm Hg decrease in updated mean systolic blood pressure was associated with reductions in risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications.

The UKPDS provides evidence that long-term elevations in HbA1c and systolic blood pressure are associated with increased risks of diabetes microvascular and macrovascular complications and death. As such, the UKPDS provides an important

[c] Calculated for each individual from baseline to each year of follow-up (mean duration of 10 years)

benchmark to assess whether observed changes in biological parameters associated with cancer would likely be of sufficient size and duration to increase the risks of diabetes complications in cancer patients.

1.2 AIM OF THESIS

The aim of this thesis was to examine the quality and outcomes of diabetes care in patients diagnosed with cancer, throughout the continuum of cancer care from diagnosis and initial treatment through long-term follow-up. By doing so, I sought to investigate whether underlying diabetes was overlooked during cancer treatment and follow-up, and if so, whether this resulted in excess morbidity and mortality due to diabetes, thereby addressing an important concern raised by leading cancer organizations in the UK.

1.3 METHODS OF RESEARCH

The methods of research included a systematic review and qualitative synthesis of the literature on the quality of diabetes care in patients diagnosed with cancer, as well as primary research using the Clinical Practice Research Datalink (CPRD), which at the time contained health records for approximately 11.3 million patients from 674 general practices in the UK.[26]

1.4 RESEARCH OBJECTIVES

The specific research objectives were as follows:

1. Perform a systematic review and qualitative synthesis of the literature on the quality of diabetes care in patients diagnosed with cancer.

2. Conduct primary research on the quality and outcomes of diabetes care in older patients diagnosed with breast, colorectal, or prostate cancer using the UK CPRD:

2.1 Identify three cohorts of patients with pre-existing diabetes, each subsequently diagnosed with breast, colorectal, or prostate cancer.

2.2 Match the cancer patients to non-cancer controls who also had pre-existing diabetes.

2.3 Construct a fourth cohort consisting of all three cohorts of cancer patients and controls combined.

2.4 Compare the quality of diabetes care between cancer patients and controls.

2.5 Compare patterns of clinical measures and laboratory test results, e.g., blood pressure, HbA1c and cholesterol, between cancer patients and controls.

2.6 Compare rates of diabetes microvascular and macrovascular complications between cancer patients and controls.

2.7 Compare overall and diabetes-related mortality between cancer patients and controls.

As stated, the research objectives for the thesis focus primarily on (A) whether cancer disrupted the delivery of recommended diabetes services in primary care, (B) whether the aggregate effect of disruptions in primary care diabetes services, lapses in patient self-management, and cancer treatment was to increase levels of biological parameters that also are risk factors for diabetes complications, and (C) whether the aggregate effect of the mechanisms above, including their direct and/or indirect impact on levels of important biological parameters, was to increase the risk of diabetes complications and mortality. The objectives—and selection of the methods and data source for the

primary research, as described below—were not designed to directly compare patterns of diabetes self-management between cancer patients and controls. Nor were they designed to directly estimate the impact of cancer treatment on short and long-term complications of diabetes. However, the indirect impacts of these mechanisms on important biological parameters, and on the outcomes of diabetes are addressed in objectives 2.5-2.7 above.

Breast, colorectal, and prostate cancer were selected for inclusion in the primary research for the following reasons: combined, they comprise more than 41% of all new cancers diagnosed in the UK; breast cancer is the most common cancer newly diagnosed (incident) in females, and prostate cancer is the most common cancer newly diagnosed in males; as with type II diabetes, the incidences of all three cancers increase with age; the relative survival of breast, colorectal, and prostate cancer all have improved substantially over the past four decades, [27] which may make it more likely that overlooking other medical conditions during treatment and follow-up of these specific cancers could undermine those gains in relative survival—a concern raised by CRUK and other organizations, such as Macmillan Cancer Support;[3,4] and evidence indicates several types of treatment for these cancers increase the risk of diabetes complications.[6,21]

Although, lung cancer is among the four most common cancers in males and females in the UK, and its incidence increases with age,[27] unfortunately there has been little improvement of relative survival, due primarily to the fact that the majority of lung cancer patients are diagnosed with advanced disease, and prognosis in these patients generally is poor.[27] Therefore, lung cancer was not included among the cancers selected

for the primary research. However, all types of cancer were included in the systematic review.

1.5 THESIS STRUCTURE

1.5.1 Chapter 2. Systematic Review

Chapter 2 presents the systematic review of the literature on the quality of diabetes care in patients diagnosed with cancer, which was based on 15 studies[12-19,28-34] from five countries. It describes the methods of research used, the characteristics of the studies, and the results from the individual studies by type of quality measure reported; and, it concludes with a discussion of the major findings, including the strengths and limitations of the systematic review, as well as the implications for conducting the primary research reported in Chapters 3-6.

1.5.2 Chapter 3. Methods of Primary Research

Chapter 3 describes the methods of primary research on the quality and outcomes of diabetes care in 3,382 patients diagnosed with breast, colorectal, or prostate cancer compared to 11,135 matched, non-cancer controls, which was conducted using data from the CPRD and data held under the CPRD Linkage Scheme. This chapter also reports the baseline demographic and clinical characteristics of the patient cohorts that were constructed from the CPRD data to conduct the research in Chapters 4-6.

1.5.3 Chapter 4. Quality of Diabetes Care

Chapter 4 presents the methods and results of the primary research in which the *quality of diabetes care,* consisting of 14 measures based on the QOF Diabetes Mellitus Indicator Set[10] that include blood pressure, cholesterol, and HbA1c control, diabetes

services, e.g., foot examination, and other general primary care services, e.g., influenza immunisation, was compared between the cancer patients and controls from Chapter 3.

1.5.4 Chapter 5. Clinical and Laboratory Values Over Time

Chapter 5 presents the methods and results of the primary research in which longitudinal patterns of *actual clinical and laboratory values*, consisting of blood pressure, cholesterol, and HbA1c, were compared between the cancer patients and controls from Chapter 3.

1.5.5 Chapter 6. Diabetes Complications and Mortality

Chapter 6 presents the methods and results of the primary database research in which *rates of microvascular and macrovascular complications of diabetes* were compared between the cancer patients and controls from Chapter 3. Microvascular complications consisted of chronic kidney disease (stage 4 or 5), nephropathy, neuropathy, and retinopathy. Macrovascular complications consisted of acute myocardial infarction or acute coronary syndrome, cerebrovascular accident, lower limb amputation, and peripheral arterial disease. This chapter also presents the methods and results of the analyses in which *diabetes-related and overall mortality* were compared between cancer patients and controls.

1.5.6 Chapter 7. Discussion and Conclusions

Chapter 7 provides a summary of the major findings from the systematic review and from the primary research of the thesis. Overall, the findings indicate that, in the UK, diabetes is not overlooked in older patients diagnosed with breast, colorectal, or prostate cancer; and, that the quality and outcomes of diabetes care in cancer patients

are, for the most part, comparable to that in diabetic, non-cancer patients throughout the continuum of cancer treatment and long-term follow-up, with the exception, perhaps, of short-term HbA1c and cholesterol control in cancer.

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CHAPTER TWO

Systematic Review

II SYSTEMATIC REVIEW

2.1 CHAPTER AIM

The aim of this chapter is to present the methods and findings of a systematic review to address the following "patients, exposures, outcomes" (PEO) research question: Among patients with diabetes, does a diagnosis of cancer impact the quality of diabetes care? Information from studies included in the review was used to help frame the design of the primary research reported in Chapters 3-6, and also has been included in two articles submitted for publication:

Griffiths RI, McFadden EC, Stevens RJ, Valderas JM, Lavery BA, Khan NF, Keating NL, Bankhead CR. Quality of Diabetes Primary Care in Breast, Colorectal, and Prostate Cancer.

Griffiths RI, Valderas JM, McFadden EC, Bankhead CR, Lavery BA, Khan NF, Stevens RJ, Keating NL. Outcomes of Pre-Existing Diabetes Mellitus in Breast, Colorectal, and Prostate Cancer.

2.2 METHODS OF RESEARCH

The Methods of Research and Results sections of this systematic review are reported according to the checklist included in the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[1,2]

2.2.1 Objective

The objective of the systematic review was to address the following PEO research question: Among patients with diabetes, does a diagnosis of cancer impact the quality of diabetes care?

2.2.2 Protocol

A draft protocol for this systematic review (dated 12 May, 2014) was developed under the guidance of thesis supervisors Clare Bankhead and Nancy Keating, with input from others (Nada Khan and Claire Snyder) who had previously conducted research pertinent to the topic of the review, and who each had a paper included in this systematic review.

2.2.3 Eligibility Criteria

With respect to the PEO question, the "patients" of interest were those diagnosed with diabetes, including type I and type II diabetes, and including (A) those with diabetes that preceded cancer, and (B) those with diabetes that may have been diagnosed after cancer, but before the beginning of the observation period for outcomes. The "exposure" of interest was cancer of any type; and, the "outcomes" of interest were diabetes quality of care measures. Several types of observational cohort studies were considered for inclusion. First, longitudinal cohort studies in which patients with pre-existing diabetes were followed from before to after diagnosis of cancer for changes in diabetes quality of care—so called "before and after" studies—were eligible. These included both studies with, and those without, non-cancer control groups. A control group for studies with a "before and after" design was not required since, in these instances, cancer patients can serve as their own controls. However, control groups can be useful to account for secular trends in care, e.g., improved quality of diabetes care over time due to the introduction of quality measures, that could confound "before and after" effects observed exclusively in exposure groups.

Second, longitudinal cohort studies in which patients with pre-existing diabetes were followed from the time of cancer diagnosis, for diabetes quality of care, were

considered. In this instance, these studies were required to include a non-cancer control group to adjust for potential confounding. Third, longitudinal studies in which patients with diabetes were followed from a specific time point, e.g. three years, after diagnosis of cancer, were eligible. Studies in which cancer patients are followed beginning a number of years after diagnosis often are called survivor studies. In this instance, diabetes had to have been diagnosed before the beginning of the observation period, but not necessarily before the diagnosis of cancer. Also, these studies were required to include a non-cancer control group. A minimum duration of follow-up for any type of longitudinal cohort study was not required.

Finally, cross-sectional studies in which patients with underlying diabetes and cancer were observed for diabetes quality of care during a discrete time interval, e.g., one calendar year, after the diagnoses of diabetes and cancer had been established, were considered. All cross-sectional studies required a non-cancer control group.

Longitudinal cohort and cross-sectional studies were eligible for inclusion if they reported on diabetes quality of care outcomes, including patterns of physician visits and examinations, monitoring and testing, control of clinical or laboratory values, or medication use (diabetes and other related). Studies reporting exclusively on diabetes complications or survival were not eligible for inclusion, since these outcomes were beyond the scope of the PEO question. Access to translation services was not available. Therefore, only English language articles, and only those published between 1996 and the present, as it has been argued that this period constitutes the era of modern diabetes care,[3] were considered for inclusion in the review.

2.2.4 Information Sources

Using an OVID platform, systematic searches of Medline and Embase, from 1996 to the present (9/2016), were conducted to identify studies on the quality of diabetes care in patients diagnosed with cancer. The searches were conducted only in Medline and Embase based on findings from a previous study that showed these two databases are sufficient for identifying English language papers on diabetes epidemiology.[4] In addition, the bibliographies of those articles retrieved for review were searched, and several authors were contacted to request any additional references they might have in their research bibliographies.

2.2.5 Search

The search began by tabulating Medical Subject Headings (MeSH) terms [5] (see Appendix to this chapter) from eight articles [6-13] previously reviewed as part of developing the topic for this thesis, and of preparing the preliminary protocol for the systematic review, and which were known to address the PEO statement for this review. Second, those MeSH terms shared in common across these eight articles, according to the PEO statement for the review, were identified. The patients of interest in this systematic review were those diagnosed with diabetes. However, not all of these articles included "diabetes" or some derivative of "diabetes" as a MeSH term. Therefore, MeSH terms were added for "chronic disease" and "comorbidity" to the search terms for patients. The exposure of interest in this systematic review was cancer. All eight articles included a MeSH term either for "neoplasms" or for "carcinoma." Therefore, these were used to identify the exposure of interest. All eight articles included a MeSH term for "quality," "disease management," or "disease progression." Therefore, these were used to identify

studies reporting outcomes of potential interest for the systematic review. MeSH terms for survival or for other clinical outcomes of diabetes or cancer were not included, as these outcomes were beyond the scope of the review.

A preliminary search based on the strategy above produced in excess of 20,000 articles (see Results for full details) Therefore, in order to narrow the search, the next step was to examine the titles of the original eight articles, and to identify keywords shared in common. (see Appendix to this chapter) "Cancer" was included in the title of all eight articles. "Cormorbid" or "diabetes" or "chronic" was included in the title of 7/8: the exception was Earle et al (2004),[13] which also was the earliest article included in either the preliminary or the full review. Therefore, the search was restricted to those articles with both "cancer" and any of "cormorbid" or "diabetes" or "chronic" in the title.[d] The search terms and Boolean operators used in the final searches are shown in Box 2.1.

[d] Earle et al (2004)[13] also was retained.

Box 2.1: Search Terms and Boolean Operators Used in Final Searches of Medline and Embase

1	exp Neoplasms/
2	exp Carcinoma/
3	exp Diabetes Mellitus, Type 1/ or exp Diabetes Complications/ or exp Diabetes Mellitus, Type 2/ or exp Diabetes Mellitus/
4	exp Chronic Disease/
5	exp Comorbidity/
6	exp Quality Improvement/ or exp "Quality of Health Care"/ or exp Quality Assurance, Health Care/ or exp Quality-Adjusted Life Years/ or exp Quality Indicators, Health Care/ or exp "Quality of Life"/ or exp Total Quality Management/
7	exp Disease Management/
8	exp Disease Progression/
9	1 or 2
10	3 or 4 or 5
11	6 or 7 or 8
12	9 and 10 and 11
13	Humans/
14	exp Adult/
15	12 and 13 and 14
16	Cancer.m_titl.
17	15 and 16
18	Diabetes.m_titl.
19	Comorbid.m_titl.
20	Chronic.m_titl.
21	Surviv.m_titl.
22	18 or 19 or 20 or 21
23	17 and 22
24	limit 23 to English language

2.2.6 Study Selection

Screening studies for selection consisted of reviewing titles and abstracts of all articles obtained through the Medline and Embase searches described above. The following inclusion criteria were used: 1) longitudinal or cross sectional observational study; 2) population consisted of diabetes patients; 3) exposure consisted of cancer of any type; and 4) outcomes consisted of measures of the quality of diabetes care, including health care visits, monitoring and testing, glucose and other control, or use of diabetes and other related medications. Studies that examined the risk of cancer associated with diabetes or the impact of diabetes on cancer outcomes ("patients" and "exposures" reversed relative to the PEO statement) were eliminated from further consideration. Also, articles were eliminated that reported only on quality of life or clinical outcomes, except monitoring and test results. Articles that could not be eliminated based on these criteria were retrieved and reviewed for further examination.

2.2.7 Data Collection Process and Data Items

A structured data collection form was developed to abstract information on the design of each study included in the systematic review, including the overall study design, country of origin, data source(s), patients, study enrolment period, length of follow-up, outcome measures, and methods of adjustment. (See Table 2.1) Also, a structured form was developed for each category of outcomes, consisting of 1) physician visits, exams, or diabetes education (collectively "health care visits"), 2) monitoring and testing, 3) glucose and other control, and 4) medication use and adherence (See Tables 2.5-2.8). Using these forms, each relevant outcome in each study was recorded, including point estimates and 95% confidence intervals (CI). In instances where 95% CIs were not

reported, attempts[e] were made to calculate them using other information reported in the article, including patient counts for proportions and standard deviations/errors for rates and means. Percentages, including reported and calculated 95% CIs, were rounded to the nearest whole unit where this was sufficient to convey differences between groups.

Each outcome result was classified as one of the following: A) "better in cancer than controls," which could be defined as either better after versus before cancer in longitudinal cohort studies of diabetes patients followed from before to after cancer, or as better in cancer patients than controls; or B) no different between cancer patients and controls; or C) worse in cancer patients than controls. Assignment was based on the statistical significance of observed differences in quality measures, either after compared to before diagnosis in single cohorts of cancer patients, or between cancer patients and controls. During tabulation, further classification of these differences according to absolute size or clinical significance was not attempted. However, these considerations were incorporated into the interpretation of the results.

2.2.8 Quality Assessment

The quality of each article was assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies.[14] This scale consists of four items for patient selection, one for comparability of study cases and controls, and three for outcomes. In this instance, the maximum score for a longitudinal cohort study that included a control group, with either matching or statistical adjustment for potential confounding, was eight stars; the

[e] This was not always feasible, for example in instances where sample sizes for calculating specific proportions or standard deviations/errors were not reported.

maximum score for a longitudinal study with a "before and after" design that included only an exposure group, i.e., patients with cancer, was five stars; and the maximum score for a cross-sectional study with a control group was seven stars. (See Tables 2.2 and 2.3 for scoring)

Although a total quality score was assigned to each article, fundamentally, the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies is qualitative, requiring the reviewer(s) to exercise a high degree of discretion, both in tailoring the criteria on which the assessment is based to the specific research questions of the systematic review, and in deciding whether a specific article meets each of the criteria.[14] Therefore, the results of the quality assessment of studies included in this systematic review (see Section 2.3.3) are described keeping in mind the qualitative nature of the Scale itself.

2.2.9 Risk of Bias in Individual Studies

Although there is overlap between measures of quality and bias, the risk of bias was assessed in addition to assessing quality. The risk of bias in individual studies was examined using questions from an item bank developed for the US Agency for Healthcare Research and Quality (AHRQ) to assess the risk of bias and confounding for observational studies of interventions or exposures.[15] For this systematic review, questions from the item bank that the majority of the AHRQ working group convened for this project considered to be very or somewhat important for evaluating the risk of bias were selected and adapted. (Box 2.2)

Box 2.2: Questions Used to Assess the Risk of Bias in Individual Studies

Q1: Were the inclusion/exclusion criteria similar across the comparison groups of the study?
Q2: Were valid and reliable measures, implemented consistently across all study participants, used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?
Q3: Were there reasonable attempts to balance the allocation between the groups or
match groups (e.g., through stratification, matching, propensity scores).
Q4: Were important confounding variables taken into account in the design and/or other statistical adjustment such as instrumental variables)?
Q5: Are results believable taking study limitations into consideration?

2.2.10 Summary Measures

For binary outcomes, summary measures included proportions/percentages with 95% CIs, as well as risk ratios (RR)/odds ratios (OR) with 95% CIs. In instances where they were not reported, attempts were made to calculate the summary measures using other information, e.g., cross tabulations of exposure (cancer/control) by outcome.[16] For binary time-to-event variables, hazard ratios (HR) with 95% CIs were included wherever possible. For continuous variables, summary measures consisted of means and 95% CIs.

2.2.11 Synthesis of Results

Performing a formal synthesis of the findings was considered. However, there was considerable heterogeneity in the design of the studies included in the systematic review, including the types of cohort studies, types of cancers, length of follow-up, and specification of the outcomes variables. Also, in all instances where formal synthesis of findings across studies would have been desirable, only one or, at most, two studies

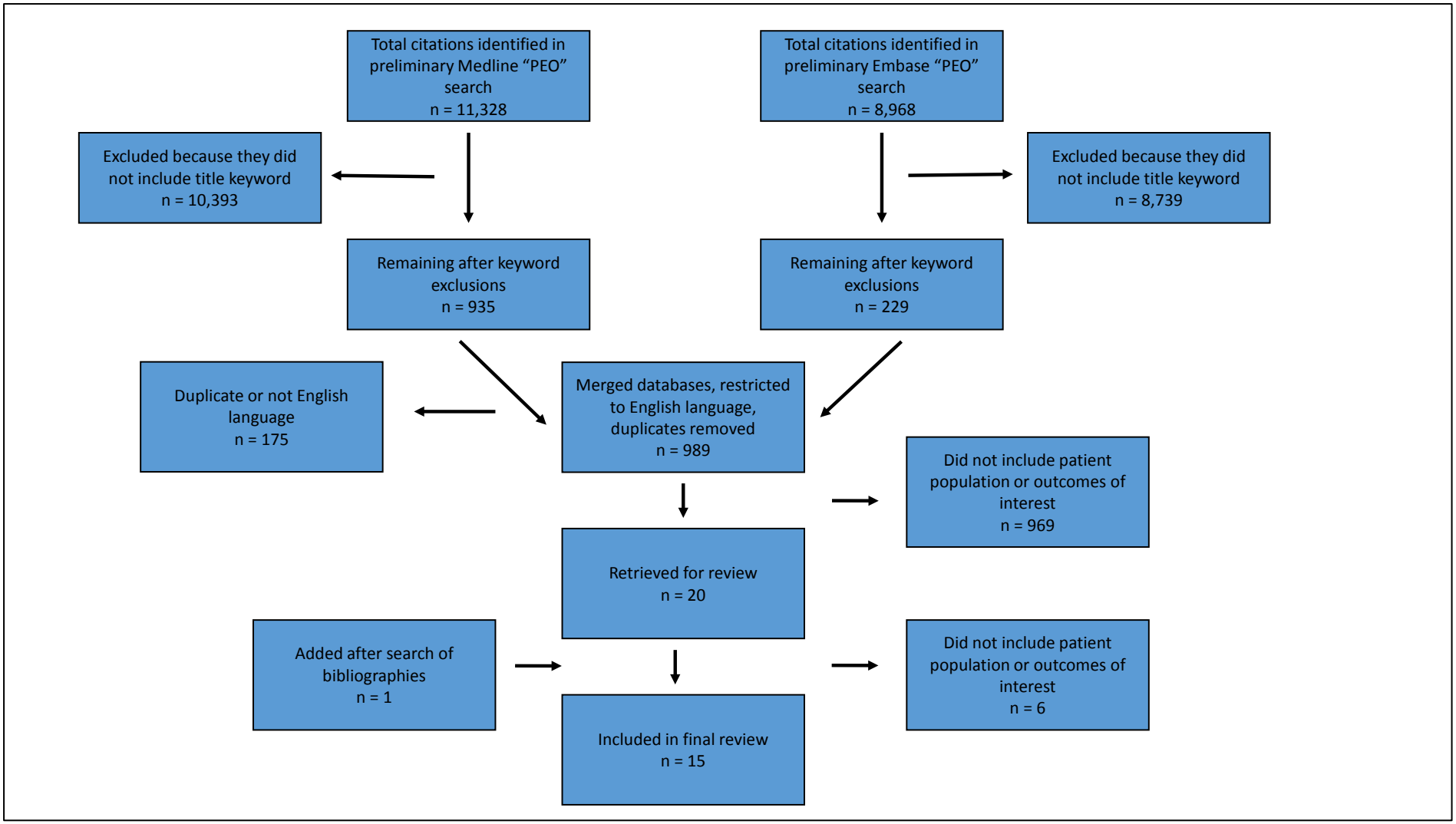
reporting the outcome of interest also reported sufficient information to pool findings across the studies. In many instances, this was due to the fact that diabetes patients comprised only a subset of the patient population, and the authors did not report the sample size for this subset. Therefore, a formal synthesis of the results was not undertaken.

2.3 RESULTS

2.3.1 Study Selection

The preliminary searches in Medline and Embase, which were based on MeSH terms alone, resulted in identifying 11,328 and 8,968 articles respectively. (Figure 2.1) After applying the title keyword exclusion criteria, eliminating duplicates, and excluding non-English language articles, 989 remained for preliminary review, of which 20 were retrieved for full review, and one additional article was identified from a search of the bibliographies. Upon full review six were found not to include either the patient population or an outcome of interest, leaving 15 articles [6-13, 17-23] for inclusion in the systematic review. The final set included all eight articles reviewed in conjunction with researching the topic for this thesis and with developing the preliminary protocol for the systematic review of the thesis, [6-13] plus seven more published after the most recent of the original eight. [17-23]

Figure 2.1: Flowchart of Search Results



2.3.2 Study Characteristics

The characteristics of all 15 articles included in the systematic review are summarized in Table 2.1, in reverse chronological order of publication. There was a substantial amount of heterogeneity among the studies. There were six (40%; 95% CI, 15%-65%) longitudinal cohort studies in which patients with pre-existing diabetes were followed from before to after incident diagnosis of cancer, [8,9,17-20] six (40%; 95% CI, 15%-65%) longitudinal cohort studies in which patients with diabetes were followed only after cancer, [6,7,10,11,13,21] and three (20%; 95% CI, 0%-40%) retrospective cross-sectional studies in which patients with historical diagnoses of diabetes and cancer were assessed for quality of care during a fixed window of time (usually one calendar year) after both diagnoses.[12,22,23] The majority of studies (10/15: 67%; 95% CI, 43%-91%) were from the US, [6-9,11-13,17,18,20] with two from the Netherlands,[19,21] and one each from Australia,[23] Korea,[22] and the UK.[10] The most common types of cancers studied were breast (8/15: 53%; 95% CI, 28%-79%),[6,8,10,11,17,18,20,23] colorectal (5/15: 33%; 95% CI, 9%-57%),[6,8-10,13] and prostate (4/15: 27%; 95% CI, 4%-49%).[6,8,10,23]

Among the longitudinal "before and after" studies,[8,9,17-20] the minimum reported duration of observation prior to cancer was one year, [9,17,18,20] and the maximum was a mean of 3.7 years.[19] The minimum follow-up after cancer was one year,[9] with a maximum of five years.[8] There was considerable variation in the design of longitudinal studies that followed patients only after cancer. One followed patients from cancer diagnosis;[11] others followed patients from a fixed interval of time, e.g., one year, after diagnosis;[6,21] and several followed patients during specific calendar intervals, [7,10,13] with[10] or without pre-specifying a minimum period of time from cancer diagnosis to the

beginning of follow-up. In at least one instance,[7] it was not possible to determine whether diabetes had been diagnosed before cancer. However, in all studies patients had been diagnosed with both diabetes and cancer prior to the beginning of follow-up. All studies except one[7] described one or more approaches to address confounding between cancer cases and non-cancer controls, including matching cases to non-cancer controls as part of patient selection,[6,10,11,13,18,19,21] propensity score matching,[12,14] and multivariate analyses.[22,23]

Table 2.1: Study Characteristics [continued on the following seven pages]

	Study Characteristics						
Author Year Country	**Study Design**	**Data Source**	**Patients**	**Enrolment Period**	**Length of Follow-up**	**Outcomes Measures**	**Methods of Adjustment**
Yang 2016[17] US	Cohort study of diabetes patients who were followed from before to after diagnosis of cancer.	National health care claims (insurance) database.	3,424 women age >18 years, who were diagnosed with early-stage breast cancer (ESBC), and who obtained at least 1 diabetes prescription drug both before and after ESBC treatment. No control group.	First received a diagnosis of ESBC between January 1, 2009 and December 31, 2013.	From 1 year before ESBC diagnosis (index date) through 1.5 years after ESBC diagnosis, with a 6-month washout period after the index date.	Adherence to diabetes medications, defined as a medication possession ratio (MPR) ≥0.8, during the period after as compared to before the index date. MPR was defined as the ratio of the sum of the days' supply for all diabetes medication fills divided by the number of days between the first fill and the last fill plus the days' supply of the last fill.	Since adherence was compared before and after ESBC diagnosis, diabetes patients served as their own controls.

	Study Characteristics						
Author Year Country	**Study Design**	**Data Source**	**Patients**	**Enrolment Period**	**Length of Follow-up**	**Outcomes Measures**	**Methods of Adjustment**
Santorelli 2016[18] US	Cohort study of diabetes patients who were followed from before to after diagnosis of cancer (cases) or an assigned date for non-cancer controls.	Surveillance Epidemiology and End Results (SEER) multi-regional cancer registry data linked to Medicare health care claims.	298 women, age ≥66 years, who were diagnosed with stage I-III breast cancer (BC), survived at least 2 years after BC diagnosis, had a diagnosis of diabetes during the year before BC diagnosis, and filled at least 2 prescriptions for an oral diabetes medication during the year before BC diagnosis. Control group of 1,192 women without cancer who met all the selection and cohort enrolment criteria and were frequency matched to BC patients by age and geographic area of residence at 4:1.	First received a diagnosis of BC (cases) in 2008, or were alive at the end of 2007 (controls).	From 1 year before BC diagnosis (cases) or assigned date (controls) through 2 years after the index date.	Non-adherence to oral diabetes medications, defined as having a proportion of days covered (PDC) <0.8. Sensitivity analysed at PDCs of 0.7 and 0.9. Medication non-persistence defined as being without diabetes medication for ≥26 days.	Comparisons of persistence and adherence between cancer patients and matched controls also adjusted for other factors. Adherence also was compared before and after BC diagnosis (cases) or assigned date (controls), so diabetes patients served as their own controls.
Zanders 2015[19] Netherlands	Cohort study of diabetes patients who were followed from before to after diagnosis of cancer (cases) or an assigned date for non-cancer controls.	Eindhoven Cancer Registry (ECR) linked to the PHARMO (PHARmacoMOrbidity) Database Network.	3,281 incident users of glucose-lowering drugs (GLDs), age >30 years, who were subsequently diagnosed with cancer (excluding non-melanoma skin). 12,891 matched, non-cancer controls.	First received GLDs between January 1, 1998 and December 31, 2011.	From start of GLDs to cancer diagnosis (cases) or assigned date (controls), and after the index date until the end of the data. Mean of 3.7 years before index date and of 6.6 years overall.	Adherence to diabetes medications, using MPR as the indicator.	Comparisons of adherence between cancer patients and matched controls. Adherence also compared before and after cancer diagnosis (cases) or assigned date (controls), so GLD patients served as their own controls.

	Study Characteristics						
Author Year Country	**Study Design**	**Data Source**	**Patients**	**Enrolment Period**	**Length of Follow-up**	**Outcomes Measures**	**Methods of Adjustment**
Calip 2015[20] US	Cohort study of diabetes patients who were followed from before to after diagnosis of BC.	Group Health Cooperative Commonly Used Medications and Breast Cancer Outcomes (COMBO) study.	509 women who were diagnosed with early stage (I, II) invasive BC, and who had ≥1 dispensings of Group Health's first line diabetes medications in the year before cancer diagnosis. No control group.	First received a diagnosis of breast cancer between 1/1990 and 8/2007.	From 1 year before BC diagnosis up to the end of BC treatment plus 3 years.	Adherence to diabetes medications, defined as an MPR ≥0.8, during the period(s) after as compared to before the index date. Discontinuation rate, where discontinuation was defined as a ≥90-day gap between the end of the previous prescription's days' supply and the subsequent dispensing of the next diabetes medication.	Since adherence and persistence were compared before and after BC diagnosis, diabetes patients served as their own controls.
Heins 2015[21] Netherlands	Cohort study of diabetes patients who were followed after diagnosis of cancer (cases) or after an assigned date for non-cancer controls.	NIVEL Primary Care Database.	629 patients, age ≥55, who were diagnosed with non-skin cancer, had at least 2 years of follow-up after cancer diagnosis, and were diagnosed with diabetes before the end of 2 years after cancer diagnosis. Control group of 1,223 patients without cancer who met the other selection and cohort enrolment criteria, matched on age, sex, and practice.	First received a diagnosis of cancer between 1/2002 and 12/2010.	From 2 to 5 years after cancer diagnosis (cases) or assigned date (controls).	Annual general practitioner consultation rates: overall; diabetes; and other.	Comparisons between cancer patients and matched controls.

	Study Characteristics						
Author Year Country	**Study Design**	**Data Source**	**Patients**	**Enrolment Period**	**Length of Follow-up**	**Outcomes Measures**	**Methods of Adjustment**
Shin 2014[22] Korea	Cross-sectional cohort study of diabetes patients who were classified as cancer survivors, non-cancer chronic disease controls, or non-cancer non-chronic disease controls.	2007-2011 Korea National Health and Nutrition Examination Survey (KNHANES).	136 cancer survivors, 1,628 non-cancer chronic disease controls, and 896 non-cancer non-chronic disease controls, all age ≥30 years at diabetes diagnosis and time of survey.	Participated in KNHANES survey between 2007-2011.	Not applicable as this was a cross-sectional study.	Patient awareness of their diabetes status, defined as having been diagnosed with diabetes by a clinician. Diabetes treatment defined as being on pharmacological treatment for diabetes. Adequate glycaemic control defined as HbA1c <7%.	Multivariate comparisons of outcomes among the three groups, adjusting for age, sex, education, and body mass index.
Onitilo 2013[23] Australia	Cross-sectional cohort study of diabetes patients who reported a history of BC or prostate cancer (PC), plus a control group consisting of diabetes patients without a history of cancer.	Patients identified within Australia's National Diabetes Services Scheme and surveyed for additional information, including history of cancer.	158 patients, age ≥18, who reported a history of BC or PC. Control group consisted of 3,308 patients who did not report a history of cancer.	Completed a questionnaire in 2008.	Not applicable as this was a cross-sectional study.	Metformin use (yes/no). Self-reported HbA1c result.	Multivariate comparison of metformin use stratified by type of cancer, adjusted for age and duration of diabetes.

	Study Characteristics						
Author Year Country	**Study Design**	**Data Source**	**Patients**	**Enrolment Period**	**Length of Follow-up**	**Outcomes Measures**	**Methods of Adjustment**
Snyder 2013[6] US	Cohort study of cancer patients and controls with diabetes, who were followed after diagnosis of cancer (cases) or an assigned date for controls.	SEER national cancer registry data linked to Medicare health care claims.	1,984 patients who were diagnosed with loco-regional BC, colorectal cancer (CC), or PC, were age ≥66 years at diagnosis, survived ≥3 years after diagnosis, and were identified as having diabetes within 1 year after diagnosis. 3,769 non-cancer controls who met the other eligibility criteria, were matched on age, race, and SEER region.	Diagnosed with cancer (cases) in 2004, or assigned an index date of January 1, 2004 (controls).	From day 366 through day 1,095 (3 years) after index date.	Visit every 6 months. Eye examination every year. HbA1c or fructosamine every 6 months.	Comparisons between cancer patients and matched controls.
Irizarry 2013[7] US	Cohort study of patients with diabetes and cancer (cases), and a control group of diabetes and no cancer.	Health care claims (insurance) database.	Patients age ≥60 years diagnosed with diabetes and cancer (cases), or diabetes and no cancer (controls). Sample sizes not reported.	Not reported.	Outcomes assessed in 2005-2007.	Diabetes education.	None stated.
Bayliss 2011[8] US	Cohort study of patients with diabetes followed from before to after diagnosis of BC, CC, or PC.	Diabetes registry within a single health maintenance organization.	582 patients diagnosed with diabetes and subsequently diagnosed with BC, CC, or PC. No control group.	Diagnosed with diabetes between 1/1998 and 9/2008, and diagnosed with cancer ≥60 days later.	From prior to, up to 5 years after, cancer diagnosis.	Changes in HbA1c, systolic blood pressure (SBP), and LDL cholesterol over 6 periods from before to after cancer diagnosis.	Since HbA1c, SBP, and LDL cholesterol were compared before and after cancer diagnosis, diabetes patients served as their own controls.

	Study Characteristics						
Author Year Country	**Study Design**	**Data Source**	**Patients**	**Enrolment Period**	**Length of Follow-up**	**Outcomes Measures**	**Methods of Adjustment**
Chiao 2010[9] US	Cohort study of patients with diabetes followed from before to after diagnosis of CC.	Electronic medical records at a single medical center.	122 patients diagnosed with diabetes and subsequently diagnosed with CC. No control group.	Diagnosed with cancer between 1/1999 and 12/2006.	From 1 year before, up to 1 year after, cancer diagnosis.	Changes in HbA1c, blood pressure, and cholesterol. Changes in primary care clinic and eye clinic visits. Changes in blood pressure, HbA1c, and cholesterol checks. All from 1 year before to 1 year after cancer diagnosis.	Since measures were compared before and after CC diagnosis, diabetes patients served as their own controls.
Khan 2010[10] UK	Cohort study of patients with diabetes who were followed beginning ≥5 years after diagnosis of BC, CC, or PC, and a control group of patients with diabetes but no cancer.	General Practice Research Datalink.	673 patients, age ≥30 years, with diabetes, who survived at least 5 years after diagnosis of BC, CC, or PC. 673 non-cancer controls meeting other eligibility criteria and matched to cancer patients on age, sex, and primary practice.	Entry in to the analysis from September 1, 2003 to August 30, 2006.	From the latter of 5 years after cancer diagnosis or September 1, 2003, to up to August 31, 2006.	Blood pressure, cholesterol, and HbA1c monitoring. Adequate control of blood pressure, cholesterol, and diabetes.	Comparisons between cancer patients and matched controls, with additional covariates included in multivariate analyses.

	Study Characteristics						
Author Year Country	**Study Design**	**Data Source**	**Patients**	**Enrolment Period**	**Length of Follow-up**	**Outcomes Measures**	**Methods of Adjustment**
Hanchate 2010[11] US	Cohort study of patients with diabetes who were followed after diagnosis of cancer, and a control group of patients with diabetes but no cancer	Pathology reports and tumor registry data linked to health care claims (insurance).	Subset of 422 patients, age ≥65 years, who were newly diagnosed with stage I-IIIA BC, who also had diabetes prior to cancer diagnosis. Control group comprised of a subset of 1,656 non-cancer controls meeting other eligibility criteria and matched to cancer patients on age, race, and location. Exact Ns for the diabetes subset not given.	1997-1999.	Five years after cancer diagnosis or matched index date (controls).	Biennial lipid test, annual HbA1c test, biennial eye exam.	Comparisons between cancer patients and matched controls, with additional covariates included in multivariate analyses (latter not reported in paper).
Keating 2007[12] US	Cross-sectional study of patients diagnosed with diabetes and cancer, and a control group of patients with diabetes but no cancer.	Clinical and administrative data from a large integrated health system.	5,773 patients, age ≥21 years, who were diagnosed with diabetes by December 31, 2002, were alive through the end of 2003, and were diagnosed with invasive cancer during 1994 through 2001. Control group comprised of 23,092 non-cancer patients who met the other eligibility criteria. Propensity-matched cohort consisted of a subset of these.	1994-2002 was the period used to establish both diabetes and cancer.	Outcomes assessed in 2003.	HbA1c test in past 6 months, most recent HbA1c <8.0%, LDL cholesterol test in past year, most recent LDL cholesterol <100 mg/dL, microalbumin test in past year, dilated retinal exam, most recent blood pressure <103/80 mm Hg for patients with hypertension, use of ACE I/ARB for patients with hypertension, use of statin for patients with elevated LDL cholesterol.	Comparisons between cancer patients and controls in propensity-matched subset.

	Study Characteristics						
Author Year Country	**Study Design**	**Data Source**	**Patients**	**Enrolment Period**	**Length of Follow-up**	**Outcomes Measures**	**Methods of Adjustment**
Earle 2004[13] US	Cohort study of patients diagnosed with diabetes and cancer, and a control group of patients with diabetes but no cancer.	SEER national cancer registry data linked to Medicare health care claims.	Subset of 14,884 patients, age ≥65, who were diagnosed with invasive CC in 1991 or 1992, who survived through the end of 1998, and who also had a diagnosis of diabetes before the beginning of the observation period (1997-1998). Control group comprised of a subset of 16,659 matched, non-cancer patients meeting the same eligibility criteria as the cancer patients. Control group matched on age, sex, race, and geographic location.	1991-1996 (interpreted as end of qualification for diabetes subset).	Outcomes assessed in 1997-1998.	Visit every 6 months. Eye examination every year. HbA1c or fructosamine every 6 months.	Comparisons between cancer patients and matched controls.

2.3.3 Study Quality

Overall, the quality of the 15 studies, which was assessed using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies,[14] was high. (Tables 2.2 and 2.3) The main limitation was that studies were not necessarily representative of the national population of cancer patients, according to types of cancers included, patient age, and/or geographic representation. (Item 1 under Selection in the Scale) For example, most studies included some combination of breast, [6,8,10,11,17,18,20,23] colorectal, [6,8-10,13] and prostate cancer patients, [6,8,10,23] but did not include other types of solid tumours, e.g. lung cancer, or haematological malignancies. Also, the majority of studies were from the US, [6-9,11-13,17,18,20] and most of these did not include populations that were nationally representative of patients with those types of cancers. For instance, the studies based on the US SEER-Medicare national cancer registry linked to medical insurance claims excluded patients age less than 65 years old.[6,13,18]

Table 2.2: Quality Scoring of Longitudinal Cohort Studies with a Control Group (Maximum Score of Eight Stars)

	Study							
	Santorelli 2016[18]	**Zanders 2015[19]**	**Heins 2015[21]**	**Snyder 2013[6]**	**Irizarry 2013[7]**	**Khan 2010[10]**	**Hanchate 2010[11]**	**Earle 2004[13]**
Newcastle-Ottawa Criteria								
Representativeness of the exposed cohort		*	*					
Selection of the non-exposed cohort	*	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*	*
Comparability of cohorts								
Study controls for age	*	*	*	*		*	*	*
Study controls for additional factors	*	*	*	*		*	*	*
Assessment of outcome	*	*	*	*	*	*	*	*
Follow-up long enough for outcomes to occur	*	*	*	*	*	*	*	*
Adequacy of follow-up of cohorts	*	*	*	*	*	*	*	*
Total Score	**7/8**	**8/8**	**8/8**	**7/8**	**5/8**	**7/8**	**7/8**	**7/8**

Table 2.3: Quality Scoring of Longitudinal Studies without a Control Group (Maximum Score of Five or Seven Stars†)

	Study						
	Yang 2016[17]	**Calip 2015[20]**	**Shin 2014[22]**	**Onitilo 2013[23]**	**Bayliss 2010[8]**	**Chiao 2010[9]**	**Keating 2007[12]**
Newcastle-Ottawa Criteria							
Representativeness of the exposed cohort							
Selection of the non-exposed cohort	NA	NA	*	*	NA	NA	*
Ascertainment of exposure	*	*	*	*	*	*	*
Comparability of cohorts							
Study controls for age	NA	NA	*	*	NA	NA	*
Study controls for additional factors	NA	NA		*	NA	NA	*
Assessment of outcome	*	*	*	*	*	*	*
Follow-up long enough for outcomes to occur	*	*	*	*	*	*	*
Adequacy of follow-up of cohorts	*	*	NA	NA	*	*	NA
Total Score	**4/5**	**4/5**	**5/7**	**6/7**	**4/5**	**4/5**	**6/7**

†Either longitudinal cohort studies with a pre- post- design (maximum five stars) or cross-sectional (maximum seven stars) studies

NA – not applicable, study was "before and after" and did not include a control group.

2.3.4 Risk of Bias within Studies

The results of the analysis of bias within individual studies (Table 2.4) were consistent with the quality analyses. All but one study[7] met all the applicable criteria for minimizing the risk of bias. Irizarry at al.[7] did not report methods for balancing the allocation between the cancer and non-cancer control groups, or other methods to control for confounding. Nevertheless, this study was included since it reported only one outcome of interest—diabetes education—with very low rates of adherence in both cancer cases and controls, and no difference between the two groups.

Table 2.4: Risk of Bias Within Studies [continued on the following page]

	Study						
Criteria	**Yang 2016[17]**	**Santorelli 2016[18]**	**Zanders 2015[19]**	**Calip 2015[20]**	**Heins 2015[21]**	**Shin 2014[22]**	**Onitilo 2013[23]**
Q1: Were the inclusion/exclusion criteria similar across the comparison groups of the study?	NA	*	*	NA	*	*	*
Q2: Were valid and reliable measures, implemented consistently across all study participants, used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?	*	*	*	*	*	*	*
Q3: Were there reasonable attempts to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores)?	NA	*	*	NA	*	*	*
Q4: Were important confounding variables taken into account in the design and/or other statistical adjustment such as instrumental variables?	NA	*	*	NA	*	*	*
Q5: Are the results believable taking study limitations into consideration?	*	*	*	*	*	*	*

Criterion	Study							
	Snyder 2013[6]	Irizarry 2013[7]	Bayliss 2010[8]	Chiao 2010[9]	Khan 2010[10]	Hanchate 2010[11]	Keating 2007[12]	Earle 2004[13]
Q1: Were the inclusion/exclusion criteria similar across the comparison groups of the study?	*	*	NA	NA	*	*	*	*
Q2: Were valid and reliable measures, implemented consistently across all study participants, used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?	*	*	*	*	*	*	*	*
Q3: Were there reasonable attempts to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores)?	*		NA	NA	*	*	*	*
Q4: Were important confounding variables taken into account in the design and/or other statistical adjustment such as instrumental variables)?	*		NA	NA	*	*	*	*
Q5: Are the results believable taking study limitations into consideration?	*	*	*	*	*	*	*	*

NA – not applicable, study was "before and after" and did not include a control group.

2.3.5 Results of Individual Studies

Measures of the quality of diabetes care in the 15 studies consisted of health care visits (6/15 studies: 40%; 95% CI, 15%-65%), [6,7,9,11,13,21] monitoring/testing (6/15 studies: 40%; 95% CI, 15%-65%), [6,9-13] glycaemic/other control (6/15 studies: 40%; 95% CI, 15%-65%), [8-11,20,22] and medication use (7/15 studies: 47%; 95% CI, 21%-72%).[12,17-20,22,23] (Tables 2.5-2.8, respectively)

2.3.5.1 Health Care Visits

Six studies reported on health care visits (Table 2.5): five from the US [6,7,9,11,13] and one from the Netherlands.[21] Outcome measures consisted primarily of the rates/proportions of general practitioner/other visits [6,9,13] and eye exams (which also can be considered a process or quality measure), [6,9,11,13] with one study reporting on diabetes education.[7] In most instances, observed differences between cancer patients and controls were small and not statistically significant (Table 2.5, centre column), and even the differences between cancer patients and controls that were statistically significant (Table 2.5, left or right-hand columns: showing either higher or lower quality of care in cancer patients) were relatively small. For instance, Snyder et al. [6] found a statistically significantly higher proportion of cancer patients (overall) than controls had a physician visit every six months. However, the absolute difference was only 5% (86% cancer compared to 81% controls). Earle et al. [13] found a statistically significantly lower proportion of colorectal cancer patients than controls had an eye exam every year. However, the absolute difference was only -3% (27% cancer compared to 30% controls).

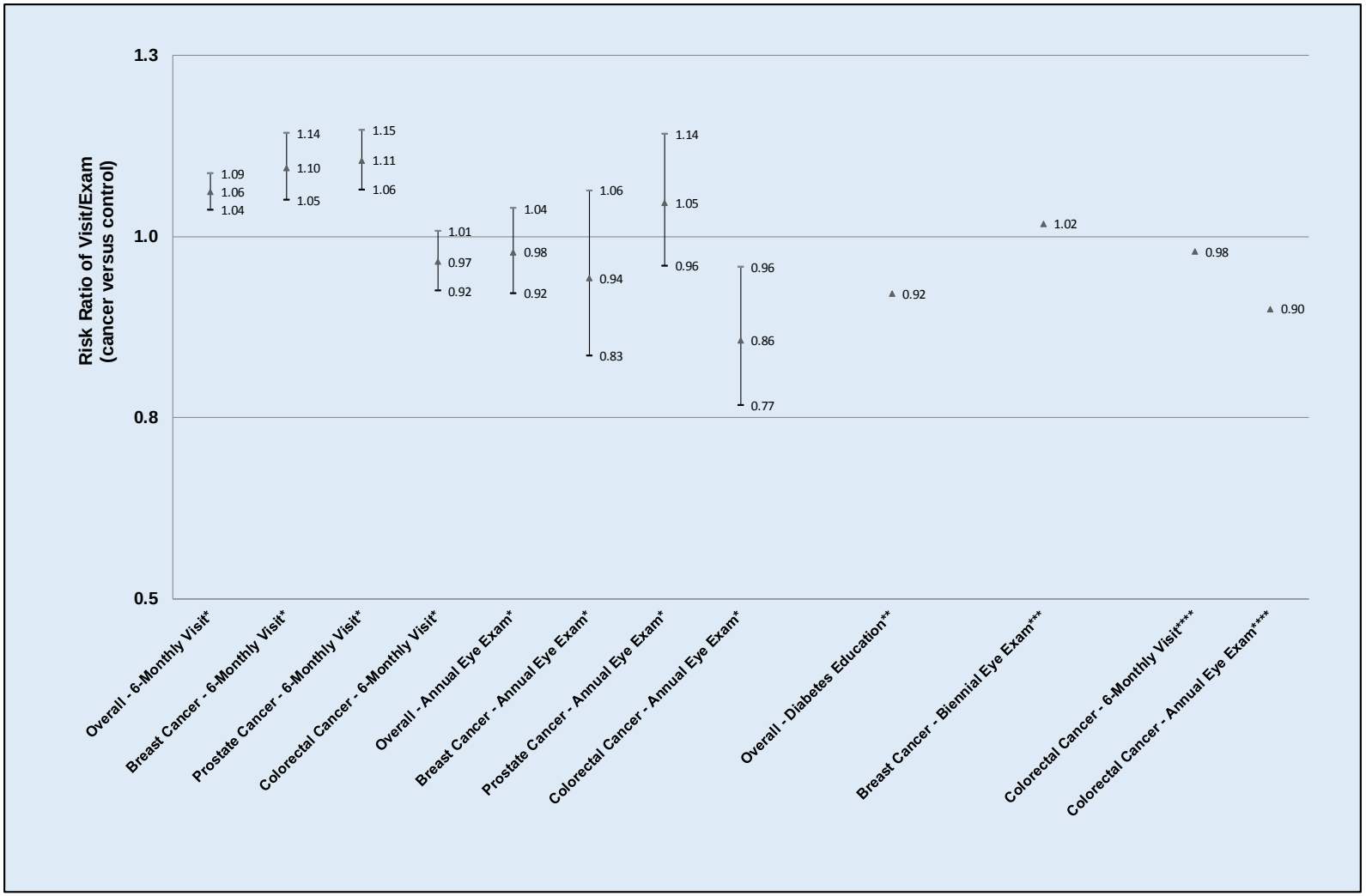
Risk Ratios (cancer versus control) were calculated for outcomes from four studies [6,7,11,13] that compared the proportions of cancer patients and controls with health care visits, (Figure 2.2) regardless of whether[6] or not [7,11,13] there was sufficient information to calculate the CIs. As shown, there was a narrow distribution of RRs around 1.0, indicating that, in the majority of instances, the proportions of cancer patients and non-cancer controls with a visit/exam were quite similar, even though several RRs were statistically significantly different from 1.0 (Figure 2.2). Plots of the rates per patient per year (PPPY) of cancer patients with a visit/exam before compared to after cancer diagnosis illustrate that, for the most part, within-patient changes also were small (Figure 2.3).

Table 2.5: Health Care Visits [continued on the following page]

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Heins 2015[21]	Cancer patients had more general practitioner CONTACTS FOR ANY REASON per year than controls (cancer, mean 11.9; 95% Confidence Interval (CI) 10.9-12.9 *versus* control, mean 10.0; 95% CI, 9.5-10.5). Cancer Patients had more general practitioner CONTACTS FOR CONDITIONS OTHER THAN DIABETES per year than controls (cancer, mean 8.3; 95% CI, 7.6-9.0 versus control, mean 7.1; 95% CI, 6.7-7.5).	There was no difference in the number of general practitioner CONTACTS FOR DIABETES per year between cancer patients and controls (cancer, mean 2.7; 95% CI, 2.4-3.0 *versus* control, mean 2.9; 95% CI, 2.7-3.1).	
Snyder 2013[6]	Overall a higher percent of cancer patients than controls had a 6-MONTHLY VISIT (cancer, 86%; 95% CI, 84%-88% *versus* control, 81%; 95% CI, 80%-82%) A higher percent of breast cancer (BC) patients than controls had a 6-MONTHLY VISIT (cancer, 92%; 95% CI, 89%-95% *versus* control, 84%; 95% CI, 81%-87%) A higher percent of prostate cancer (PC) patients than controls had a 6-MONTHLY VISIT (cancer, 84%; 95% CI, 82%-86% *versus* control, 76%; 95% CI, 74%-78%).	There was no difference between the percent of colorectal cancer (CC) patients and controls who had a 6-MONTHLY VISIT (cancer, 83%; 95% CI, 80%-86% *versus* control, 86%; 95% CI, 84%-88%). Overall, there was no difference between the percent of cancer patients and controls who had an ANNUAL EYE EXAM (cancer, 45%; 95% CI, 43%-47% *versus* control, 46%; 95% CI, 44%-48%). There was no difference between the percent of BC patients and controls who had an ANNUAL EYE EXAM (cancer, 49%; 95% CI, 44%-54% *versus* control, 52%; 95% CI, 48%-56%). There was no difference between the percent of PC patients and controls who had an ANNUAL EYE EXAM (cancer, 45%; 95% CI, 42%-48% *versus control,* 43%; 95% CI, 41%-45%).	A lower percent of CC patients than controls had an ANNUAL EYE EXAM (cancer, 42%; 95% CI, 38%-46% *versus* control, 49%; 95% CI, 46%-52%).

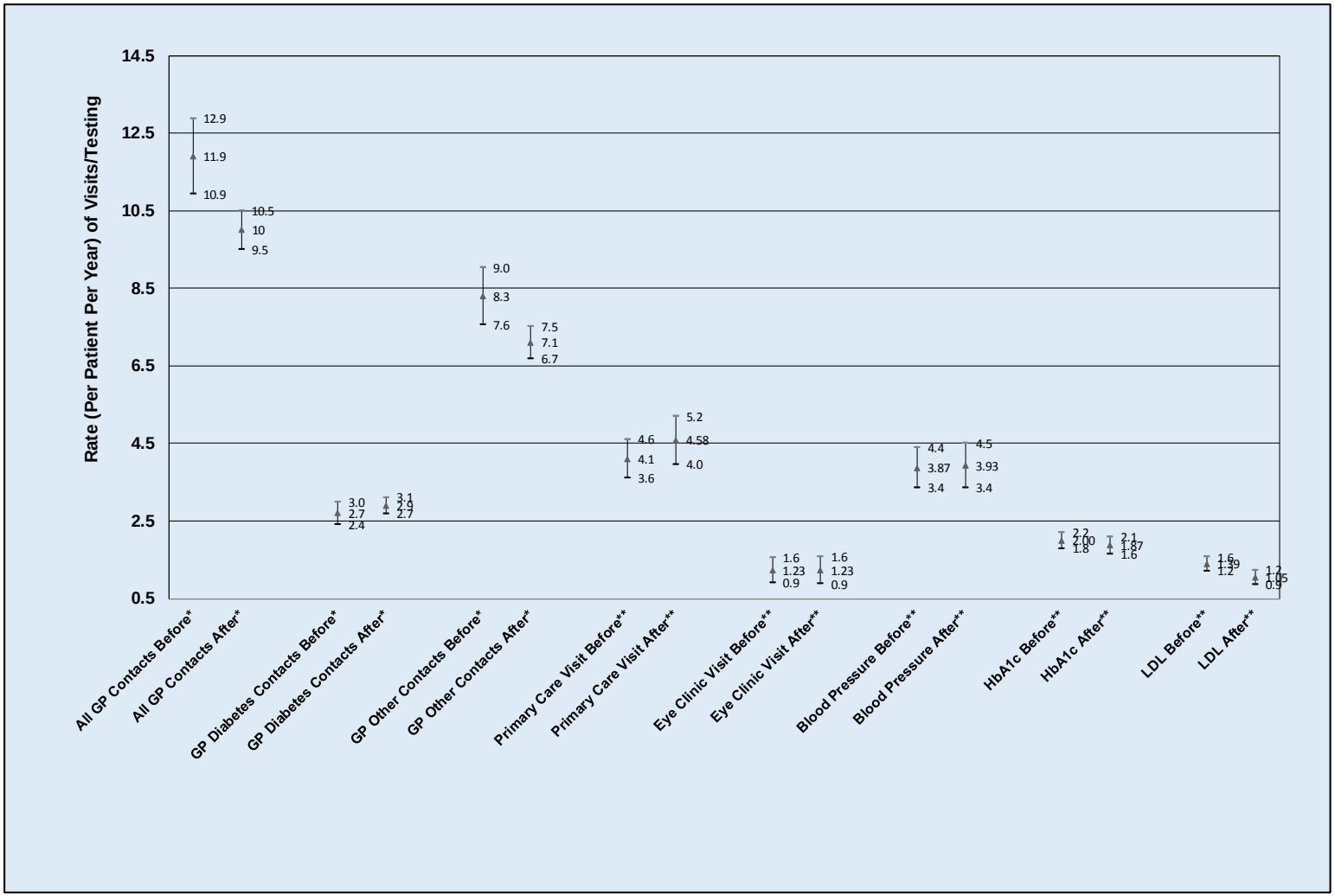
Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Irizarry 2013[7]		There was no difference between the percent of cancer patients and controls receiving DIABETES EDUCATION (cancer, 3.5% versus control, 3.8% [*insufficient data to calculate CIs]*).	
Chiao 2010[9]		There was no difference between the rate (per patient) of PRIMARY CARE VISITS per year before and after CC diagnosis (mean before, 4.1; 95% CI, 3.6-4.6 *versus* mean after, 4.6; 95% CI, 4.0-5.2). There was no difference between the rate (per patient) of EYE CLINIC VISITS per year before and after CC diagnosis (mean before, 1.2; 95% CI, 0.9-1.6 *versus* mean after, 1.2; 95% CI, 0.9-1.6).	
Hanchate 2010[11]		There was no difference between the percent of cancer patients and controls receiving a BIENNIAL EYE EXAM (cancer, 58% *versus* control, 57% *[insufficient data to calculate CIs*]).	
Earle 2004[13]			A lower percent of CC patients than controls had a 6-MONTHLY VISIT (cancer, 93%; *versus* control 95% *[insufficient data to calculate CIs*]). A lower percent of CC patients than controls had an ANNUAL EYE EXAM (cancer 27% *versus* control, 30% *[insufficient data to calculate CIs*]).

Figure 2.2: Risk Ratios for Health Care Visits



*Snyder, 2013; **Irizarry, 2013; ***Hanchate, 2010; ****Earle, 2004. Triangles are point estimates. Bars are 95% Confidence Intervals.

Figure 2.3: Rates of Cancer Patients with a Health Care Visit or Monitoring, Before Versus After Cancer



*Heins, 2015; **Chiao, 2010. Triangles are point estimates. Bars are 95% Confidence Intervals.

2.3.5.2 Monitoring and Testing

Six studies reported on patterns of monitoring and testing in diabetes patients diagnosed with cancer (Table 2.6): five from the US [6,9,11-13] and one from the UK.[10] Monitoring and testing consisted of blood pressure checks, [9,10] cholesterol testing, [9-12] and HbA1c/fructosamine testing. [6,9-13] Several studies reported a mixture of non-statistically significant differences between cancer patients and controls and statistically significantly lower rates of monitoring/testing in cancer patients than controls. However, as with patterns of health care visits, even statistically significant differences (Table 2.6, left or right-hand columns: showing either higher or lower quality of care in cancer patients) were relatively small. For example, Khan at al. [10] compared patterns of blood pressure monitoring, cholesterol testing, and HbA1c testing in long-term survivors of breast, colorectal, or prostate cancer to matched controls in the UK. Of nine comparisons made (three types of cancers and three types of monitoring/testing), they found three instances in which cancer patients and controls were equally likely to receive monitoring/testing, and six in which cancer patients were statistically significantly less likely than controls to receive monitoring/testing. However, even statistically significant differences were small, e.g. 84% (95% CI, 80%-88%) of breast cancer patients received cholesterol testing compared to 91% (95% CI, 87%-94%) of controls (absolute difference of 7%). Only one study [12] found statistically significantly higher monitoring/testing in cancer patients than controls. However, as with Khan and other studies, absolute differences were small (2%-4%).

Risk ratios (cancer versus control) were calculated based on data from five[6,10-13] studies that compared proportions of cancer patients and controls with monitoring/testing,

(Figure 2.4) regardless of whether[6,10] or not [11-13] there was sufficient information to calculate CIs for the RRs. As with visits/exams, there was a narrow distribution of RRs around 1.0, indicating that the proportions of cancer patients and controls receiving testing were quite similar. Calculated RRs were statistically significantly less than 1.0 in all instances where the study authors also had reported that the proportion of cancer patients meeting the outcome measure was statistically significantly lower than the controls. Plots of the per-patient-per-year (PPPY) rates of cancer patients with monitoring/testing, before compared to after cancer diagnosis, illustrate that, for the most part, changes were small (Figure 2.3).

Table 2.6: Monitoring and Testing [continued on the following two pages]

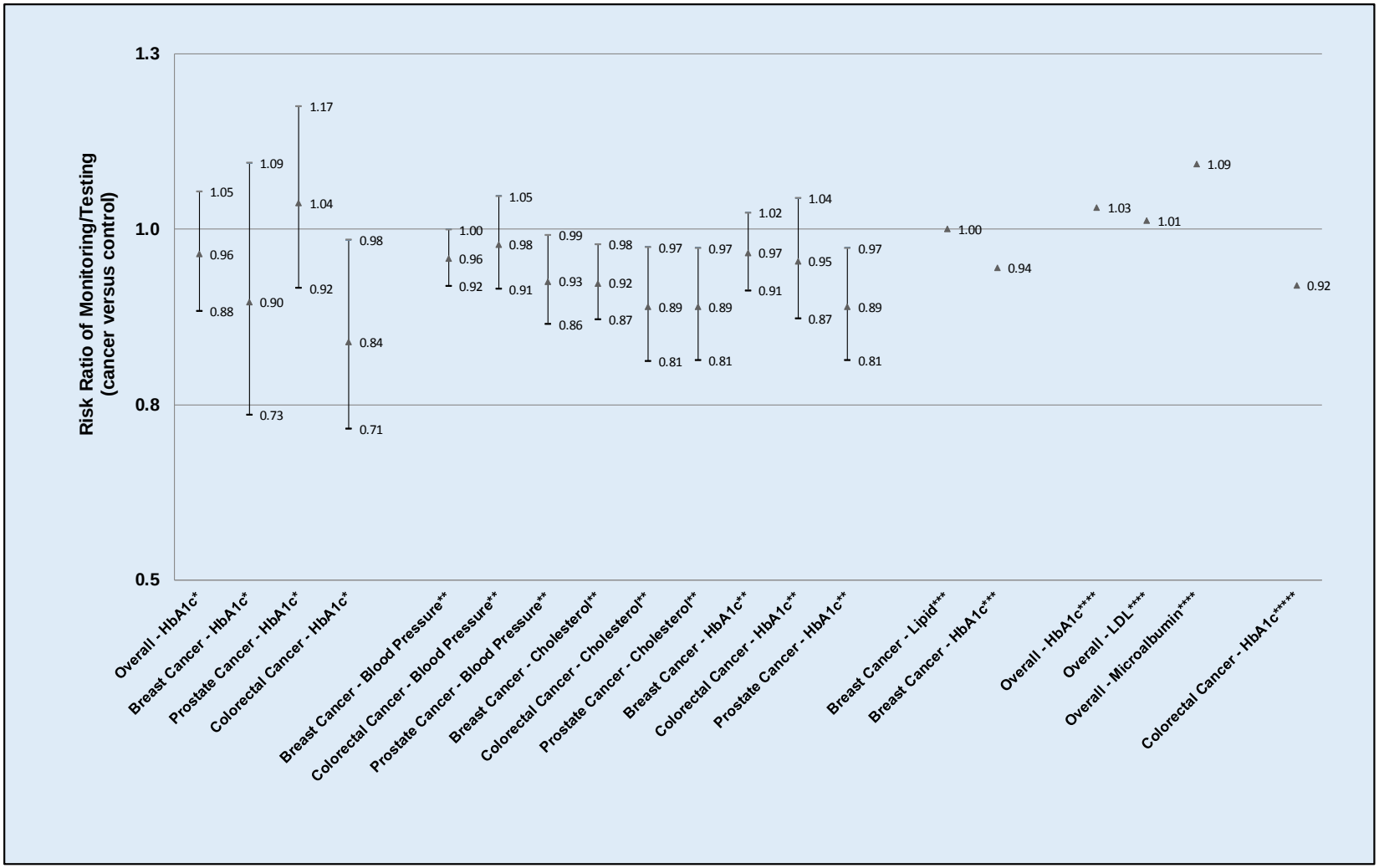
Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Snyder 2013[6]		Overall, there was no difference between the percent of cancer patients and controls who had a 6-MONTHLY TEST FOR glycosylated haemoglobin (HbA1c) OR FRUCTOSAMINE (cancer, 27%; 95% confidence interval [CI], 25%-29% *versus* control, 28%; 95% CI, 27%-29%). There was no difference between the percent of breast cancer (BC) patients and controls who had a 6-MONTHLY TEST FOR HbA1c OR FRUCTOSAMINE (cancer, 26%; 95% CI, 22%-30% *versus* control, 29%; 95% CI, 26%-32%). There was no difference between the percent of prostate cancer (PC) patients and controls who had a 6-MONTHLY TEST FOR HbA1c OR FRUCTOSAMINE (cancer, 28%; 95% CI, 25%-31% *versus* control, 27%; 95% CI, 25%-29%).	A lower percent of colorectal cancer (CC) patients than controls had a 6-MONTHLY TEST FOR HbA1c OR FRUCTOSAMINE (cancer, 26%; 95% CI, 23%-29% *versus control,* 31%; 95% CI, 28%-34%).*
Chiao 2010[9]		There was no difference in the rates (per patient per year) of BLOOD PRESSURE CHECKS before compared to after CC diagnosis (mean before, 3.9; 95% CI, 3.4-4.4 *versus* mean after, 3.9; 95% CI, 3.4-4.5). There was no difference in the rates (per patient per year) of HbA1c CHECKS before compared to after CC diagnosis (mean before, 2.0; 95% CI, 1.8-2.2 *versus* mean after, 1.9; 95% CI, 1.6-2.1).	The rate of LOW DENSITY LIPOPROTEIN (LDL) CHECKS (per patient per year) was higher before compared to after CC diagnosis (mean before, 1.4; 95% CI, 1.2-1.6 *versus* mean after, 1.1; 95% CI, 0.9-1.2).

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Khan 2010[10]		There was no difference between the percent of CC patients and controls who had a BLOOD PRESSURE MONITORING TEST OVER 3 YEARS (cancer, 90%; 95% CI, 84%-94% *versus* control, 92%; 95% CI, 87%-96%). There was no difference between the percent of BC patients and controls who had an HbA1c TEST OVER 3 YEARS (cancer, 86%; 95% CI, 82%-90% *versus* control, 89%; 85%-92%). There was no difference between the percent of CC patients and controls who had an HbA1c TEST OVER 3 YEARS (cancer, 83%; 95% CI, 77%-89% *versus* control, 87%; 81%-92%). In sensitivity analyses in which all patients who died were excluded, there were no differences between cancer patients and controls for any type of monitoring/testing.	A lower percent of BC patients than controls received a BLOOD PRESSURE MONITORING TEST OVER 3 YEARS (cancer, 91%; 95% CI, 87%-94% *versus* control, 95%; 95% CI, 92%-97%).* A lower percent of PC patients than controls received a BLOOD PRESSURE MONITORING TEST OVER 3 YEARS (cancer, 87%; 95% CI, 81-91% *versus* control, 94%; 95% CI, 90%-97%).* A lower percent of BC patients than controls received a CHOLESTEROL MONITORING TEST OVER 3 YEARS (cancer, 84%; 95% CI, 80-88% *versus* control, 91%; 95% CI, 87%-94%).* A lower percent of CC patients than controls received a CHOLESTEROL MONITORING TEST OVER 3 YEARS (cancer, 80%; 95% CI, 73-85% *versus* control, 90%; 95% CI, 84%-94%).* A lower percent of PC patients than controls received a CHOLESTEROL MONITORING TEST OVER 3 YEARS (cancer, 80%; 95% CI, 73%-85% *versus* control, 90%; 95% CI, 84%-94%).* A lower percent of PC patients than controls received an HbA1c MONITORING TEST OVER 3 YEARS (cancer, 80%; 95% CI, 74%-86% *versus* control, 90%; 85%-94%).*

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Hanchate 2010[11]		There was no difference between the percent of BC patients and controls who received a BIENNIAL LIPID TEST (cancer, 61% *versus* control, 61% [*insufficient data to calculate CIs*]). There was no difference between the percent of BC patients and controls who received an ANNUAL HbA1c TEST (cancer, 34% *versus* control, 36% [*insufficient data to calculate CIs*]).	
Keating 2007[12]	A higher percent of cancer patients than controls had an HbA1c TEST IN THE PAST 6 MONTHS (cancer, 66% *versus* control, 64% [*insufficient data to calculate CIs*]). A higher percent of cancer patients than controls had a MICROALBUMIN TEST IN THE PAST YEAR (cancer, 59% *versus control,* 55% [*insufficient data to calculate CIs*]).	There was no difference between the percent of cancer patients and controls who received a LDL CHOLESTEROL TEST IN THE PAST YEAR (cancer, 85% *versus* control, 84% [*insufficient data to calculate CIs*]).	
Earle 2004[13]		There was no difference between the percent of cancer patients and controls with a 6-MONTHLY HbA1c OR FRUCTOSAMINE TEST (cancer, 24 *versus* control, 26% [*insufficient data to calculate CIs*]).	

*Authors reported these differences as statistically significant at $p < 0.05$. In the table, the calculated 95% confidence intervals for the proportions overlap. However, the corresponding risk ratios calculated and reported in Figure 2.4 were all statistically significantly less than 1.0. Therefore, it is likely that the authors assessed the statistical significance of differences between cancer patients and controls using the risk ratio approach.

Figure 2.4: Calculated Risk Ratios for Monitoring and Testing



*Snyder, 2013; **Khan, 2010; ***Hanchate, 2010; ****Keating, 2007; *****Earle, 2004. HbA1c, Glycosylated haemoglobin. LDL, Low density lipoprotein.

2.3.5.3 Control of Blood Pressure, Cholesterol, and HbA1c

Six studies [8-10,12,20,22] reported monitoring or test results (Table 2.7) to assess control of blood pressure, [8-10,12] cholesterol, [8-10,12] and HbA1c. [8-10,12,20,22] As with other measures reported above, evidence that cancer had an adverse impact on blood pressure, cholesterol, and HbA1c control was inconsistent across cancer types and measures, both within and across the six studies. For example, Khan at al.[10] compared blood pressure, cholesterol, and HbA1c control in long-term survivors of breast, colorectal, or prostate cancer to matched controls in the UK. They found no differences in blood pressure control between cancer patients and controls in any of the three cancer cohorts, lower total cholesterol control in prostate cancer patients (but not in breast or colorectal cancer), and lower HbA1c control in colorectal cancer patients (but not in breast or prostate). Calip et al. [20] compared HBA1c control before to after breast cancer diagnosis. They found HbA1c was statistically significantly higher during three of four periods after cancer compared to before cancer diagnosis. However, these differences were small, and their clinical significance may be questionable. In contrast, Calip et al. [20] found no differences in the proportions of patients with HbA1c >8% after, compared to before, cancer diagnosis. Therefore, overall, the weight of evidence suggests cancer had little, if any, clinically meaningful impact on blood pressure, cholesterol, or HbA1c control, either around the time of cancer diagnosis or in long-term survivors.

Risk ratios (cancer versus control) were calculated based on data from two studies[10,12] that compared proportions of cancer patients and controls with adequate control of blood pressure, cholesterol, and HbA1c, (Figure 2.5) regardless of whether[10] or not[12]

there was sufficient information to calculate CIs. As with quality measures reported above, there was a narrow distribution of RRs around 1.0, indicating that the proportions of cancer patients and controls with adequate control were quite similar. Risk ratios were statistically significantly less than 1.0 in all instances where the study authors also had reported that the proportion of cancer patients meeting the outcome measure was statistically significantly lower than the controls.

Table 2.7: Control of Blood Pressure, Cholesterol, and HbA1c [continued on the following four pages]

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Calip 2015[20]		Among patients with a medication possession ratio (MPR) <80, relative to the year before breast cancer diagnosis (glycosylated haemoglobin [HbA1c], 7.32: 95% Confidence Interval [CI], 7.01-7.63), HbA1c was similar in each of four periods after cancer diagnosis: treatment period (HbA1c=7.46: 95% CI, 7.30-7.60); year +1 (HbA1c=7.52: 95% CI, 7.36-7.68); year +2 (HbA1c=7.53: 95% CI, 7.37-7.69); and year +3 (HbA1c=7.42: 95% CI, 7.28-7.56).	Overall, relative to the year before BC diagnosis (HbA1c [%], 6.96: 95% CI, 6.80-7.12), HbA1c was higher in each of four periods after cancer diagnosis: treatment period (HbA1c=7.32: 95% CI, 7.18-7.46); year +1 (HbA1c=7.41: 95% CI, 7.27-7.55); year +2 (HbA1c=7.42: 95% CI, 7.28-7.56); and year +3 (HbA1c=7.30: 95% CI, 7.17-7.43).
		Overall, relative to the year before breast cancer (BC) diagnosis (percent with HbA1c >8%=17.8%), the percent of patients with HbA1c >8% was not different in any of the four periods after cancer diagnosis.	Among patients with a MPR ≥80, relative to the year before BC diagnosis (HbA1c=6.45: 95% CI, 6.35-6.55), HbA1c was higher in each of four periods after cancer diagnosis: treatment period (HbA1c=6.83: 95% CI, 6.67-6.99); year +1 (HbA1c=6.90: 95% CI, 6.75-7.05); year +2 (HbA1c=6.96: 95% CI, 6.79-7.13); and year +3 (HbA1c=6.96: 95% CI, 6.80-7.12).
		Among patients with a MPR ≥80, relative to the year before BC diagnosis (percent with HbA1c >7%=34.7%), the percent of patients with HbA1c >7% was not different in any of the four periods after cancer diagnosis.	Overall, relative to the year before BC diagnosis (percent with HbA1c >7%=34.9%), the percent of patients with HbA1c >7% was higher during year +1, year +2, and year +3, but not during the treatment period.
		Among patients with a MPR ≥80, relative to the year before BC diagnosis (percent with HbA1c >8%=16.0%), the percent of patients with HbA1c >8% was not different in any of the four periods after cancer diagnosis.	Among patients with a MPR <80, relative to the year before BC diagnosis (percent with HbA1c >7%=35.5%), the percent of patients with HbA1c >7% was higher in 2 of the 4 periods after cancer diagnosis.

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Calip 2015[20] continued		Among patients with MPR <80, relative to the year before BC diagnosis (percent with HbA1c >8% =17.8%), the percent of patients with HbA1c >8% was not different in any of the four periods after cancer diagnosis.	

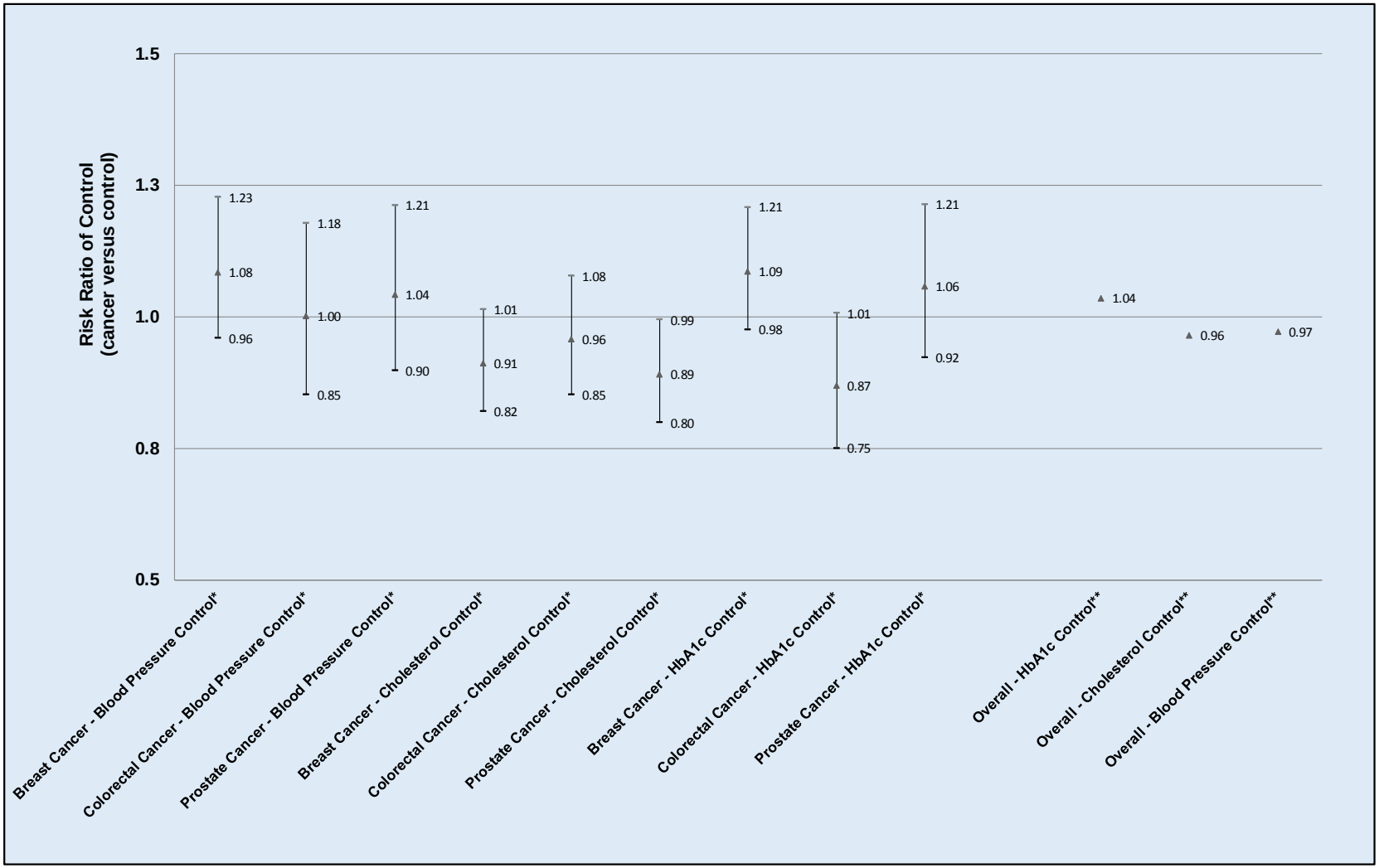
Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Shin 2014[22]		There was no difference between the percent of cancer patients and controls achieving adequate glycaemic control (HbA1c <7%): cancer survivors (25.2%: 95% CI, 17.5% - 34.8%); non-cancer, chronic disease controls (29.5%: 95% CI, 25.6% - 33.6%); and non-cancer, non-chronic disease controls (18.7%: 95% CI, 15.1% -22.8%).	
Bayliss 2011[8]	Low density lipoprotein (LDL) cholesterol (mmol/L) decreased over 6 time periods from before to after cancer diagnosis (-24 - -6 months, mean 101; 95% CI, 98-104: -6-0 months, mean 98; 95% CI, 95-101: 0-6 months, mean 96; 95% CI, 92-100: 6-12 months, mean, 95; 95% CI, 91-99: 12-24 months, mean 92; 95% CI, 89-95: 24-60 months, mean 85, 95% CI, 82-89).	There were no changes in HbA1c (%) over 6 time periods from before to after cancer diagnosis (-24 - -6 months, mean 7.9; 95% CI, 7.8-8.0: -6-0 months, mean 7.6; 95% CI, 7.4-7.8: 0-6 months, mean 7.7; 95% CI, 7.5-7.9: 6-12 months, mean, 7.8; 95% CI, 7.6-8.0: 12-24 months, mean 7.9; 95% CI, 7.7-8.1: 24-60 months, mean 7.8, 95% CI, 7.6-8.0). There were no changes in systolic blood pressure (SBP; mm Hg) over 6 time periods from before to after cancer diagnosis (-24 - -6 months, mean 132; 95% CI, 131-133: -6-0 months, mean 132; 95% CI, 130-134: 0-6 months, mean 134; 95% CI, 132-136: 6-12 months, mean, 132; 95% CI, 130-134: 12-24 months, mean 131; 95% CI, 129-133: 24-60 months, mean 132, 95% CI, 130-134).	

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Khan 2010[10]		There was no difference between BC patients and controls in the percent of quarters with blood pressure control (cancer, 62.8%; 95% CI, 58.9%-66.6% *versus* 57.9%; 95% CI, 54.1%-61.8%). There was no difference between colorectal cancer (CC) patients and controls in the percent of quarters with blood pressure control (cancer, 63.7%; 95% CI, 57.7%-69.7% *versus* control, 63.6%; 95% CI, 57.9%-62.3%). There was no difference between prostate cancer (PC) patients and controls in the percent of quarters with blood pressure control (cancer, 67.9%; 95% CI, 61.7%-74.0% *versus* control, 65.1%; 95% CI, 59.7%-70.5%). There was no difference between BC patients and controls in the percent of quarters with total cholesterol control (cancer, 64.2%; 95% CI, 59.7%-68.8% *versus* control, 70.4%; 95% CI, 66.1%-74.6%). There was no difference between CC patients and controls in the percent of quarters with total cholesterol control (cancer, 75.3%; 95% CI, 69.1%-81.6% *versus* control, 78.6%; 95% CI, 73.0%-84.1%). There was no difference between BC patients and controls in the percent of quarters with HbA1c control (cancer, 69.6%; 95% CI, 59.6%-68.7% *versus* control, 64.1%; 95% CI, 59.6%-68.7%). There was no difference between PC patients and controls in the percent of quarters with HbA1c control (cancer, 72.5%; 95% CI, 66.0%-79.1% *versus* control, 68.5%; 95% CI, 62.1%-74.9%).	PC patients had a lower percent of quarters with total cholesterol control than controls (cancer, 74.6%; 95% CI, 68.2%-80.9% *versus* control, 83.7%; 95% CI, 78.6%-88.7%).* PC patients had a lower percent of quarters with HbA1c control than controls (cancer, 63.7%; 95% CI, 57.2%-70.4% *versus* control, 73.3%; 95% CI, 67.7%-78.9%).*

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Chiao 2010[9]	HbA1c (%) was lower after compared to before CC diagnosis (mean before, 7.16; 95% CI, 6.9-7.4 *versus* mean after, 6.73; 95% CI, 6.5-7.0. *Note that even though calculated confidence intervals overlap, authors report a p-value of 0.02-discrepancy probably because p-value based on paired t-test*). LDL cholesterol (mmol/L) was lower after compared to before colorectal cancer diagnosis (mean before, 95.6; 95% CI, 89.8-101.4 *versus* mean after, 85.7; 95% CI, 78.2-93.2. *Note that even though calculated confidence intervals overlap, authors report a p-value of 0.04-discrepancy probably because p-value based on paired t-test*).	Diastolic blood pressure (mm Hg) was similar after compared to before CC diagnosis (mean before, 72.7; 95% CI, 70.8-74.6 *versus* mean after, 71.8; 95% CI, 69.8-73.8). Systolic blood pressure (mm Hg) was similar after compared to before CC diagnosis (mean before, 141.9; 95% CI, 137.4-146.4 *versus* mean after, 137.5; 95% CI, 134.2-140.8). Total cholesterol (mmol/L) was similar after compared to before CC diagnosis (mean before, 165.6; 95% CI, 158.0-173.2 *versus* mean after 155.8; 95% CI, 146.3-165.3).	
Keating 2007[12]	The percent of cancer patients whose most recent HbA1c was <8.0% was higher than controls (cancer, 73.4% *versus* control, 70.9% [*insufficient data to calculate CIs*]).	The percent of cancer patients whose most recent blood pressure was <130/80 mm Hg was similar to controls (cancer, 31.3% *versus* control, 32.2% [insufficient data to calculate CIs]).	The percent of cancer patients whose most recent LDL cholesterol was <100 mg/dL was lower than controls (cancer, 40.7% *versus* control, 42.2% [*insufficient data to calculate CIs*]).

*Authors reported these differences as statistically significant at p <0.05. In the table, the calculated 95% confidence intervals for the proportions overlap. One of the corresponding risk ratios calculated and reported in Figure 2.5 was statistically significantly less than 1.0, and the other narrowly failed to meet the threshold for statistical significance. Therefore, it is likely that the authors assessed the statistical significance of differences between cancer patients and controls using the risk ratio approach.

Figure 2.5: Calculated Risk Ratios for Control of Blood Pressure, Cholesterol, and HbA1c



*Khan, 2010; **Keating, 2007. Triangles are point estimates. Bars are 95% Confidence Intervals.

2.3.5.4 Medication Use and Adherence

Seven studies reported on adherence to diabetes [17-20,22,23] and other [12] medications (Table 2.8). In contrast to other outcomes reported above, there was stronger evidence to indicate cancer had an adverse impact on adherence to medications, with the majority of studies finding at least one instance in which medication adherence was either poorer after compared to before cancer diagnosis,[17-20] or poorer in cancer patients compared to controls.[12,23] Also, effect sizes were larger compared to other outcomes discussed above. For example, Yang et al. [17] found that adherence to diabetes medications, defined as a medication possession ratio (MPR) ≥80%, decreased from 80% (95% CI, 79%-81%) before to 53% (95% CI, 51%-55%) after breast cancer diagnosis. Santorelli et al. [18] found breast cancer patients had an increased adjusted odds of diabetes medications *non-adherence* (proportion of days covered [PDC] <80%) compared to non-cancer controls (OR=1.44: 95% CI, 1.07-1.95), and the effect was similar when the PDC threshold was changed to 70% and 90%. Nevertheless, results were not entirely consistent either across or within studies. For example, Zanders et al.[19] found that, overall, cancer patients experienced a significant decline in MPR at the time of cancer diagnosis and an ongoing monthly decline thereafter. However, prostate cancer patients had an increased average MPR at the time of cancer diagnosis, and there was no change in breast cancer patients. Overall, the weight of the evidence suggests cancer had a meaningful adverse impact on use of diabetes medications. Due to wide variation in study design and reporting, medications data are not summarized in a figure.

Table 2.8: Medication Use and Adherence [continued on the following three pages]

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Yang 2016[17]			Relative to the year before breast cancer (BC) diagnosis, the percent of patients adhering to diabetes medications (defined as a medication possession ratio (MPR) ≥80%) was lower during 1.5 years after diagnosis (before, 80%; 95% Confidence Interval [CI] 79%-81% *versus* after, 53.1%; 95% CI, 51%-55%.
Santorelli 2016[18]		The adjusted odds ratios (OR) for non-adherence pre- post cancer (or control date in controls) were not statistically significantly different between cancer patients and controls, when the proportion of days covered (PDC) was set at <70% (ratio of OR cancer to control = 1.24: p = 0.32), set at <80% (ratio of OR cancer to control = 1.35: p = 0.09), or set at <90% (ratio of OR cancer to control = 1.31: p = 0.07).	BC patients had increased adjusted odds of diabetes medications *non-adherence* (PDC <80%) compared to non-cancer controls (OR = 1.44: 95% CI, 1.07-1.95). The effect was similar when PDC threshold was changed to 70% and 90%. BC patients were more likely than controls to be *non-persistent* with diabetes medications (adjusted Hazard Ratio [HR], 1.31: 95% CI, 1.04-1.66), where non-persistence was defined as discontinuation of diabetes medications.

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Zanders 2015[19]	Prostate cancer (PC) patients experienced a statistically significant increase in MPR at the time of cancer diagnosis (2.1%: 95% CI, 1.4%- 2.8%).	BC patients experienced no change in MPR at the time of cancer diagnosis.	Overall, cancer patients experienced a statistically significant drop in MPR at the time of cancer diagnosis (-6.3%: 95% CI, -6.5% - -6.0%), and a significant monthly ongoing decline thereafter (-0.20% per month: 95% CI, -0.21% - -0.20%). PC patients experienced a statistically significant monthly ongoing decline in MPR after the month of cancer diagnosis (-0.09% per month: 95% CI, -0.10% - -0.07%). BC patients experienced a statistically significant monthly ongoing decline in MPR after the month of cancer diagnosis (-0.07% per month: 95% CI, -0.09% - -0.05%). Colorectal, *oesophagael, stomach, pancreas, or liver,* pulmonary, and urinary cancer patients all experienced a statistically significant drop in MPR at the time of cancer diagnosis, and a significant monthly ongoing decline thereafter.

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Calip 2015[20]		Relative to the year before BC diagnosis (discontinuation episodes =1.23; 95% CI, 1.11-1.35), the number of discontinuation episodes was similar in each of four periods after cancer diagnosis: treatment period (1.06; 95% CI, 0.95-1.17); year +1 (1.16; 95% CI, 1.02-1.30); year + 2 (1.22; 95% CI, 1.07 -1.37); and year +3 (1.97; 95% CI, 1.71-2.23). Relative to the year before BC diagnosis (proportion of patients discontinuing = 75%; 95% CI, 71%-78%), the proportion of patients discontinuing diabetes medications was similar in three of four periods after cancer diagnosis: treatment period (59%; 95% CI, 55%-64%); year +1 (76%; 95% CI, 72%-80%); year +2 (72%; 95% CI, 67%-76%); and year +3 (71%; 95% CI, 66%-75%).	Relative to the year before BC diagnosis (MPR = 86%; 95% CI, 84%-88%), diabetes MPR was lower in each of four periods after cancer diagnosis: treatment period (49%; 95% CI, 46%-52%); year +1 (48%;95% CI, 45%-51%); year +2 (48%; 95% CI, 45%-51%); and year +3 (52%; 95% CI, 49%-55%). Relative to the year before BC diagnosis (proportion of adherent users [MPR ≥80%] = 75%; 95% CI, 72%-79%), the proportion of diabetes medication adherent users was lower in each of four periods after cancer diagnosis: treatment period (25%; 95% CI, 21%-28%); year +1 (27%; 95% CI, 23%-31%); year +2 (24%; 95% CI, 20%-28%); and year +3 (32%; 95% CI, 27%-36%).
Shin 2014[22]		There was no difference in the percent of patients receiving diabetes treatment between cancer survivors (60.5%: 95% CI, 49.4%-70.5%) and non-cancer, chronic disease controls (65.0%: 95% CI, 60.9%-68.9%) or non-cancer, non-chronic disease controls (51.1%: 95% CI, 46.0%-56.2%).	

Study	Difference Between Cancer Patients and Controls		
	Better in Cancer than Controls	**No Difference**	**Worse in Cancer than Controls**
	(or *after* compared to *before* cancer depending on the study design)	**(or *after* compared to *before* cancer depending on the study design)**	**(or *after* compared to *before* cancer depending on the study design)**
Onitilo 2013[23]			Patients with a history of BC were less likely to report metformin use than those without BC (cancer, 43%; 95% CI, 40%-45% *versus* control, 58%; 95% CI, 55%-61%). Patients with a history of PC were less likely to report metformin use than those without PC (cancer, 47%; 95% CI, 45%-49% versus control, 58%; 95% CI, 55%-61%).
Keating 2007[12]		There was no difference in the percent of cancer patients and controls receiving ACE-I/ARB for hypertension (cancer, 76% *versus* control, 77% [*insufficient data to calculate CIs]*).	Cancer patients were less likely than controls to receive a statin for elevated low density lipoprotein cholesterol (cancer, 77% *versus* control, 81% [insufficient data to calculate CIs]).

2.4 DISCUSSION AND CONCLUSIONS

2.4.1 Summary of Findings

This chapter has presented the methods and results of a systematic review that was conducted to examine whether, among patients with diabetes, a diagnosis of cancer impacts the quality of diabetes care. Within 15 studies included in the final review, 88 comparisons of the quality of diabetes care were identified and classified—either between cancer patients and controls, or before versus after cancer—as A) no different between cancer patients and controls, B) better in cancer patients than controls, or C) worse in cancer patients than controls. Of these 88, which comprised health care visits, monitoring/testing, control of blood pressure, cholesterol, or HbA1c, and adherence to diabetes and other medications, 47 (53%; 95% CI, 43%-64%) were no different, 12 (14%; 95% CI, 6%-21%) were better in cancer patients, and 29 (33%; 95% CI, 23%-43%) were worse in cancer patients than controls.

Findings differed both within and between studies, with most reporting a mixture of outcomes that fell into each of the three categories – no different, cancer better, cancer worse. No clear patterns emerged according to study design, patient population, or methods of adjustment, and differences that were reported as statistically significant in the articles tended to be small and of questionable clinical relevance, as indicated by the narrow ranges of RRs (generally between 0.9 and 1.1) that were calculated. There was some evidence from a study of long-term survivors of breast, colorectal, or prostate cancer in the UK[10] that cancer may have had an adverse effect on blood pressure, cholesterol, and HbA1c. However, these effects also were modest in size.

2.4.2 Strengths and Limitations

The search strategy for the systematic review has several limitations. First, the searches were conducted only in Medline and Embase. Although findings from a previous study showed these two databases are sufficient for identifying English language papers on diabetes epidemiology,[4] it is possible that additional articles/information would have been discovered had other databases such as the Cochrane Library,[24] CINAHL,[25] and PsycINFO[26] been included, if the search strategy had included grey literature resources, dissertations and theses, and conference proceedings,[27] and if non-English language articles had been included. Second, the search began by tabulating MeSH[5] terms from eight articles [6-13] previously reviewed as part of developing the topic for this thesis. This approach could have resulted in failing to find relevant articles, which otherwise might have been identified if lists of keywords and index/subject terms had been constructed independently of those included in the original eight articles, or if lists had been obtained/constructed from other sources, such as WebMD.[28] Third, the preliminary search produced in excess of 20,000 articles, and at that point the search was narrowed to those articles with both "cancer" and any of "comorbid" or "diabetes" or "chronic" in the title. An alternative approach would have been to review the titles, and possibly also the abstracts, of all 20,000+ articles in the preliminary search, which could have resulted in retaining articles that were inadvertently excluded when the search was narrowed based on the presence of key terms in the title.

Overall, the quality of the 15 studies, which were assessed using an established instrument,[14] was high, and all but one study[7] met all of the applicable criteria for

minimizing the risk of bias. High quality notwithstanding, there were insufficient data for performing a formal synthesis of outcomes across individual studies. First, even within the four broad categories of diabetes quality of care measures defined for the systematic review, there was considerable heterogeneity in the study designs, patient populations, beginning of follow-up, duration of follow-up, and definitions of the outcomes variables across the studies reporting those measures. Second although visual inspection of the results—for instance in Figures 2.2, 2.4, and 2.5—showed little evidence of statistical heterogeneity, few studies reported sufficient data, e.g., sample sizes for the proportions reported, to perform a formal synthesis. For example, of the four studies [6,7,11,13] that were used to calculate RRs of health care visits for cancer patients versus controls (Figure 2.4), only one[6] reported sufficient information on sample sizes. Of the six studies [8-10,12,20,22] that reported monitoring or test results (Table 2.7) to assess control of blood pressure, [8-10,12] cholesterol, [8-10,12] and/or HbA1c, [8-10,12,20,22] only one[10] provided sufficient data for a formal synthesis of the proportions of patients achieving control. Had a formal synthesis been feasible, it is possible more statistically significant differences in the quality of diabetes primary care measures between the cancer cases and non-cancer controls would have been detected.

2.4.3 Conclusions

There was no consistent evidence that cancer is associated with lower, or worsening in the case of before and after studies, quality of diabetes care. However, given several findings from a UK study of long-term survivors,[10] and the fact that several recent studies of incident cancer in patients with pre-existing diabetes have detected

differences in outcomes, primary research could be useful for examining the impact of incident cancer on a broad range of diabetes quality of care and outcomes indicators in the UK.

2.4.4 Implications for Future Primary Research in the UK

The findings from the systematic review have several implications for the design of future primary research.

First, only one of the 15 studies included in the systematic review was conducted in the UK.[10] This well-designed and executed study sheds important light on the impact of cancer on the quality of diabetes care in long-term cancer survivors.[10] However, as described in Section 1.1 of Chapter 1, the authors acknowledged several important limitations, the main one being that it was not designed to assess the impact of cancer during the first five years after diagnosis, and called for future research on the shorter-term consequences of cancer.[10]

Therefore, an important objective of future primary research conducted in the UK would be to assess the impact of cancer on the quality and outcomes of diabetes care from initial diagnosis and treatment of cancer through long-term follow-up.

Second, most studies included in the review were conducted using databases that were not necessarily representative of the national population of cancer patients, according to types of cancers included, patient age, and/or geographic representation. In particular, several studies in the US included only patients age 65 years or older from specific geographic areas covered by the SEER cancer registry.

Future primary research conducted in the UK should be based on data that are nationally representative of cancer patients, both in terms of age and geographic distribution. However, given the variability in underlying patient demographic and clinical characteristics, diagnosis, treatment, follow-up, and outcomes among different types of cancers, it is probably not advisable to include all types of cancer in a single study.

Third, in the systematic review, many of the most important adverse effects of cancer on the quality of diabetes care were reported in studies that included incident (as opposed to prevalent) cohorts of cancer patients, who were followed throughout the continuum of cancer care from diagnosis to treatment and long-term follow-up. This may be due to the fact that the greatest disruptions in the delivery of high quality diabetes services, lapses in patient self-management, and biological effects of cancer and cancer treatment occur during the early phases of cancer care.

Future research should include incident cohorts of cancer patients. These patients should be followed from prior to cancer diagnosis through initial treatment and long-term follow-up to capture the full effects of cancer on the quality and outcomes of diabetes care, and also to assess where, in the continuum of cancer care, interventions should be implemented to preserve/enhance the continuity of high quality diabetes care.

Fourth, most studies included in the systematic review incorporated one or more approaches to adjust for confounding between the exposure (cancer) and the outcomes (diabetes quality of care), such as including a comparison group of non-cancer patients, and/or a "before and after" design, in which patients with pre-existing diabetes were followed from before to after diagnosis of cancer for changes in diabetes quality of care.

F*uture research should incorporate a longitudinal "before and after" design, preferably also with a non-cancer control group, in part to adjust for secular trends in the delivery of routine diabetes care over time.*

Furthermore, in order to fully realize the benefits of a "before and after" study design, statistical methods should allow for comparison of diabetes quality of care within cancer patients over time, as well as comparisons between cancer patients and non-cancer controls over time. Longitudinal data analysis using multilevel, mixed-effects modelling[29] is ideally suited to the requirements of the proposed design for future research.

Propensity score matching[30] of non-cancer controls to cancer cases on underlying demographic and clinical characteristics would improve the efficiency of the statistical modelling as well as simplify the graphical depiction of results from the adjusted analyses.

These design considerations were incorporated into the methods of primary research for this thesis, which are presented in Chapters 3-6 of the thesis.

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CHAPTER THREE

Methods of Primary Research

III METHODS OF PRIMARY RESEARCH

3.1 CHAPTER AIM

The aim of this chapter is to present the methods of primary research used to compare the quality and outcomes of diabetes care between cancer patients and non-cancer controls. This research was conducted to address concerns raised by leading cancer organizations in the UK that overlooking other medical conditions during cancer treatment and follow-up could result in excess morbidity and mortality, thereby undermining gains associated with early detection and improved treatment of cancer.[1,2] The methods of primary research were designed to incorporate the implications of the findings from the systematic review for future primary research, as summarized in the previous chapter (section 2.4.4). Excerpts from this chapter have been included in two articles submitted for peer-review publication:

Griffiths RI, McFadden EC, Stevens RJ, Valderas JM, Lavery BA, Khan NF, Keating NL, Bankhead CR. Quality of Diabetes Primary Care in Breast, Colorectal, and Prostate Cancer.

Griffiths RI, Valderas JM, McFadden EC, Bankhead CR, Lavery BA, Khan NF, Stevens RJ, Keating NL. Outcomes of Pre-Existing Diabetes Mellitus in Breast, Colorectal, and Prostate Cancer.

3.2 METHODS OF RESEARCH

3.2.1 Aim and Objectives

The overall aim of this research was to compare the quality and outcomes of diabetes care in older (age ≥50 years at cancer diagnosis) breast, colorectal, and prostate cancer patients to matched non-cancer controls using the CPRD.

The specific objectives were as follows:

- Identify three cohorts of patients with pre-existing diabetes, each subsequently diagnosed with breast, colorectal, or prostate cancer;
- Match the cancer patients to diabetic, non-cancer controls;
- Construct a fourth cohort combining all cancer patients and controls;
- Compare the quality of diabetes care between cancer patients and controls – *Additional methods and results reported in Chapter 4*;
- Compare patterns of clinical and laboratory values e.g., HbA1c, between cancer patients and controls – *Chapter 5;*
- Compare rates of diabetes microvascular and macrovascular complications; and
- Compare overall and diabetes-related mortality between cancer patients and controls – *Both in Chapter 6.*

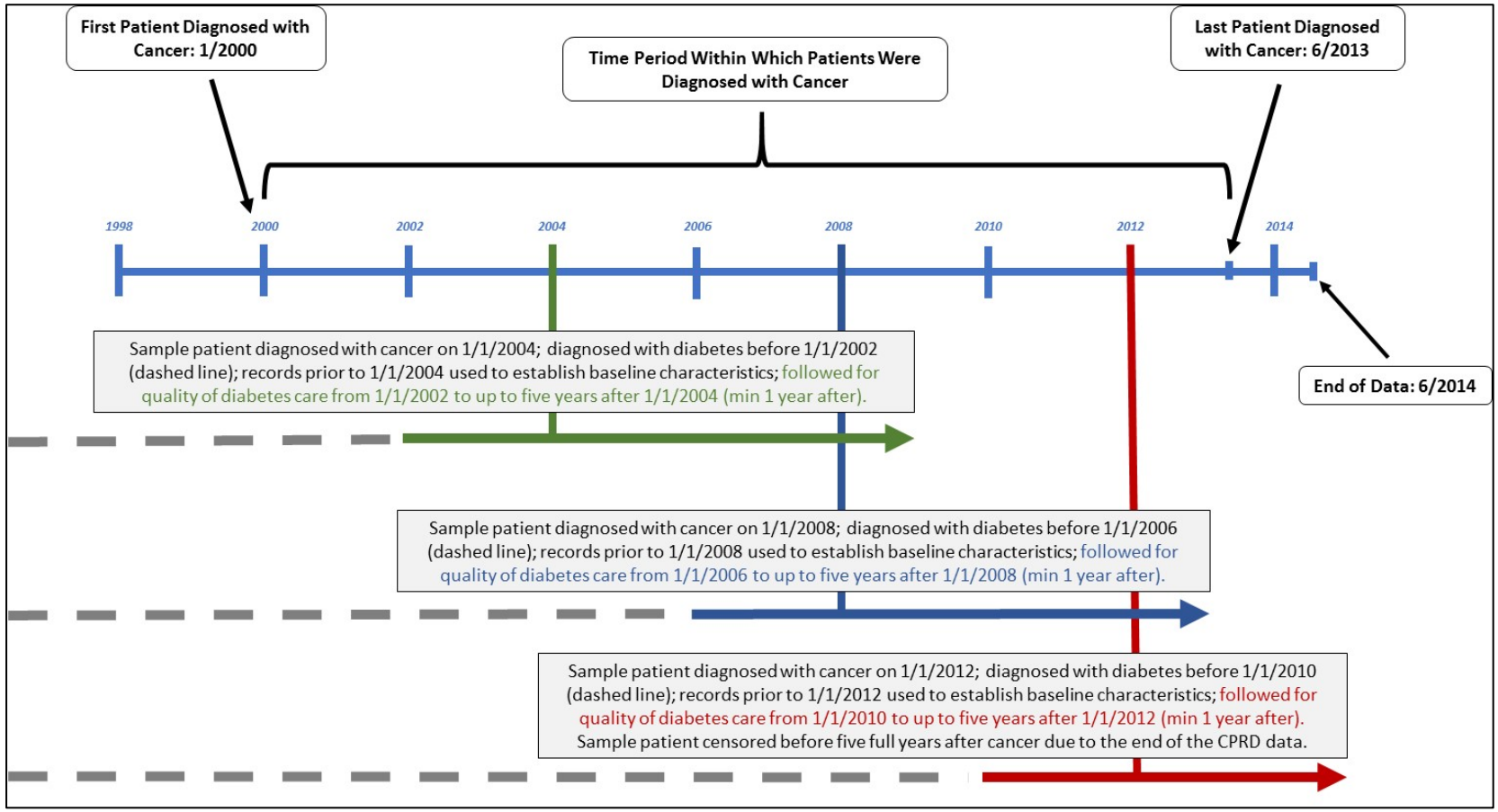
3.2.2 Study Design and Data Source

This was an historical cohort study using the CPRD and data held under the CPRD Linkage Scheme.[3] The overall study design is depicted in Figure 3.1. The CPRD contains information on demographics, symptoms, tests, diagnoses, therapies, health-related behaviour, and referrals to secondary care for over 11.3 million patients from 674

general practitioner (GP) practices in the UK.[4] There are 4.4 million active (alive, currently registered) patients in the database, which is approximately 6.9% of the UK population. These patients are broadly representative of the UK general population in terms of age, sex, and ethnicity.

As described in Section 1.1 of Chapter 1, high quality diabetes care depends on a partnership between the patient and a team of healthcare professionals, which is best served through regular delivery of recommended diabetes services by the healthcare team, plus ongoing participation in diabetes self-management activities by the patient. Therefore, disruptions in the delivery of services and/or patient self-management activities could adversely affect the quality and outcomes of diabetes care, directly and/or through their impact on biological parameters that also are risk factors for diabetes outcomes. The CPRD is an excellent source of data with which to examine these mechanisms. However, it does not contain sufficient data to directly assess disruptions in patient self-management activities such as adherence to diet and exercise regimens, or changes in patient attitudes toward diabetes care during cancer treatment.

Figure 3.1: Study Design



This figure depicts the overall study design for the primary research using the Clinical Practice Research Datalink (CPRD). As shown, breast, colorectal, and prostate cancer patients were included if they were first diagnosed with cancer between 1/2000 and 6/2013. Cancer patients were required to have had at least two years of eligible data before cancer, and to have been diagnosed with diabetes *at least* two years before cancer. Baseline characteristics were defined using information in their health records prior to cancer. Patients were followed for the quality of diabetes care from two years before cancer, to a minimum of one year, and to a maximum of five years, after cancer. This is illustrated with three sample cancer patients who were diagnosed at different points within the data window. Matched, non-cancer control patients also were included in the primary research, but they are not shown in the figure.

The CPRD is ideally suited to the primary research. First, patients can be followed without interruption over relatively long periods of time for changes in health status and use of medical services. Second, there are strong incentives for primary care practices to accurately record diagnoses, provision of specific medical services, results of clinical and laboratory investigations, and medication prescribing, especially for those conditions, such as diabetes, that are part of the QOF.

In contrast, limitations of some of the US databases commonly used for health services research on cancer and comorbidity, notably the National Cancer Institute's SEER cancer registry data linked to Medicare (SEER-Medicare) health insurance claims,[5] are that often they are not representative (SEER-Medicare includes data only for patients age 65 years or older, and those who are disabled) of the general population of cancer patients, and they do not contain the level of clinical detail required to establish comparability of "exposure" and "control" groups in observational studies, or to construct more clinically relevant outcomes variables, especially those that may be based on the results of clinical measures or laboratory tests.

At the time this study was conducted, the CPRD Data Linkage Scheme included Hospital Episode Statistics (HES)[6] hospitalised care, Office for National Statistics (ONS)[7] mortality data including causes of death, Index of Multiple Deprivation (IMD) and Townsend Scores (deprivation data),[8] and cancer registry data from the National Cancer Intelligence Network (NCIN).[9] At the time of data acquisition, the CPRD Data Linkage Scheme did not include the HES data for hospital outpatient or for accident and emergency visits.[3] Unfortunately, it was not possible to obtain the NCIN data within the timeframe of the primary research.

3.2.3 Patient Selection – Diabetic Cancer Patients

Diabetic cancer patients were included if they met all of the following criteria: (A) diagnosed with breast, colorectal, or prostate cancer on or after 1 January, 2000; (B) diagnosed with type 1 or type 2 diabetes at least two years before their date of cancer diagnosis (index date); (C) had no other cancer diagnosis, except non-melanoma skin cancer, before their index date; (D) were age ≥50 years at their index date; (E) had at least two years of eligible CPRD data before their index date, where "eligible CPRD data" was defined as the later of their GP practice up-to-standard date or their practice registration date; (F) had an index date before the end of the eligible CPRD data, where "end of the eligible CPRD data" was defined as the earliest of death, transfer out of the GP practice, or the date of their practice's last data upload; and (G) survived at least one year after cancer diagnosis. According to these criteria, the first cancer patient included in the study was diagnosed in January, 2000, and the last was diagnosed in June, 2013.[f] Men with breast cancer were excluded.

Diabetes was identified in CPRD[g] using Read codes from several sources. First, ranges of Read codes used to identify patients who qualify for inclusion on the QOF diabetes registry were obtained from the Department of Health, Data and Business Rules, Diabetes Mellitus Indicator Set, Version No. 25.0., *Qualifying Diagnostic Codes*.[10] Second, the National Health Service (NHS), Information Service, Clinical Terminology Browser,[11] was used to identify all Read codes within those ranges. Third, code lists were obtained

[f] Exact dates not given to protect patient anonymity. June 2013 was the latest a patient could be diagnosed with cancer and still have at least one full year of follow-up after cancer diagnosis, but before the end of the available CPRD data.

[g] Since CPRD data contain Medcodes and not Read codes, a "cross-walk" table of these two codes was merged into the CPRD data prior to searching for Read codes.

from other researchers (Nada Khan, José Valderas, and Sarah Stevens) who previously had conducted studies on diabetes patients using CPRD. Other cardiovascular conditions, consisting of atrial fibrillation, coronary heart disease, heart failure, hypertension, and stroke or transient ischaemic attack (TIA), were identified using the same process. Ranges of Read codes for breast (B34%), colorectal (B13% colon; B141 rectum), and prostate (B46) cancer were obtained from the Thames Valley Cancer Network.[12] These ranges were then expanded to full lists using the Clinical Terminology Browser[11] as described above. Lists of Read codes for diabetes, cancer, and the other cardiovascular conditions are provided in the Appendix to this chapter.

3.2.4 Patient Selection – Diabetic, Non-Cancer, Control Patients

Each diabetic cancer patient was matched to up to four diabetic, non-cancer controls on GP practice number, sex (colorectal only), and age (±1 year) at cancer diagnosis. Breast cancer controls were restricted to females, and prostate cancer controls were restricted to males. Matched controls were assigned an index date within one year of their cancer case, and also required to have met inclusion criteria B–G above. In addition to three separate cancer/control cohorts, cancer patients and controls were combined into a single cohort ("combined cancer cohort"). According to the study inclusion criteria described above, cancer patients could appear in only one cohort. However, control patients could appear in more than one cohort, and control patients appearing in more than one cohort could have different index dates and baseline characteristics depending on the cancer case to which they were matched. Therefore, duplicate controls were identified during the process of constructing the combined cohort and excluded.

3.2.5 Propensity Matched Cohorts

Propensity matched cohorts also were constructed from the full cohorts. The propensity score is "the conditional probability of assignment to a particular treatment given a vector of observed covariates", and "adjustment for the scalar propensity score is sufficient to remove bias due to all the observed covariates."[13] In this study, the propensity score was the conditional probability of being diagnosed with one of the three types of cancers that defined entry into the cohorts for the cancer cases. There are at least three ways propensity scores may be used to balance groups based on an exposure: include the propensity score as a covariate in statistical analyses; use the propensity score to match based on the exposure of interest; or stratify based on the propensity score.[14] In this instance, the propensity score was used to match cancer cases and controls, as described in more detail below.

First, binary logistic regression using backwards stepwise elimination of predictors[15,16] with a probability (p) value >0.2 was used to estimate the conditional probability of "assignment" to cancer or control given the following vector of demographic and clinical covariates: demographic characteristics consisting of age at index date, sex, calendar year of index date, most recent smoking status, most recent drinking status, and IMD quintile, from least deprived=1 to most deprived=5; clinical characteristics consisting of body mass index (BMI), Charlson Comorbidity Index, history of other cardiovascular disease (atrial fibrillation, coronary heart disease, heart failure, hypertension, and stroke/TIA), history of microvascular complications of diabetes (retinopathy, neuropathy, nephropathy, and chronic kidney disease), history of macrovascular complications of diabetes (peripheral arterial disease, acute myocardial infarction,

cerebrovascular accident, and lower limb amputation), and history of anti-diabetic medications; and laboratory characteristics consisting of blood pressure (mm Hg), total cholesterol (mmol/L), and HBA1c (mmol/mol). Second, the predicted conditional probabilities of cancer from the final models were transformed into logits (ln[p/1-p]) to normalize their distributions.[14] Third, nearest neighbor matching within a caliper of 0.25σ was used to match controls 1:1 to cancer cases. Propensity matching was implemented in STATA[17] using code adapted from Guo and Fraser.[14]

3.2.6 Observation Period

Patients were followed from two years before, to up to five years after their index date (Figure 3.1). As described in detail in Chapters 4 and 5, following patients from two years before, to up to five years after, their index date allowed examination of within-person changes in the quality of diabetes care (Chapter 4), and in levels of blood pressure, cholesterol, and HbA1c (Chapter 5). Examining within-person changes over time can eliminate a significant source of bias inherent in observational studies that rely exclusively on comparison to a control group to estimate the marginal effects of an exposure, namely confounding introduced by unobserved differences between the characteristics of the exposed and control groups.

Since all patients were required to have survived at least one year after their index date, the minimum observation period was three years. Following the end of the first year after the index date, patients were censored at the earliest of the following: death, last date of eligible data, or five years after their index date. The observation period was extended to up to 10 years after the index date for the analyses of diabetes complications and mortality.

3.2.7 Baseline Characteristics

Baseline demographic characteristics consisted of age at index date, sex, calendar year of index date, most recent smoking and drinking status, both of which were ascertained using the most recent information from up to two years prior to the patient's index date, and IMD quintile, from least deprived (1) to most deprived (5). Baseline clinical characteristics included BMI, Charlson Comorbidity Index,[18] which was constructed using STATA code provided by Nada Khan based on her study that adapted and validated the index for CPRD,[19] history of other cardiovascular disease, microvascular complications of diabetes, and macrovascular complications of diabetes. Cancer was excluded from the Charlson Comorbidity Index.[18,19] However, since all patients had diabetes, one was the minimum score on the Index. Microvascular and macrovascular complications of diabetes were identified using published lists of Read codes[20] present in patients' records at any time prior to the index date. Lists of these Read Codes are presented in the Appendix.

Baseline laboratory values consisted of blood pressure (mm Hg), total cholesterol (mmol/L), and HbA1c (mmol/mol). These were identified using the most recent value within one year prior to the index date. Categorical variables for laboratory values were constructed using cut points that corresponded to the thresholds for meeting the corresponding laboratory-based QOF performance indicators: blood pressure ≤140/80 mm Hg, total cholesterol ≤5 mmol/L, and HbA1c ≤59, 59-≤64, 64-≤75, and >75 mmol/mol.

Baseline medications included antidiabetic agents, lipid lowering agents, and medications for blood pressure. Baseline medications were identified using British

National Formulary (BNF) codes in the CPRD Therapy file[21] within one year prior to the index date: Any antidiabetic agent "06010"; insulin "06010101" or "06010102"; biguanide "06010202"; sulphonylurea "06010201"; and, other antidiabetic agents "06010200" or "06010203". The same process was used to identify use of other medications including: statins "02120400"; ACE-I "02050501"; angiotensin receptor blocker (ARB) "02050502"; beta blocker "0204"; calcium channel blocker "020602"; and thiazide-related diuretic "020201".

3.2.8 Missing Data

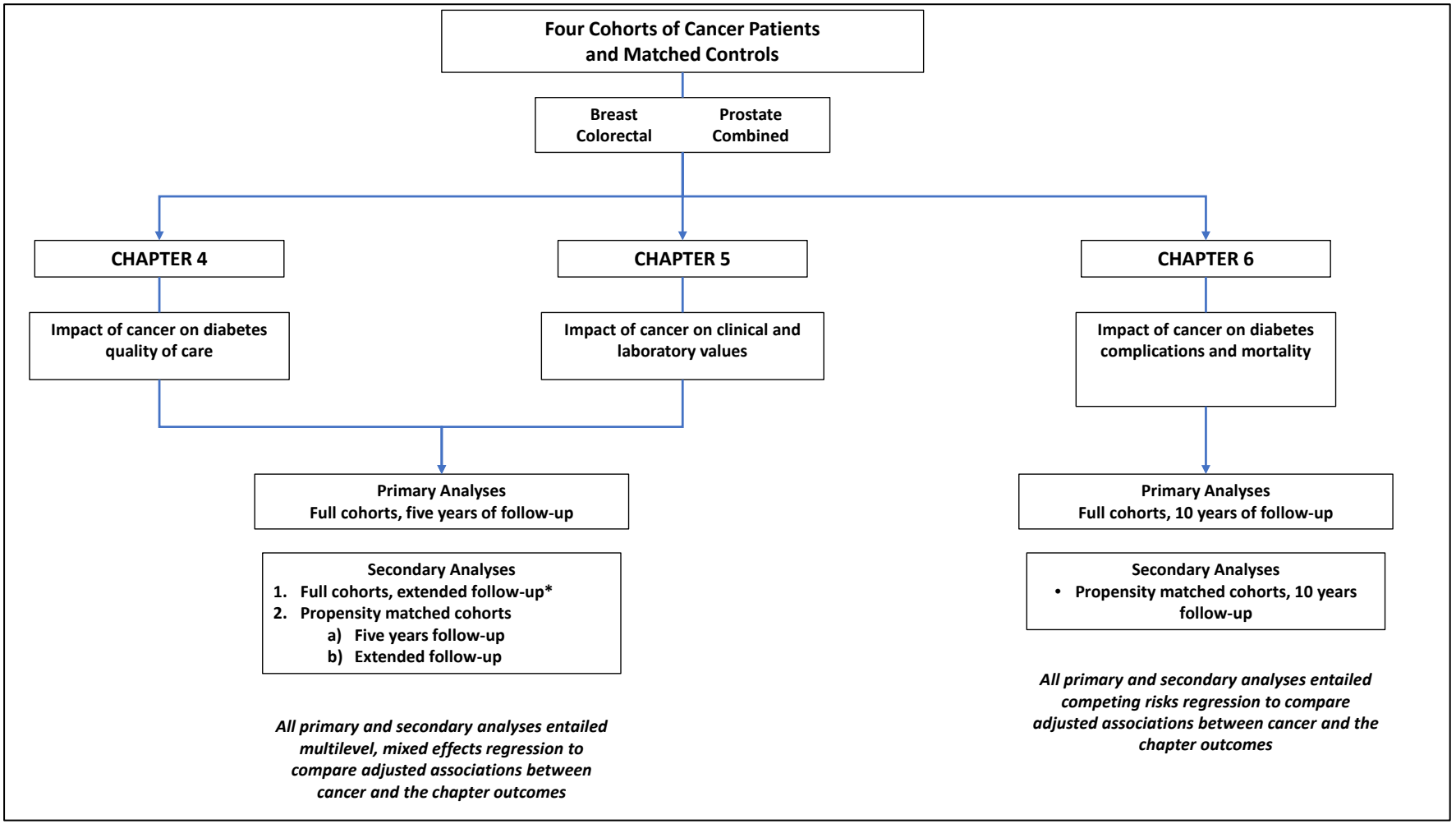
Several approaches to addressing the problem of missing data, including multiple imputation,[22] were considered for this study. However, absence of data on important baseline variables such as smoking status, BMI, and HbA1c could have been informative, i.e., indicators of poor quality of care or lower GP contact prior to the index date. Therefore, where applicable, separate categories for missing data were constructed for baseline demographic, clinical, and treatment variables.[h] Therefore, patients with missing data could be—and were—included in all analyses.

3.2.9 Analytic Plan

The analytic plan for comparing the quality and outcomes of diabetes care in cancer patients to matched, non-cancer controls is summarized in Figure 3.2. All analyses were performed on each of the four cohorts (breast, colorectal, prostate, and combined). The following three chapters of the thesis are devoted to describing, in detail, the methods of research and results of the analyses comparing quality of diabetes care (Chapter 4),

[h] Specific language used to explain this choice was provided by Richard Stevens.

Figure 3.2: Analytic Plan



This figure depicts the analytic plan for the primary research using the Clinical Practice Research Datalink (CPRD). *Extended follow-up was from two years before, up to five years after, the index date.

clinical and laboratory values (Chapter 5), and diabetes complications and mortality (Chapter 6) between cancer patients and controls.

Analyses in each chapter were classified as primary or secondary. In all instances, the primary analyses were conducted on the full cohorts (as opposed to the propensity matched cohorts). As shown in Figure 3.2, analyses of diabetes quality of care, and of clinical and laboratory values, share the same structure. Primary analyses were conducted using up to five years of data (see Section 3.2.6 above) after the index date.

Secondary analyses were conducted on the full cohorts using all the data from two years before, up to five years after, the index date (extended follow-up). As described above, examining within-person changes "before and after" an exposure (in this case, the diagnosis of cancer, which defined the index date) can minimize an important source of potential confounding introduced by unobserved differences between the characteristics of the exposed and control groups. Secondary analyses also were conducted with the propensity matched cohorts, first using up to five years of follow-up, and then again using extended follow-up. Propensity matching was performed to balance the cancer cases and non-cancer controls on demographic and clinical characteristics not included in the matching process implemented during patient selection (see Sections 3.2.3 and 3.2.4).

All primary and secondary analyses of diabetes quality of care, and of clinical and laboratory values, entailed multilevel, mixed effects regression analyses to compare adjusted associations between cancer and the outcomes variables (described in detail in the applicable chapter) over time. In this instance, propensity matching greatly

increased the computational efficiency of the statistical analyses, because it eliminated the need to include other patient demographic and clinical variables in the models to adjust for confounding.

The primary analyses of diabetes complications and mortality were conducted using 10 years of follow-up. Secondary analyses were performed using the propensity matched cohorts. Since all analyses in Chapter 6 entailed comparing the risks of new complications associated with cancer, "before and after" analyses using extended follow-up were not applicable in this instance. Primary and secondary analyses entailed competing risks regression to compare adjusted associations between cancer and the outcomes. As above, propensity matching increased the computational efficiency of the statistical analyses.

3.2.10 Origination of the CPRD Research

The CPRD research for this thesis was conducted as part of a 32-month, £248,000 grant from CRUK, which I wrote with my former DPhil supervisor, José Valderas before I matriculated into Oxford in October 2012. I was responsible for developing the study concept, drafting and submitting the CRUK grant application, addressing referees' comments, and submitting the final version. Once we received the award from CRUK, I was responsible for drafting the application to the Independent Scientific Advisory Committee (ISAC) to acquire and use the CPRD data, the study protocol, and the statistical analysis plan. Also, I developed and ran STATA code to construct the study cohorts, baseline characteristics, quality outcomes measures, and analytic datasets, and to perform the descriptive and multivariate analyses. I served as principal investigator

on the grant following Dr. Valderas' departure from the University of Oxford in 2013 until it ended in February, 2017.

The CRUK award entailed investigating the quality of care for six cardiovascular conditions (atrial fibrillation, coronary heart disease, diabetes, heart failure, hypertension, and stroke/TIA) in breast, colorectal, and prostate cancer patients. Based on previous primary research I conducted in the US using the SEER-Medicare database,[23-26] I elected to focus on the quality and outcomes of diabetes care in cancer patients for my DPhil research. However, it was critical to the success of the CRUK-funded project that the research methods were consistent across all six cardiovascular conditions. Therefore, final decisions regarding patient selection, coding of quality indicators, and approaches to statistical analysis were made collectively by the CRUK project team, which consisted of my supervisors Clare Bankhead and Nancy Keating, as well as Richard Stevens, Emily McFadden, Bernadette Lavery (medical oncologist), Nada Khan, and José Valderas.

Also, although I wrote and ran the preliminary STATA code to construct the cohorts and baseline variables for the six cardiovascular cohorts based on a test set of the data provided by Sarah Stevens, my code was subsequently modified and re-run by Emily McFadden, project statistician, on the full CPRD data to ensure identical selection criteria were applied to all the cardiovascular conditions. I wrote and executed all the STATA code required to generate the propensity-matched cohorts, as well as to produce the results reported in this chapter and in all subsequent chapters of this thesis reporting the results of the primary research.

3.2.11 Research Support

Research support for this study, *but not directly for my DPhil thesis*, was received from the Population Research Committee, CRUK. "Quality and Outcomes of Care for Chronic Conditions in Older Patients Diagnosed with Breast, Colorectal, or Prostate Cancer Compared to Non-Cancer Controls: An Observational Study Using the Clinical Practice Research Datalink (CPRD)". Reference # 16609. 1 July 2013–28 February, 2017.

3.2.12 Independent Scientific Advisory Committee Protocol

The protocol (see Appendix to this chapter) for this study was approved by the ISAC to the CPRD on 1 August, 2013 (ISAC reference number 13_124RA). Conditions other than diabetes also were pre-specified in the protocol, and were the subject of additional research conducted outside this thesis. An amended protocol, which included use of primary care rather than NCIN data to identify cancer cases, subsequently was approved by ISAC on 22 May, 2014. Since then, the patient inclusion and exclusion criteria were modified to include only those patients with at least one year of follow-up, because preliminary findings showed that analyses that included patients with less than one year of follow-up were subject to substantial informative censoring bias.

3.3 RESULTS

3.3.1 Patient Counts

There were 14,517 patients in the combined cancer cohort: 3,382 (23.3%) were cancer patients and 11,135 (76.7%) were controls (ratio of 3.3:1 control to cancer). (Table 3.1) The ratio of controls to cancer patients was highest in colorectal cancer 3.8:1, and similar in breast (3.1:1) and prostate cancer (3.0:1) patients. Breast cancer patients

accounted for 30.6%, colorectal cancer patients accounted for 31.6%, and prostate cancer patients accounted for 37.8% of cancer patients in the combined cohort.

Table 3.1: Counts of Patients Included in the Primary Research

	Cancer		Control		Total	
Cohort	**n**	**%**	**n**	**%**	**n**	**%**
Breast	1,036	24.5	3,194	75.5	4,230	100
Colorectal	1,069	20.9	4,047	79.1	5,116	100
Prostate	1,277	24.7	3,894	75.3	5,171	100
Combined	3,382	23.3	11,135*	76.7	14,517*	100

*412 patients were dropped from the control group of the combined cancer cohort since they appeared as a control in more than one individual cancer cohort.

3.3.2 Baseline Demographic Characteristics

Characteristics of the combined cohort are presented below. Characteristics of the individual cancer cohorts are presented in the Appendix to this chapter. Overall, the average age at cancer diagnosis (matched date for controls) was 72.3 years (Table 3.2) and 19.9% of patients were age 80 years or older. Males accounted for 58.7% of patients, and 40.8% were diagnosed—had their index date—in 2010 or later. As expected, there were no statistically significant differences in age and sex between cancer patients and controls, since these characteristics were used as matching criteria in constructing the cohorts. Patients in the cancer cohort were slightly more likely than non-cancer patients to have an index date in 2000-2004, although this difference was not statistically significant (p=0.09).

Smoking status was well-reported at 91.4%. Overall 10.8% were current smokers, and 50.6% were former smokers. The distributions of smoking status were statistically significantly different (chi-square: $p < 0.001$) between cancer patients and controls, with control patients more likely to be current smokers. Drinking status was not as well-

Table 3.2: Baseline Demographic Characteristics

	Cancer		Control		Total	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Total	**3,382**	**100**	**11,135**	**100**	**14,517**	**100**
Age						
50-59	248	7.3	800	7.2	1,048	7.2
60-69	946	28.0	3,098	27.8	4,044	27.9
70-79	1,498	44.3	5,041	45.3	6,539	45.0
≥80	690	20.4	2,196	19.7	2,886	19.9
mean (SD)	3,382	72.4(8.4)	11,135	72.3(8.1)	14,517	72.3(8.2)
Sex						
Male	1,974	58.4	6,551	58.8	8,525	58.7
Female	1,408	41.6	4,584	41.2	5,992	41.3
Year of Diagnosis						
2000-2004	546	16.1	1,649	14.8	2,195	15.1
2005-2009	1,500	44.4	4,902	44.0	6,402	44.1
≥2010	1,336	39.5	4,584	41.2	5,920	40.8
						p=0.09
Smoking Status						
Non-Smoker	991	29.3	3,364	30.2	4,355	30
Former Smoker	1,716	50.7	5,633	50.6	7,349	50.6
Current Smoker	324	9.6	1,240	11.1	1,564	10.8
Not Reported	351	10.4	898	8.1	1,249	8.6
						p <0.001
Drinking Status						
Drinker	1,481	43.8	4,794	43.1	6,275	43.2
Non-Drinker	448	13.2	1,660	14.9	2,108	14.5
Not Reported	1,453	43.0	4,681	42.0	6,134	42.3
						p=0.06
Index of Multiple Deprivation						
1	438	13.0	1,430	12.8	1,868	12.9
2	494	14.6	1,605	14.4	2,099	14.5
3	479	14.2	1,597	14.3	2,076	14.3
4	425	12.6	1,431	12.9	1,856	12.8
5	281	8.3	1,019	9.2	1,300	9.0
Not Reported	1,265	37.4	4,053	36.4	5,318	36.6

SD Standard Deviation. P P-value. To simplify the content of the table, only p-values <0.10 are reported. All others not shown were ≥0.10.

reported at only 67.8%. Overall, 43.2% reported being drinkers. There were slightly more non-drinkers among the controls, although this difference was not statistically significant (p=0.06). Reporting of IMD was dependent upon linkage of the CPRD data to the IMD file in the CPRD Linkage Scheme. Consequently, only 63.4% of patients had IMD reported, with 12.9% in the least deprived quintile of IMD (Score=1) and 9.0% in the most deprived quintile (Score=5).

3.3.3 Baseline Clinical Characteristics

Overall, the average BMI was 29.8 kg/m^2, and did not differ significantly between cancer patients (29.7 kg/m^2) and controls (29.8 kg/m^2) (p=0.08). (Table 3.3) The categorical variable for BMI indicates a statistically significant difference (chi-square: $p < 0.001$) in the distribution of BMI categories between the two groups, with a larger proportion of control patients having a BMI ≥30 kg/m^2, and a smaller proportion with BMI not reported. A slightly higher proportion of control patients (14.9%) had a Charlson Comorbidity Index ≥4 (chi-square: p=0.02). More than two thirds of patients had hypertension, and 10.5% had a history of stroke or TIA prior to cancer diagnosis or to the matched date for controls. There were no statistically significant ($p \leq 0.05$) differences between cancer patients and controls in the proportions of patients who had other specific cardiovascular conditions.

Table 3.3: Baseline Clinical Characteristics

	Cancer		Control		Total	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Total	**3,382**	**100**	**11,135**	**100**	**14,517**	**100**
Body Mass Index						
<25	579	17.1	1,932	17.4	2,511	17.3
25-29	1,272	37.6	4,183	37.6	5,455	37.6
≥30	1,344	39.7	4,656	41.8	6,000	41.3
Not Reported	187	5.5	364	3.3	551	3.8
						p <0.001
mean (SD)	3,195	29.7(5.5)	10,771	29.8(5.7)	13,966	29.8(5.6)
						p=0.08
Charlson Comorbidity Index						
1-2	1,878	55.5	5,898	53.0	7,776	53.6
3-4	1,044	30.9	3,578	32.1	4,622	31.8
>4	460	13.6	1,659	14.9	2,119	14.6
						p=0.02
Atrial Fibrillation						
No	3,090	91.4	10,168	91.3	13,258	91.3
Yes	292	8.6	967	8.7	1,259	8.7
Coronary Heart Disease						
No	3,034	89.7	9,957	89.4	12,991	89.5
Yes	348	10.3	1,178	10.6	1,526	10.5
Heart Failure						
No	3,175	93.9	10,366	93.1	13,541	93.3
Yes	207	6.1	769	6.9	976	6.7
Hypertension						
No	1,076	31.8	3,509	31.5	4,585	31.6
Yes	2,306	68.2	7,626	68.5	9,932	68.4
Stroke or Transient Ischaemic Attack						
No	3,054	90.3	9,942	89.3	12,996	89.5
Yes	328	9.7	1,193	10.7	1,521	10.5
						p=0.09

SD Standard Deviation. P P-value. To simplify the content of the table, only p-values <0.10 are reported. All others not shown were ≥0.10.

3.3.4 Baseline Microvascular Complications of Diabetes

Microvascular complications consisted of retinopathy, neuropathy, nephropathy, and chronic kidney disease (Table 3.4), and 30.0% of patients had a history of at least one of these. The proportion was slightly lower in cancer patients (28.7%) than in controls (30.4%), although this difference did not reach statistical significance (p=0.06). Retinopathy was the most common microvascular complication (23.6%), followed by neuropathy (8.2%), while nephropathy (1.2% overall) and chronic kidney disease (1.7% overall) were uncommon. Chronic kidney disease was slightly less common in cancer patients than controls.

Table 3.4: Baseline Microvascular Complications of Diabetes

	Cancer		Control		Total	
Complication	**n**	**%**	**n**	**%**	**n**	**%**
Total	**3,382**	**100**	**11,135**	**100**	**14,517**	**100**
Any Microvascular Complication of Diabetes						
No	2,412	71.3	7,750	69.6	10,162	70.0
Yes	970	28.7	3,385	30.4	4,355	30.0
						p=0.06
Retinopathy						
No	2,615	77.3	8,475	76.1	11,090	76.4
Yes	767	22.7	2,660	23.9	3,427	23.6
Neuropathy						
No	3,119	92.2	10,210	91.7	13,328	91.8
Yes	263	7.8	925	8.3	1,189	8.2
Nephropathy						
No	3,347	99.0	10,999	98.8	14,346	98.8
Yes	35	1.0	136	1.2	171	1.2
Chronic Kidney Disease*						
No	3,337	98.7	10,933	98.2	14,270	98.3
Yes	45	1.3	202	1.8	247	1.7
						p=0.06

P P-value. To simplify the content of the table, only p-values <0.10 are reported. All others not shown were ≥0.10. *Stage 4 or 5 kidney disease

3.3.5 Baseline Macrovascular Complications of Diabetes

Overall, 21.7% of patients in the combined cancer cohort had a history of macrovascular complications (Table 3.5). The most common macrovascular complication was acute myocardial infarction (10.5%), followed by peripheral arterial disease (8.1%). A significantly larger proportion of control patients (8.4%) than cancer patients (7.0%) had a history of peripheral arterial disease (chi-square: p=0.01). Lower limb amputation was uncommon in the study population (0.9%).

Table 3.5: Baseline Macrovascular Complications of Diabetes

	Cancer		Control		Total	
Complication	**n**	**%**	**n**	**%**	**n**	**%**
Total	**3,382**	**100**	**11,135**	**100**	**14,517**	**100**
Any Macrovascular Complication of Diabetes						
No	2,681	79.3	8,684	78.0	11,365	78.3
Yes	701	20.7	2,451	22.0	3,152	21.7
Peripheral Arterial Disease						
No	3,145	93.0	10,200	91.6	13,345	91.9
Yes	237	7.0	935	8.4	1,172	8.1
						p=0.01
Acute Myocardial Infarction						
No	3,034	89.7	9,957	89.4	12,991	89.5
Yes	348	10.3	1,178	10.6	1,526	10.5
Cerebrovascular Accident						
No	3,177	93.9	10,411	93.5	13,588	93.6
Yes	205	6.1	724	6.5	929	6.4
Lower Limb Amputation						
No	3,357	99.3	11,025	99.0	14,382	99.1
Yes	25	0.7	110	1.0	135	0.9

P P-value. To simplify the content of the table, only p-values <0.10 are reported. All others not shown were ≥0.10.

3.3.6 Baseline Clinical and Laboratory Values

Clinical and laboratory values consisted of blood pressure, total cholesterol, HbA1c, and serum creatinine (Table 3.6). Almost all (98.5%) patients had a blood pressure reading in the year prior to cancer diagnosis or matched date for controls. Overall, the mean systolic blood pressure was 136 mm Hg, the mean diastolic blood pressure was 74 mm Hg, and 60.6% of patients had a blood pressure reading ≤140/80 mm Hg, which is the threshold for the diabetes QOF performance measure dm003. There was no statistically significant difference between cancer patients and controls in either mean systolic or mean diastolic blood pressure. In the categorical data analysis of blood pressure, the distribution of blood pressure between cancer patients and controls was statistically significantly different (chi-square: $p < 0.001$). A slightly higher percent of control patients (60.8%) than cancer patients (59.9%) had a baseline blood pressure reading ≤140/80 mm Hg, but a higher proportion of cancer patients (3.1%) did not have a blood pressure reading in the year before cancer.

As with blood pressure, most patients (96.3%) had a serum total cholesterol test result prior to cancer diagnosis or matched date for controls. Overall, the mean serum total cholesterol was 4.2 mmol/L, and the mean was statistically significantly lower ($p < 0.001$) in cancer patients than controls, even though the absolute difference (0.1 mmol/L) was unlikely to have been of clinical significance.

Table 3.6: Baseline Clinical and Laboratory Values

	Cancer		Control		Total	
Laboratory Value	**n**	**%**	**n**	**%**	**n**	**%**
Total	**3,382**	**100**	**11,135**	**100**	**14,517**	**100**
Blood Pressure ≤140/80 mm Hg						
Yes	2,026	59.9	6,770	60.8	8,796	60.6
No	1,250	37.0	4,252	38.2	5,502	37.9
Not Reported	106	3.1	113	1.0	219	1.5
						p <0.001
systolic mean(SD)	3,276	136(15)	11,022	136(16)	14,298	136(16)
diastolic mean(SD)	3,276	74(9)	11,022	74(9)	14,298	74(9)
						p=0.09
Total Cholesterol ≤5mmol/L						
Yes	2,706	80.0	8,971	80.6	11,677	80.4
No	475	14.0	1,826	16.4	2,301	15.9
Not Reported	201	5.9	338	3.0	539	3.7
						p <0.001
mean(SD)	3,181	4.2(0.9)	10,797	4.3(1.5)	13,978	4.2(1.4)
						p <0.001
HbA1c (mmol/mol)						
≤59	2,179	64.4	6,995	62.8	9,174	63.2
59-≤64	310	9.2	1,054	9.5	1,364	9.4
65-≤75	322	9.5	1,074	9.6	1,396	9.6
>75	185	5.5	702	6.3	887	6.1
Not Reported	386	11.4	1,310	11.8	1,696	11.7
mean(SD)	2,996	54.0(12.5)	9,825	54.5(13.1)	12,821	54.3(13.0)
						p=0.04
Serum Creatinine (umol/L)						
≤130	2,730	80.7	8,861	79.6	11,591	79.8
>130	322	9.5	984	8.8	1,306	9.0
Not Reported	330	9.8	1,290	11.6	1,620	11.2
						p=0.01

P P-value. To simplify the content of the table, only p-values <0.10 are reported. All others not shown were ≥0.10.

In the categorical data analysis of serum total cholesterol, the distribution of total cholesterol test results between cancer patients and controls also was statistically

significantly different (chi-square: p <0.001). A slightly higher percent of control patients (80.6%) than cancer patients (80.0%) had a baseline serum total cholesterol result ≤5 mmol/L, which is the threshold for the diabetes QOF performance measure dm004, but a higher proportion of cancer patients (5.9%) did not have a valid test result in the year before cancer.

Overall, 88.3% of patients had an HbA1c test result in the year before cancer or matched date for controls. The mean HbA1c was 54.3 mmol/mol, and the difference in means between cancer patients and controls (0.5 mmol/mol) was small, but the mean was statistically significantly (p=0.04) higher in controls. There was no difference in the distributions of HbA1c test result categories between cancer patients and controls. This is notable since the cut points for these categories were set at the thresholds of the three diabetes QOF HbA1c performance measures (≤59, ≤64, and ≤75 mmol/mol).

Serum creatinine also was well-reported, and 88.8% had a test result. The difference in distributions of test results between cancer patients and controls was statistically significant (p=0.01). However, this may be due in large part to a difference in the proportion of patients without a test result (9.8% cancer versus 11.6% control).

3.3.7 Baseline Antidiabetic Medications

Overall, 78.4% received at least one antidiabetic medication in the year prior to cancer diagnosis or matched date for controls (Table 3.7). The proportion was slightly higher in controls than cancer patients, and the difference narrowly failed to meet the threshold for statistical significance (p=0.06). The most common class of agents was biguanides (58.6%), which includes metformin, followed by sulfonylureas (35.7%), and insulin (16.6%). There were no statistically significant differences between cancer patients and controls in the proportion of patients using specific classes of antidiabetic agents.

Table 3.7: Baseline Antidiabetic Medications

		Cancer		Control		Total	
Antidiabetic Agent		**n**	**%**	**n**	**%**	**n**	**%**
	Total	**3,382**	**100**	**11,135**	**100**	**14,517**	**100**
Any Antidiabetic Agent							
	No	769	22.7	2,363	21.2	3,132	21.6
	Yes	2,613	77.3	8,772	78.8	11,385	78.4
							p=0.06
Insulin							
	No	2,847	84.2	9,266	83.2	12,113	83.4
	Yes	535	15.8	1,869	16.8	2,404	16.6
Biguanide							
	No	1,418	41.9	4,588	41.2	6,006	41.4
	Yes	1,964	58.1	6,547	58.8	8,511	58.6
Sulfonylurea							
	No	2,189	64.7	7,149	64.2	9,338	64.3
	Yes	1,193	35.3	3,986	35.8	5,179	35.7
Other Antidiabetic Agent							
	No	3,021	89.3	9,879	88.7	12,900	88.9
	Yes	361	10.7	1,256	11.3	1,617	11.1

P P-value. To simplify the content of the table, only p-values <0.10 are reported. All others not shown were ≥0.10.

3.3.8 Baseline Use of Other Medications

Proportions of patients receiving other types of medications in the year prior to cancer diagnosis or matched date for controls are shown in Table 3.8. As expected, the proportions of patients receiving cholesterol lowering agents, anti-hypertensive medications, and other cardiovascular agents were all quite high. However, there were no statistically significant differences between cancer patients and controls.

Table 3.8: Baseline Use of Other Medications

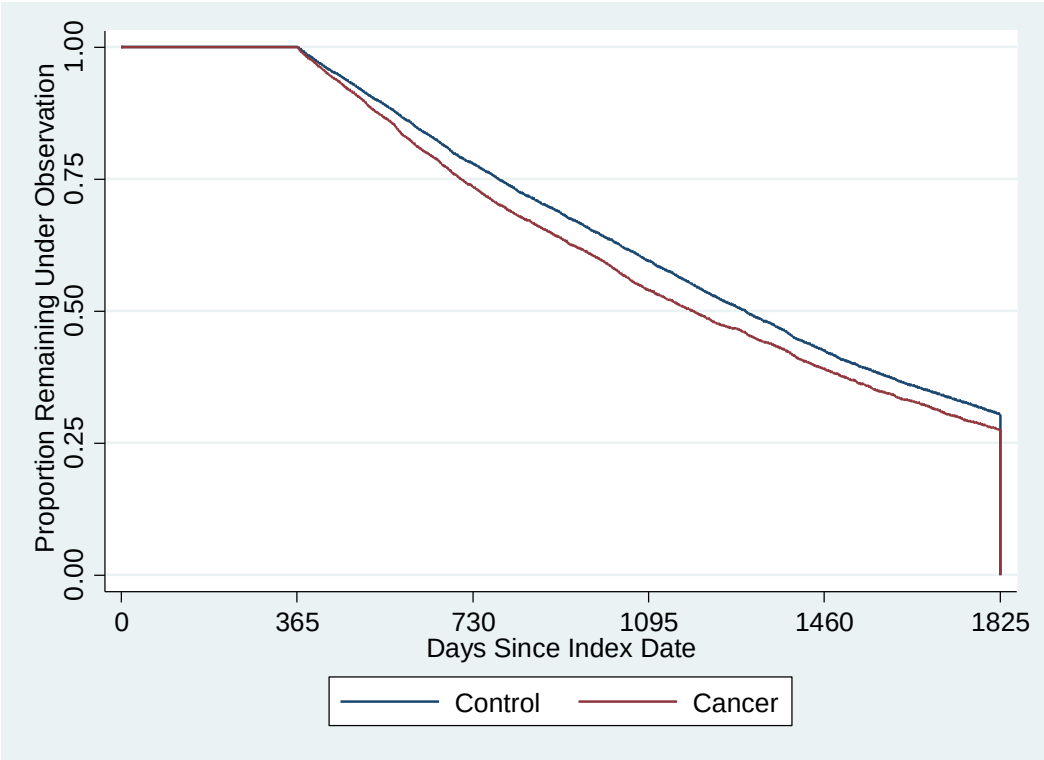
Other Medication		Cancer n	Cancer %	Control n	Control %	Total n	Total %
	Total	**3,382**	**100**	**11,135**	**100**	**14,517**	**100**
Statin							
	No	842	24.9	2,634	23.7	3,476	23.9
	Yes	2,540	75.1	8,501	76.3	11,041	76.1
Angiotensin Converting Enzyme Inhibitor							
	No	1,604	47.4	5,149	46.2	6,753	46.5
	Yes	1,778	52.6	5,986	53.8	7,764	53.5
Angiotensin Receptor Blocker							
	No	2,739	81.0	8,906	80.0	11,645	80.2
	Yes	643	19.0	2,229	20.0	2,872	19.8
Beta Blocker							
	No	2,354	69.6	7,676	68.9	10,030	69.1
	Yes	1,028	30.4	3,459	31.1	4,487	30.9
Calcium Channel Blocker							
	No	2,079	61.5	6,904	62.0	8,983	61.9
	Yes	1,303	38.5	4,231	38.0	5,534	38.1
Thiazide Related Diuretic							
	No	2,499	73.9	8,236	74.0	10,735	73.9
	Yes	883	26.1	2,899	26.0	3,782	26.1
Other Diuretic							
	No	2,750	81.3	8,996	80.8	11,746	80.9
	Yes	632	18.7	2,139	19.2	2,771	19.1
Antiplatelet							
	No	1,482	43.8	4,811	43.2	6,293	43.3
	Yes	1,900	56.2	6,324	56.8	8,224	56.7
Anticoagulant							
	No	3,131	92.6	10,349	92.9	13,480	92.9
	Yes	251	7.4	786	7.1	1,037	7.1
Antiarrhythmic							
	No	3,272	96.7	10,770	96.7	14,042	96.7
	Yes	110	3.3	365	3.3	475	3.3
Aspirin							
	No	1,601	47.3	5,146	46.2	6,747	46.5
	Yes	1,781	52.7	5,989	53.8	7,770	53.5

P P-value. To simplify the content of the table, only p-values <0.10 are reported. All others not shown were ≥0.10.

3.3.9 Follow-Up for Quality of Diabetes Care

Kaplan-Meier curves for follow-up[i] of cancer patients and controls in the combined cancer cohort are presented in Figure 3.3.[j] As shown, all patients were required to have had at least one year of observation following the date of cancer diagnosis or matched date for controls (horizontal line in upper left corner of figure), and all patients were censored at a maximum of five years after the beginning of the observation period (vertical line in lower right corner of figure). Overall, the median length of follow-up was 1,274 days (3.5 years), and follow-up was significantly longer in control patients (median 1,295 days) than cancer patients (median 1,187 days: log-rank test for equality of survivor functions p <0.0001).

Figure 3.3: Patient Follow-Up



[i] End of follow-up was based on the day the patient was censored from the cohort (death or end of data).
[j] Information on follow-up in the individual cancer cohorts is presented in the Appendix to this chapter.

The total number of years of follow-up in the combined cancer cohort was 44,507, 9,953 (22.4%) of which were for cancer patients. (Table 3.9)

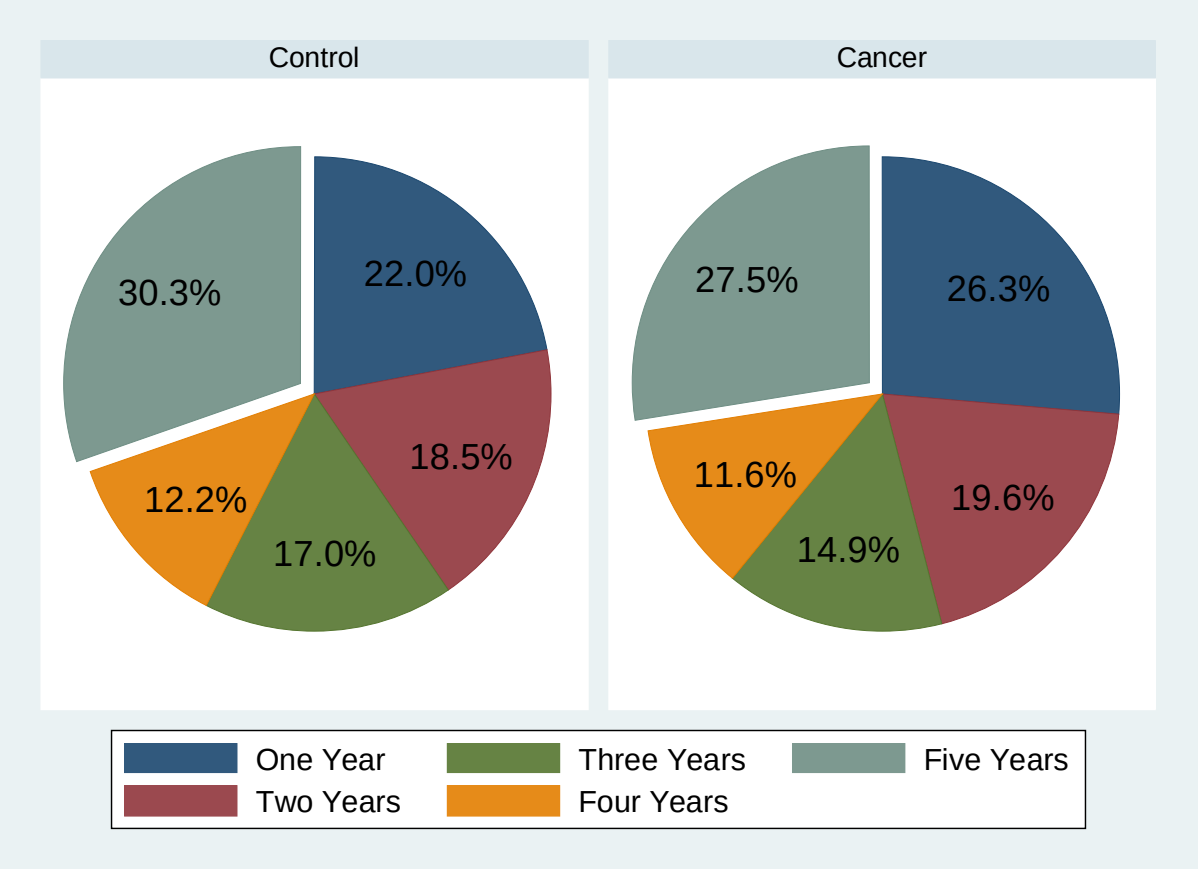
Table 3.9: Person Years of Follow-Up

Cohort	Cancer	Control	Total
	n	n	n
Breast	3,149	10,296	13,445
Colorectal	3,061	13,145	16,206
Prostate	3,743	12,456	16,199
Combined	**9,897**	**34,909***	**44,806***

*412 patients were dropped from the control group of the combined cancer cohort since they appeared as a control in more than one individual cancer cohort.

A larger proportion of control patients than cancer patients had five years of follow-up (Figure 3.4), and the distribution of follow-up times (in whole years) was statistically significantly different (chi-square: $p < 0.0001$) between the two groups. However, absolute differences in proportions were small.

Figure 3.4: Distribution of Follow-Up Times (In Years)



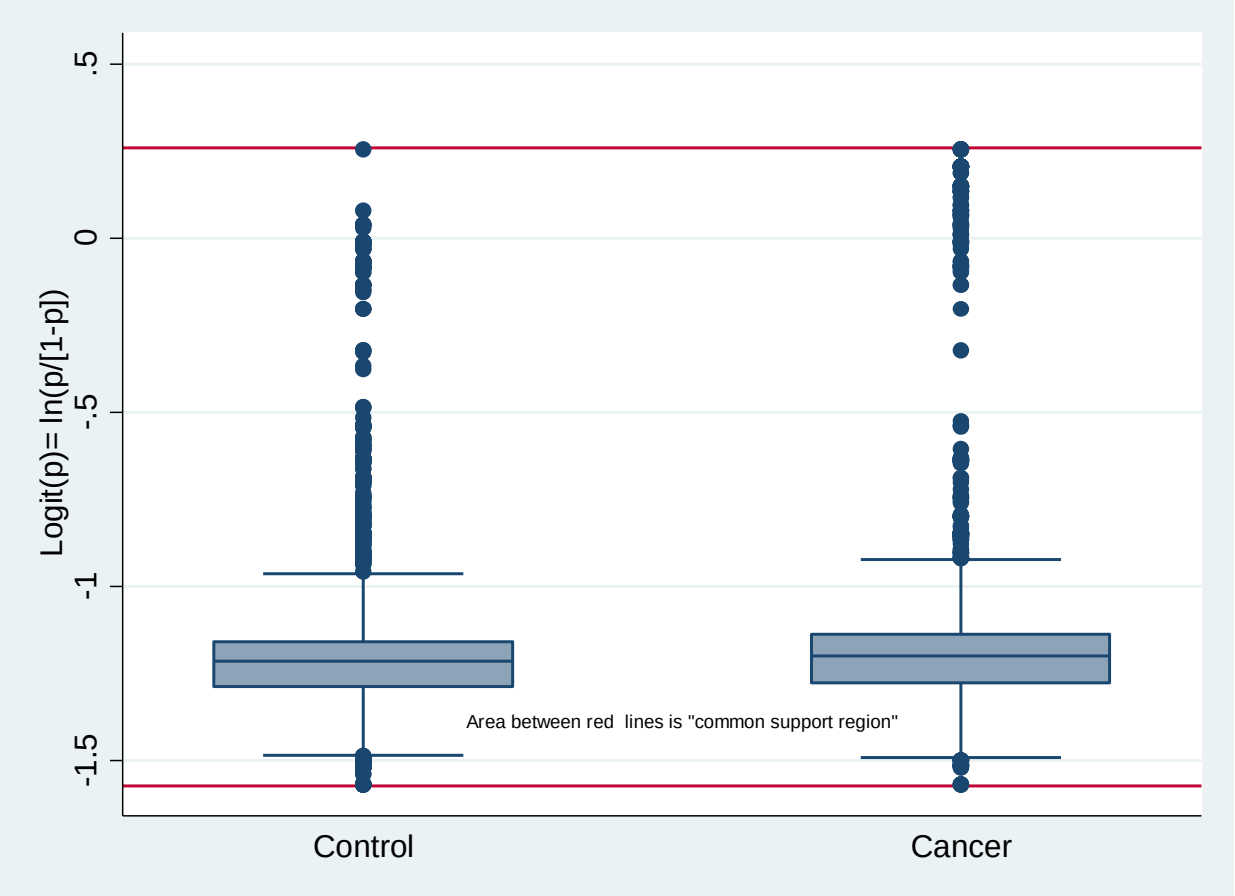
3.3.10 Propensity Score Matching

Binary logistic regression using a backwards, stepwise elimination of predictors[14,15] with a p value >0.2 resulted in a model that included cohort assignment[k] (breast, colorectal, or prostate), total cholesterol, sex, most recent drinking status, HbA1c, Charlson Comorbidity Index, and blood pressure as predictors. The distributions of logit propensity scores for cancer patients and controls from this model show a large common support region that encompasses virtually all of the cancer cases (Figure 3.5). This was expected given that cancer and control patients were already matched on

[k] Cohort assignment was included only in the model used to generate propensity scores for patients in the combined cohort. This variable was dropped when scores were generated for the individual cohorts.

several important covariates as part of the study inclusion criteria. A large common support region indicated most cancer patients should have been included in the propensity score-matched cohort. Findings were similar for the three cancer-specific cohorts (not shown).

Figure 3.5: Distributions of Logit Propensity Scores



As expected based on the level of overlapping in the common support region of the logit propensity scores, most cancer patients were included in the combined and individual cancer propensity score matched cohorts. (Table 3.10)

Table 3.10: Patients Included in the Propensity Matched Cohorts

	Cancer	Control	Total
Cohort	n (%)	n	n
Breast	1,036 (100%)*	1,036	2,072
Colorectal	1,042 (97%)	1,042	2,084
Prostate	1,237 (97%)	1,237	2,474
Combined**	3,320 (98%)	3,320	6,640

*Percent of all patients included in the propensity matched cohort

**One additional cancer patient was matched to a control patient who was not originally from the same cancer cohort

Comparison of demographic and clinical characteristics, as well as laboratory values and medications, showed substantial improvement in the balance of individual characteristics between cancer patients and controls after propensity score matching. In the combined cancer cohort, the distributions of 13 categorical variables were significantly ($p < 0.1$) different between cancer patients and controls prior to matching. After matching, only one categorical variable met this criterion, prior use of anticoagulation therapy, which was 7.4% in cancer patients and 6.2% in controls. Small differences between cancer patients and controls also remained in mean diastolic blood pressure (0.52 mm Hg higher in cancer) and in total cholesterol (0.03 mmol/L higher in cancer). Finally, a comparison of mean logit scores (propensity scores transformed by ln [P/1-P] to normalize the distributions) between cancer patients and controls confirmed no statistically significant difference after matching ($p=0.51$).

3.4 DISCUSSION AND CONCLUSIONS

3.4.1 Summary of Findings

This chapter has presented the methods of primary research used to compare the quality and outcomes of diabetes care between cancer patients and non-cancer controls. The methods of primary research were designed to incorporate the implications of the findings from the systematic review for future primary research, as summarized in the previous chapter (Section 2.4.4), including the following:

- Assess the impact of cancer on the quality and outcomes of diabetes care from initial diagnosis and treatment of cancer through long-term follow-up;
- Base the research on data that are more nationally representative of cancer patients—especially when compared to US studies that used SEER-Medicare data;
- Incorporate a longitudinal "before and after" design, also with a non-cancer control group, in part to adjust for secular trends in the delivery of routine diabetes care over time;
- Use statistical methods that allow for comparison of diabetes quality of care within cancer patients over time, as well as comparisons between cancer patients and non-cancer controls over time; and
- Use propensity score matching of non-cancer controls to cancer cases on underlying demographic and clinical characteristics to improve the efficiency of the statistical modelling, as well as to simplify the graphical depiction of results from the adjusted analyses.

Applying the study inclusion and exclusion criteria to the CPRD data resulted in identifying large cohorts of diabetic cancer patients and matched, diabetic non-cancer controls for the research. Overall, baseline characteristics of cancer patients and controls were similar, and propensity score matching eliminated virtually all statistically significant differences between the two groups. The patient cohorts constructed for this primary research are larger than in many of the studies included in the systematic review (Chapter 2). Since those studies were large enough to detect differences in the quality of diabetes care between cancer patients and controls, it is likely that the cohorts selected for this research also are sufficiently large to detect meaningful differences if they exist.

3.4.2 Strengths and Limitations

The strengths and limitations of the study design for the primary research can be assessed with the same instrument used to assess the quality of studies in the systematic review (Chapter 2), the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (Box 3.1).[27]

Box 3.1: Criteria for Assessing the Quality of Cohort Studies[27]

- **Representativeness of the exposed cohort**
- **Selection of the non-exposed cohort**
- **Ascertainment of exposure**
- **Comparability of cohorts**

  Study controls for age

  Study controls for additional factors
- **Assessment of outcome**[l]
- **Follow-up long enough for outcomes to occur**[l]
- **Adequacy of follow-up of cohorts**[l]

3.4.2.1 Representativeness of the Exposed Cohort

One strength of the study design is that it is based on CPRD, which includes patients who are broadly representative of the UK general population in terms of age, sex, geographic location, and ethnicity.[4] However, since only patients age ≥50 years at the time they were diagnosed with breast, colorectal, or prostate cancer were selected, one limitation of the study is that it does not include younger patients with diabetes, or those with diabetes who were diagnosed with other types of cancer.

3.4.2.2 Selection of the Non-Exposed Cohort

Another strength of the study design is that patients in the non-exposed cohort were matched to individual cancer patients based on age, sex, and GP practice number.

[l] These are assessed in subsequent chapters reporting the methods and results of the individual analyses.

Matched controls, like the cancer cases, had to have been diagnosed with diabetes at least two years before their index date. Therefore, selection of the non-exposed patients was designed to minimize potential confounding caused by imbalances in some of the baseline characteristics of the cancer patients and non-cancer controls, which may also have affected the outcomes. One limitation of this approach is that in order to maximize the number of cancer patients with at least one matched control, only a subset of potential confounders was included as matching criteria. However, cohorts based on propensity matching, which included a much larger set of demographic and clinical variables, also were constructed from the full cohorts; and these included almost all of the cancer patients.

3.4.2.3 Ascertainment of the Exposure

Since the aim of the primary research was to compare the quality and outcomes of diabetes care between cancer patients and non-cancer controls, cancer was the exposure in this instance. One limitation of the study design is that it was not feasible to link the CPRD data to information from the NCIN,[9] which would have allowed use of the registry data to identify cancer patients. Instead, Read codes in the primary care data, which do have a high sensitivity and specificity for identifying cancer, were used.[28]

Cancer registry data also would have allowed exclusion of patients diagnosed with metastatic disease. Read codes in the primary care data files or International Classification of Diseases, 10th Revision (ICD-10) codes in the HES[6] inpatient data were considered for use in staging patients. However, there have not been any studies in the UK that have validated the use of ICD-10 codes for this purpose, and because only two-

thirds of the patients in the research were linked to HES, doing so would have limited the sample sizes. Instead, patients who died within the first year after their index date were excluded. This approach should have resulted in excluding cancer patients with advanced disease and a relatively poor prognosis, for whom cancer care justifiably could be made an exclusive priority over diabetes care; inclusion of such patients likely would have created a bias toward finding less receipt of recommended diabetes care among cancer patients.

3.4.2.4 Comparability of the Cohorts

Several steps were taken to maximize the comparability of the cancer patients and non-cancer controls. As described above, as part of the patient selection process non-cancer controls were matched to cancer patients on age, sex, and GP practice, assigned an index date within one year of their cancer case, and also required to have been diagnosed with diabetes at least two years before their index date. Also, cohorts based on propensity matching that included a broad array of patient variables were constructed from the full cohorts. Virtually all differences in baseline demographic and clinical characteristics between propensity matched cancer patients and controls were eliminated at this stage. However, since the primary analyses for comparing the quality and outcomes of diabetes care between cancer patients and controls were based on the full cohorts, multivariate statistical methods (See Chapters 4-6 for methods specific to the outcomes) were used to adjust for differences in baseline characteristics. Also, since patients in this study were followed from before to after their index date, the quality of

diabetes care was compared "before and after" cancer, and in those analyses cancer patients served as their own controls.

The remainder of the criteria (Box 3.1) for assessing the quality of the design for the primary research of this thesis pertain to the assessment of outcomes. Therefore, these are addressed in the chapters that present the methods and results of the analyses (Chapters 4-6).

Although not included in the list above, another strength of the study design is that the study population is similar in size to, or larger than, those of other studies that have examined the impact of incident cancer on adherence to glucose-lowering treatment in diabetes,[29,30] on general practitioner consultation rates in diabetes,[31] on testing, and on control of diabetes.[32,33] Those studies were sufficiently large to detect clinically meaningful and statistically significant changes in the diabetes outcomes of interest associated with incident cancer diagnosis. Therefore, the cohort constructed to conduct the research was judged to be sufficiently large to detect differences in the outcomes of interest in this study, especially since many of the analyses (Chapters 4-6) employed repeated measures on individual patients.

Another limitation of the study design is that since patients were required to have been diagnosed with diabetes for a minimum—there was no maximum—of two years before their index date, baseline patient characteristics were established at cancer diagnosis (or the assigned date in matched, non-cancer controls), rather than at the time of diabetes diagnosis, as is usually the case in studies of newly diagnosed patients, such as the UKPDS.[34-36] Consequently, there was a lack of baseline diabetes factors. Information on

patients at the time they were diagnosed with diabetes could have revealed important, and potentially confounding, differences between cases and controls, which could have been adjusted for through multivariate analyses and/or propensity score matching.

As described in Chapter 1, Section 1.1 of the thesis, the prospective observational studies conducted by the UKPDS to determine the relations between glycaemia, blood pressure, and complications of diabetes[35,36] provide an important benchmark for assessing whether observed changes in biological parameters due to cancer would be of sufficient size and duration to substantially increase the risk of diabetes complications in the primary research. Therefore, it is useful to compare the characteristics of the populations in order to identify differences that might undermine the validity of this benchmark. Patients in the primary research were approximately 20 years older (mean 72 years) than those in the UKPDS glycaemia study (mean 53 years),[35] had higher BMI (mean 30 kg/m^2 versus 28 kg/m^2), had similar HbA1c (mean ≈54 mmol/mol in each study), and had similar SBP (mean 136 mm Hg versus 135 mm Hg). Although not reported in either observational study,[35,36] as UKPDS enrolled a cohort of patients newly diagnosed with type II diabetes, with a maximum age of 65,[34] it is likely that patients in the primary research for the thesis had higher baseline rates of comorbidities, including complications of diabetes. Perhaps the most striking difference between the two populations is the mean age. This was to be expected as breast, colorectal, and prostate cancer are diagnosed predominately in older patients. Once implication of the age difference between the two populations is that since other studies on the impact of intensive glucose control in older patients have shown fewer significant benefits,[37]

changes in biological parameters due to cancer that are comparable to those in UKPDS could result in smaller changes in the risks of complications in the primary research.

3.4.3 Conclusions and Implications

The cohorts constructed to conduct primary research on the quality and outcomes of diabetes care in cancer were sufficiently large to detect clinically meaningful differences between cancer patients and controls, and to detect "before and after" changes in cancer patients. Moreover, key variables used to adjust for potential confounding, such as smoking, BMI, baseline cholesterol, and baseline HbA1c, were well-populated in the patient cohorts for the primary research. Some imbalances in the baseline characteristics of cancer cases and controls indicated that statistical analyses should consist of both unadjusted and multivariate (adjusted for baseline characteristics) comparisons of quality and outcomes between cancer patients and controls, to adjust for potential confounding due to these imbalances. Further, they indicated secondary analyses should be conducted in the propensity-matched cohort, where the balance in the baseline characteristics was improved considerably.

3.5 CHAPTER REFERENCES

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CHAPTER FOUR

Quality of Diabetes Care

IV QUALITY OF DIABETES CARE

4.1 CHAPTER AIM

The aim of this chapter is to present the methods and results of the primary research in which changes in the quality of diabetes care over time were compared between cancer patients and controls. Excerpts from this chapter have been included in the following article submitted for peer-review publication:

Griffiths RI, McFadden EC, Stevens RJ, Valderas JM, Lavery BA, Khan NF, Keating NL, Bankhead CR. Quality of Diabetes Primary Care in Breast, Colorectal, and Prostate Cancer.

4.2 METHODS OF RESEARCH

4.2.1 Construction of a Patient-Period Dataset

In Chapter 3, patient-level datasets (one record per patient) were constructed to compare baseline demographic and clinical characteristics between cancer patients and controls. Since the research in this chapter consisted of comparing changes in the quality of diabetes care between cancer patients and controls over time, patient-period datasets were constructed. First, one patient record was created *for each full year* that the patient was included in the study. So, a patient who was followed for between one and two years after their index date had three records, one for each of two full years prior to their index date, and one for the first full year after their index date; and, a patient followed for the maximum of five full years after their index date had seven records. Second, binary variables, one for each quality measure (defined in the

following section), were constructed to serve as indicators of whether or not the patient met a specific quality measure in a specific year. Third, patient level information pertaining to each quality measure was compiled for each year, and used to determine whether the patient met the criteria for that quality measure in that year. Fourth, the binary quality measure variables were coded as 0 or 1 depending on results of step 3.

4.2.2 Quality of Care Measures

Measures used to compare the quality of diabetes care between cancer patients and controls were constructed based on the QOF Department of Health, Data and Business Rules, Diabetes Mellitus Indicator Set, Version No. 25.0, version date 28/03/13,[1] which includes indicators for blood pressure, cholesterol, and HbA1c control; diabetes services, e.g., foot examination; and other general primary care services, e.g., influenza immunisation. (Box 4.1) The Diabetes Mellitus Indicator Set[1] includes two measures for blood pressure control and three for HbA1c control. Since any adverse effect of cancer on blood pressure or HbA1c control might be more apparent in quality measures based on greater control, i.e., lower levels for meeting the measure, both blood pressure and all three HbA1c measures were included in the analyses.

Patients were considered to have met the quality measures for blood pressure, cholesterol, and HbA1c control in a specific year if their last reading/laboratory result in that year was at or below the threshold in the Diabetes Mellitus Indicator Set.[1] (Box 4.1) Those patients who had no reading/laboratory result during the year, or whose last result exceeded the threshold (irrespective of whether an earlier result in that year was below the threshold), were considered to have not met the quality measure in that year.

Box 4.1: Measures Developed to Assess the Quality of Diabetes Care

- Last blood pressure reading in the year was ≤150/90 mm Hg. (QOF DM002)
- Last blood pressure reading in the year was ≤140/80 mm Hg. (QOF DM003)
- Last total cholesterol test result in the year was ≤5 mmol/L. (QOF DM004)
- Received an albumin creatinine ratio test during the year. (QOF DM005)
- Treated with an ACE-I or an ARB during the year (applies only to those diagnosed with nephropathy or microalbuminuria). (QOF DM006)
- Last HbA1c test in the year was ≤59 mmol/mol. (QOF DM007)
- Last HbA1c test in the year was ≤64 mmol/mol. (QOF DM008)
- Last HbA1c test in the year was ≤75 mmol/mol. (QOF DM009)
- Influenza immunisation during the year. (QOF DM010)
- Retinal screening during the year. (QOF DM011)
- Foot examination during the year. (QOF DM012)
- Dietary review during the year. (QOF DM013)
- Male patient asked about erectile dysfunction during the year. (QOF DM015)
- Male patient received advice/assessment of erectile dysfunction during the year. (QOF DM016)

Quality measures for blood pressure, cholesterol, and HbA1c also were partitioned into (A) the probability of having at least one reading/test result during the year, and (B) the conditional (upon having had at least one reading/test during the year) probability that the last result was at or below the threshold. The purpose of partitioning was to help distinguish between changes in the quality of diabetes care that might have occurred due to disruptions in the continuity of services (blood pressure readings; cholesterol and HbA1c testing) due to cancer, and those that might have occurred due to changes in actual blood pressure, cholesterol, and HbA1c levels associated with the physiologic effects of cancer or cancer treatment.

Read codes from the Diabetes Mellitus Indicator Set[1] were used, often in combination with other codes in CPRD, to construct the other quality measures. (Box 4.1) A combination of Read codes ("46TC." and "46TD.") and Entity codes (152 and 165) was used to identify albumin creatinine ratio testing. Read codes ("R110.", "R110z", "C10EK", "C10FL", K190X", Kyu5G", "K08yA", "R1100", "R1103", "C10EL", and "C10FM") were used to identify patients diagnosed with nephropathy or microalbuminuria, and BNF codes (02050501 and 02050502) were then used to identify patients who also were treated with an ACE-I or ARB.

Influenza immunisation was identified using a combination of Read codes ("n47.." [excluding "n47A.", "n47B.", "n47r.", "n47s.", and "n47t"], "65ED.", "65E20", and "65ED0") and immunisation codes (4, 71-76, 78, 84, or 85). Retinal Screening was identified using Read codes ("2BB", "3128", "3129", "312E.", "312F.", "312G.", "58C1.", "68A7.", "68A8.", "66AD.", "8HBD.", "8HBG.", "8HBH.", "9N1v", "9N2U.", "9N2V.", "9N2e.", "9N2f.", or "9NNC."). Foot examination was identified using Read codes ("2G5E.", "2G5F.", 2G5G.", "2G5H.", "2G5I.", "2G5J.", "2G5K.", "2G5L.", "2G5d.", or "2G5e."). Dietary review was identified using Read codes ("66At.", "66At0", "66At1"). Measures for erectile dysfunction were identified using Read codes (asked about erectile dysfunction "1D1B." or "1ABJ.": advice/assessment of erectile dysfunction "1D1B." or "66Av.").

Patients with no record of a specific service during a specific year were considered to have not met that quality measure in that year. Because all patients had to have been diagnosed with diabetes at least two years before their index date, QOF indicator

DM014, “enrolment in a structured education programme within 9 months of diabetes diagnosis,” was not included among the quality measures.

4.2.3 Statistical Methods

Multilevel logistic regression analysis[2-4] was used to investigate changes in whether or not patients met each of the quality measures over time, and, more importantly for this research, *whether those patterns of change over time differed between cancer patients and controls*.

4.2.3.1 Primary Analyses

The primary multilevel logistic regression analyses were performed on all 14 quality measures in each of the four cohorts (cancers combined, breast, colorectal, and prostate) using up to five years of patient-period data after the index date. Unadjusted analyses included cancer (yes/no) and time (specified as a series of four indicator variables, with the index year as the reference category) as predictor variables. Adjusted analyses also included the following baseline demographic and clinical covariates as predictors: age, sex (combined cohorts, colorectal cancer), year of index date, smoking status, drinking status, BMI, type of cancer (in the analyses in which the three cancer types were combined), Charlson Comorbidity Index, IMD score, baseline blood pressure, baseline total cholesterol, baseline HbA1c, and history of diabetes medications. Adjusted analyses also were performed on the partitioned quality measures for blood pressure, cholesterol, and HbA1c. In all these analyses, the model coefficient for cancer is interpreted as the odds of meeting the quality measure in cancer patients compared to controls (OR).

Given the large number of multivariate analyses, adjustment for multiple comparisons was performed with the use of the Benjamini-Hochberg[5-7] approach, in which probability values from a family of comparisons (defined as the set of multivariate analyses performed on one cohort) were ordered from highest to lowest, and then compared with the corresponding Benjamini-Hochberg threshold for statistical significance.

4.3.2.2 Secondary Analyses

Secondary adjusted analyses were conducted on the full cohorts using all seven years of patient-period data (extended follow-up: including two years before the index date). These analyses included all the covariates in the primary adjusted analyses. In these analyses, the coefficient for cancer is interpreted as the OR of meeting the quality measure *after, compared to before, cancer.* Secondary analyses also were conducted in the propensity-matched cohorts using both five and seven years of data. Multilevel logistic regression analyses were performed in STATA 14[8] using the xtset and xtlogit commands.[3] Benjamini-Hochberg analyses were performed in Microsoft Excel (2013).[9]

4.3 RESULTS

4.3.1 Unadjusted Plots of Proportions Meeting Quality Measures

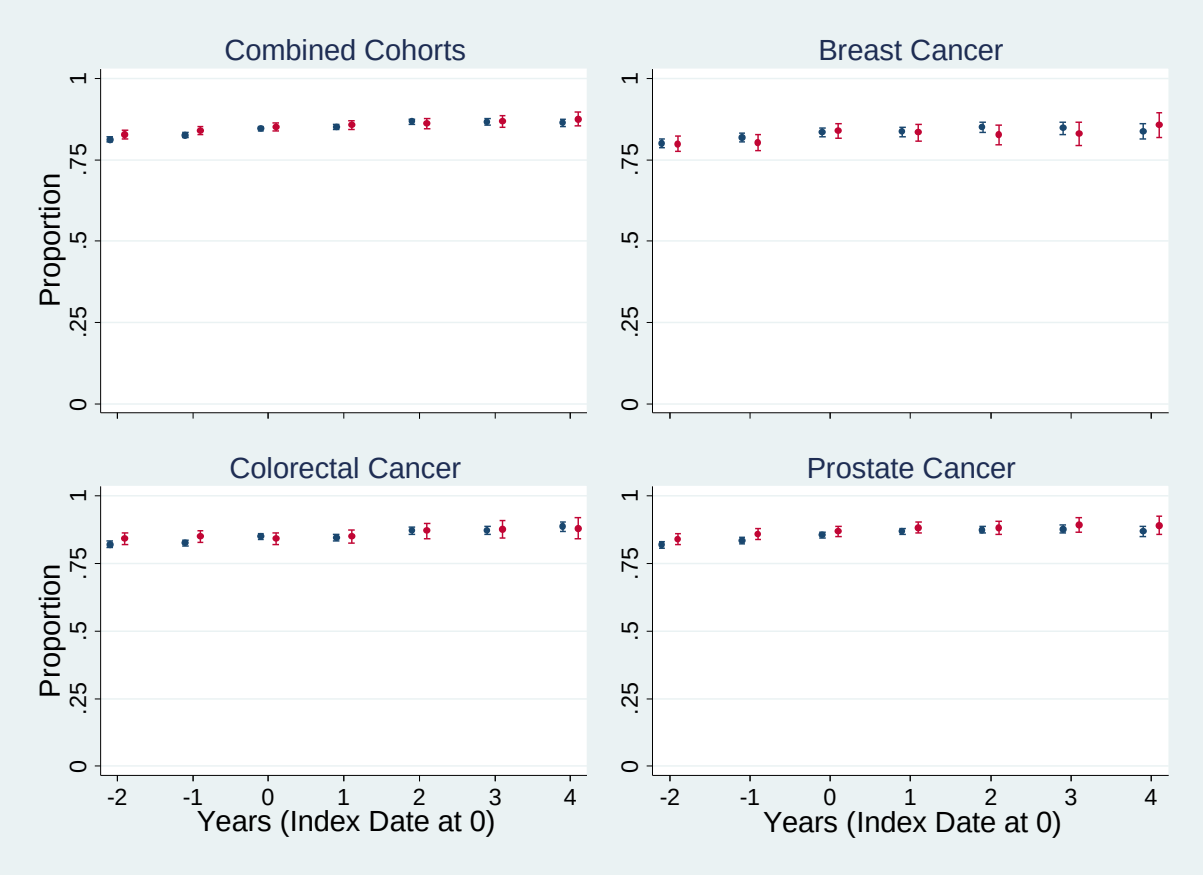
Plots of the unadjusted annual proportions (dots) and 95% CI (bars) of cancer patients (red) and controls (blue) meeting quality of diabetes care measures, from two years before (years -2 and -1 in the plots), up to five years after (years 0-4 in the plots) the date of cancer diagnosis, or matched date in the control group, are presented in Figures 4.1-4.14. The following text in this section describes the plots in the combined cohort,

with additional information on the individual cancer cohorts also provided if those plots differed substantially from the combined cohort.

4.3.1.1 Blood Pressure Control

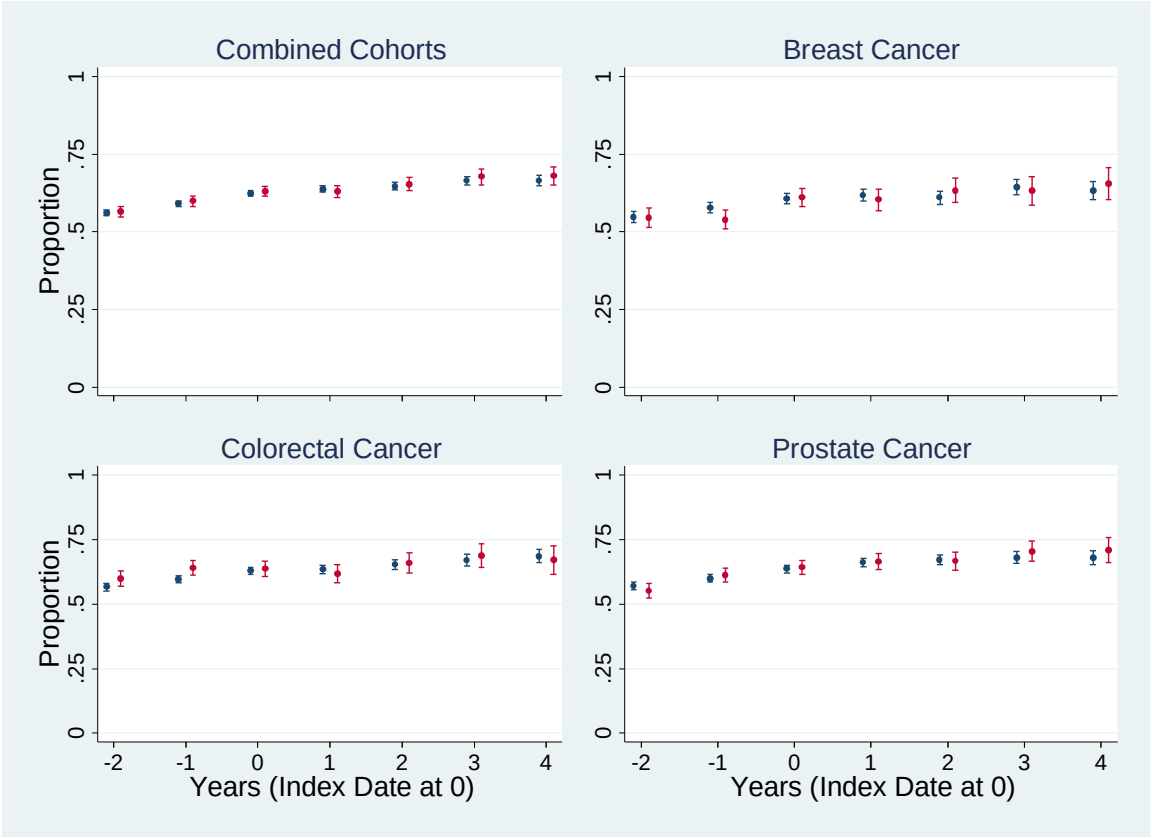
Proportions of patients meeting the quality measure for blood pressure ≤150/90 mm Hg (Figure 4.1) increased slightly from 82.7% (95% CI, 81.4%-84.0%) in cancer patients (red) and 81.2% (95% CI, 80.5%-81.9%) in controls (blue) two years before the index date (Year= -2) to 87.5% (95% CI, 85.4%-89.7%) and 86.3% (95% CI, 85.2%-87.5%), respectively, five years after the index date (Year=4). Cancer was not associated with either a change in the proportion of patients meeting this quality measure during the index year (year=0), or a change in the proportion meeting the quality measure thereafter (years 1-4).

Figure 4.1: Blood Pressure ≤150/90 mm Hg



Proportions of patients meeting the quality measure for blood pressure ≤140/80 mm Hg (Figure 4.2) were approximately 25% lower than for 150/90 mm Hg, and followed a similar pattern, but with a slightly steeper increase, over time. Proportions increased from 56.5% (95% CI, 54.8%-58.1%) in cancer patients (red) and 56.1% (95% CI, 55.1%-57.0%) in controls (blue) two years before the index date (Year= -2) to 68.0% (95% CI, 65.0%-71.0%) and 66.5% (95% CI, 64.9%-68.1%), respectively, five years after the index date (Year=4). Cancer was not associated with either a difference in the proportion of patients meeting this quality measure during the index year (year=0), or a change in the proportion meeting the quality measure thereafter (years 1-4).

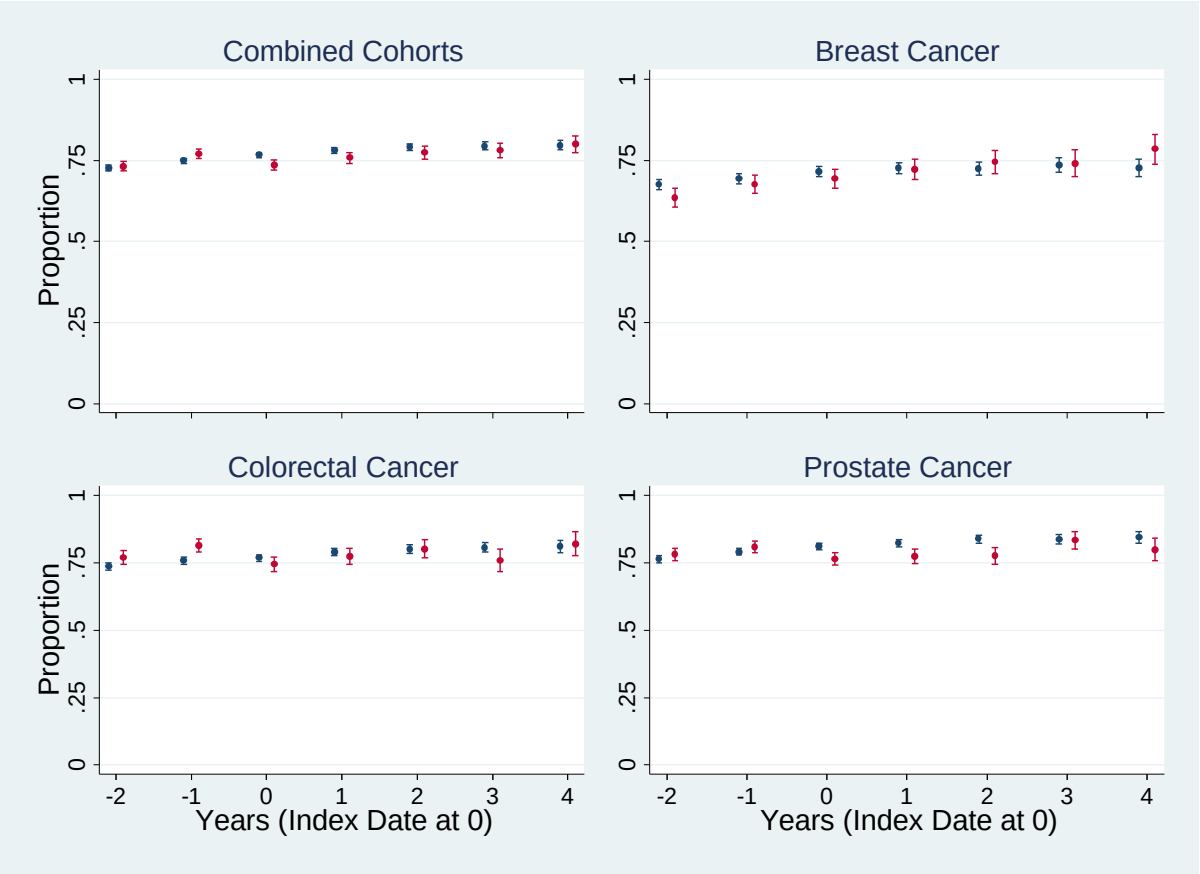
Figure 4.2: Blood Pressure ≤140/80 mm Hg



4.3.1.2 Cholesterol Control

Proportions of patients meeting the quality measure for cholesterol (Figure 4.3) increased from 73.2% (95% CI, 71.7%-74.7%) in cancer patients (red) and 72.7% (95% CI, 71.9%-73.5%) in controls (blue) two years before the index date to 80.0% (95% CI, 77.4%-82.6%) and 79.7% (95% CI, 78.3%-81.0%), respectively, five years after the index date. In the prostate cancer cohort, cancer was associated with a slight decrease in the proportion of patients meeting the quality measure during the index year (year -1 = 81.0% [95% CI, 78.8%-83.1%] versus year 0 = 76.4% [95% CI, 74.0%-78.8%]). However, there was no difference between cancer patients and controls by the end of the observation period.

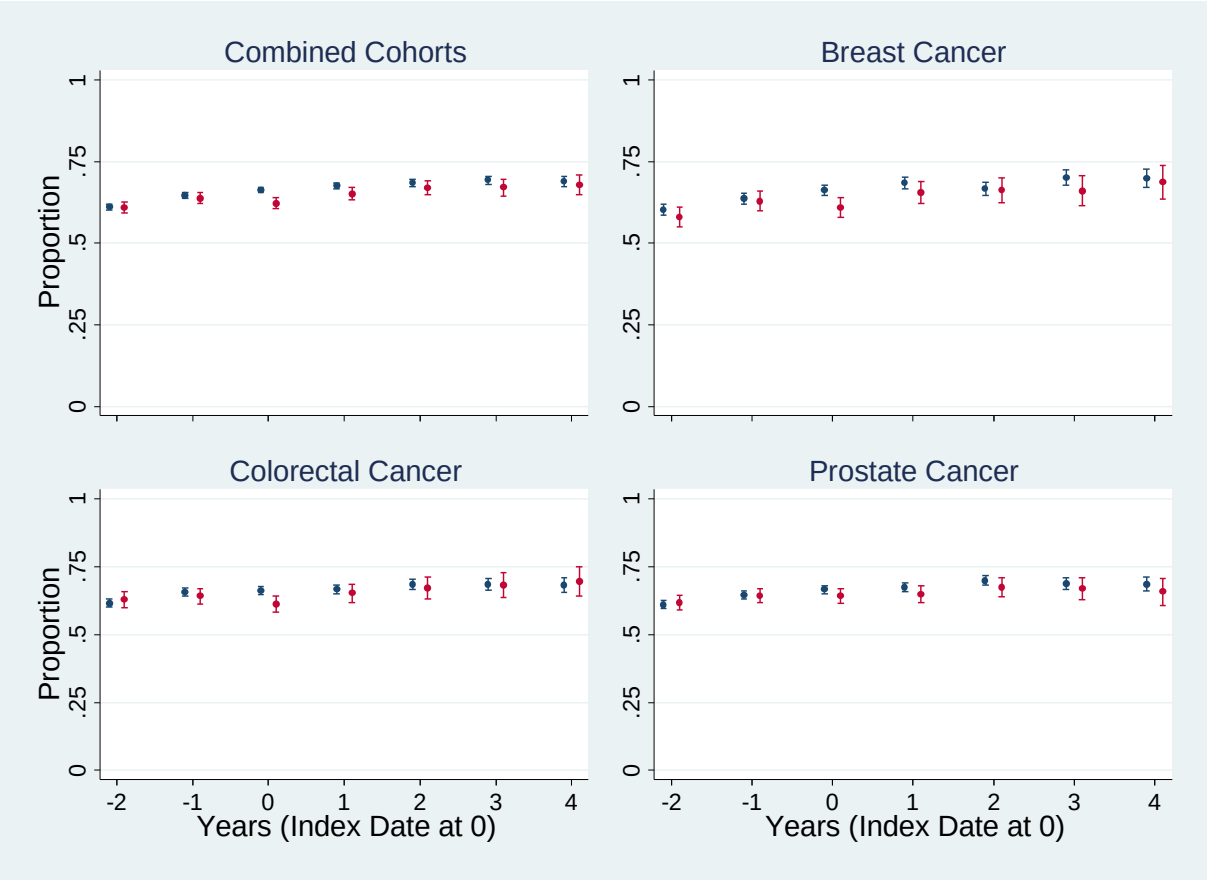
Figure 4.3: Total Cholesterol ≤5 mmol/L



4.3.1.3 Albumin Creatinine Ratio Testing

Proportions of patients meeting the quality measure for albumin creatinine ratio testing (Figure 4.4) increased from 60.9% (95% CI, 59.3%-62.6%) in cancer patients (red) and 61.0% (95% CI, 60.1%-61.9%) in controls (blue) two years before the index date to 67.8% (95% CI, 64.8%-70.9%) and 68.9% (95% CI, 67.3%-70.4%), respectively, five years after the index date. Breast and colorectal cancer were associated with slight decreases in the proportions of patients meeting this quality measure during the index year. However, there were no differences between cancer patients and controls by the end of the observation period.

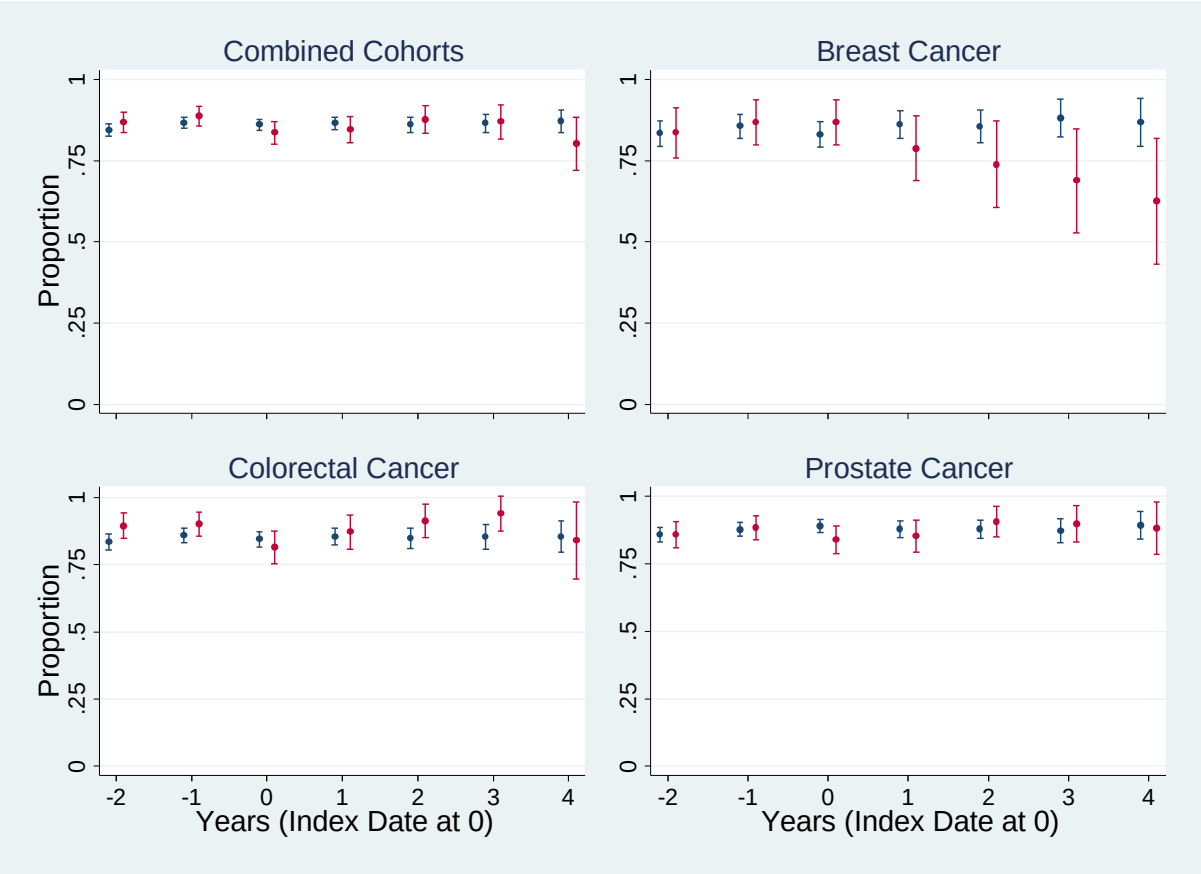
Figure 4.4: Albumin Creatinine Ratio Test



4.3.1.4 ACE-I or ARB Therapy for Nephropathy

Proportions of patients meeting the quality measure for ACE-I or ARB therapy among those diagnosed with nephropathy or microalbuminuria (Figure 4.5) remained relatively stable over time, at above 80% in cancer patients (red) and controls (blue). It appears that ACE-I or ARB therapy may have declined over time in breast cancer. However, the CIs around these proportions widened considerably in later years due to patient attrition, making this finding more difficult to interpret.

Figure 4.5 ACE Inhibitor or Angiotensin Receptor Blocker for Nephropathy/Microalbuminuria



4.3.1.5 Glycosylated Haemoglobin Control

In contrast to other quality measures, the proportions of patients meeting the quality measure for HbA1c ≤59 mmol/mol (Figure 4.6) decreased from 68.1% (95% CI, 66.5%-69.7%) in cancer patients (red) and 67.8% (95% CI, 66.9%-68.7%) in controls (blue) two years before the index date to 60.0% (95% CI, 56.9%-63.1%) and 64.2% (95% CI, 62.6%-65.8%), respectively, five years after the index date. Breast cancer was associated with a slight decrease the proportion of patients meeting the quality measure during the index year (year -1 = 66.6% [95% CI, 63.7%-69.5%] versus year 0 = 60.2% [95% CI, 57.3%-63.2%]). Colorectal cancer was associated with a decrease the proportion of patients meeting the quality measure between the index year (year 0 = 67.4% [95% CI, 64.5%-

70.2%]) and year 1 (60.3% [95% CI, 56.8%-63.7%]). Plots for HbA1c ≤64 mmol/mol (Figure 4.7) and ≤75 mmol/mol (Figure 4.8) showed similar patterns but, as expected, higher proportions of patients meeting these thresholds.

Figure 4.6: Glycosylated Haemoglobin ≤59 mmol/mol

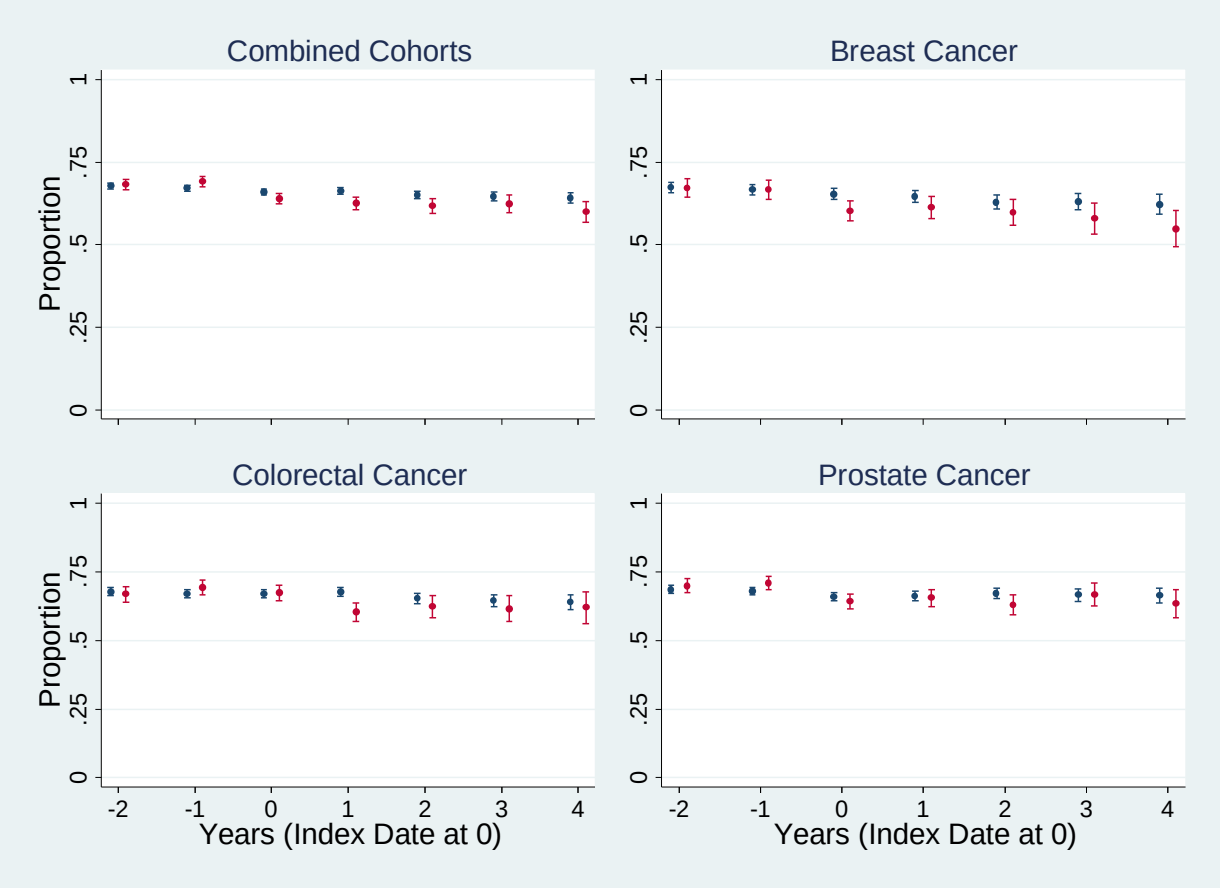


Figure 4.7: Glycosylated Haemoglobin ≤64 mmol/mol

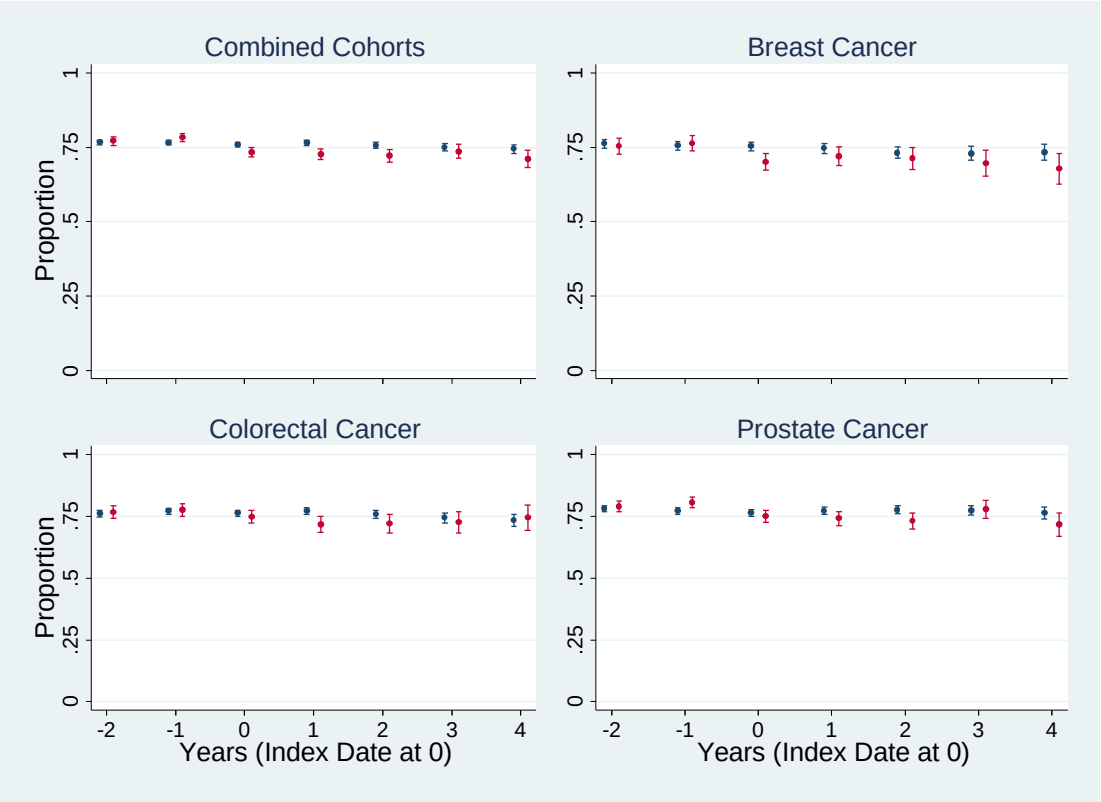
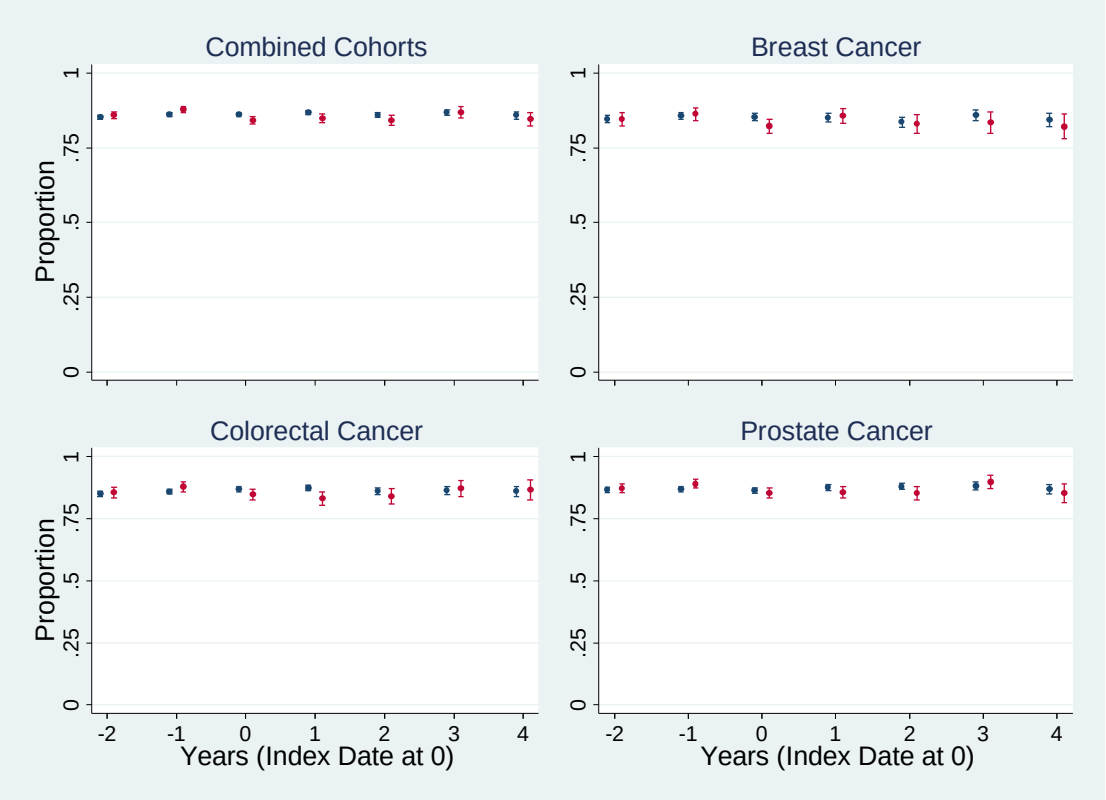


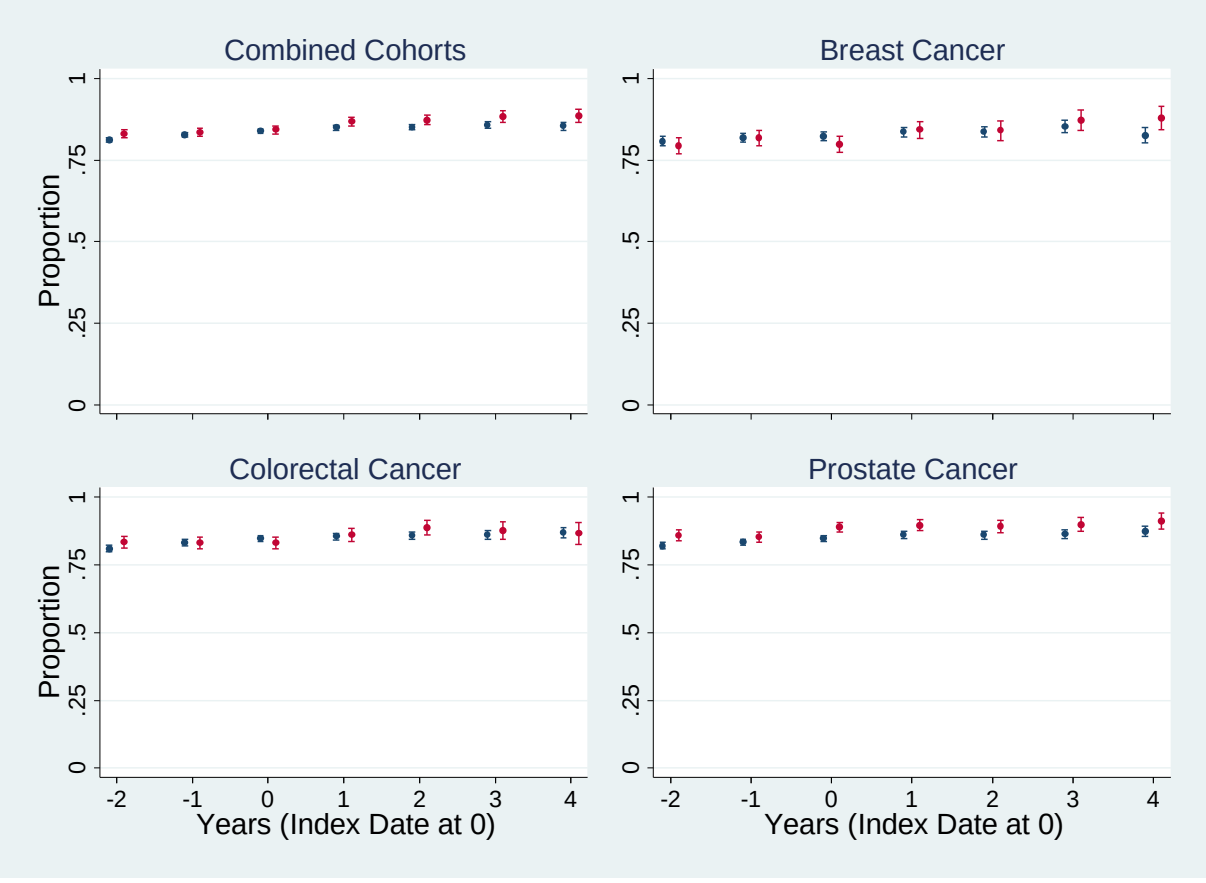
Figure 4.8: Glycosylated Haemoglobin ≤75 mmol/mol



4.3.1.6 Influenza Immunisation

Proportions of patients meeting the quality measure for influenza immunisation (Figure 4.9) increased from 83.1% (95% CI, 81.8%-84.3%) in cancer patients (red) and 81.2% (95% CI, 80.5%-81.9%) in controls (blue) two years before the index date to 88.6% (95% CI, 86.6%-90.6%) and 85.4% (95% CI, 84.2%-86.6%), respectively, five years after the index date. Prostate cancer was associated with a small increase in the proportion of patients meeting the quality measure during the index year (year 0 = 88.8% [95% CI, 87.1%-90.5%] versus year -1 = 85.2% [95% CI, 83.3%-87.1%]), which remained throughout the observation period.

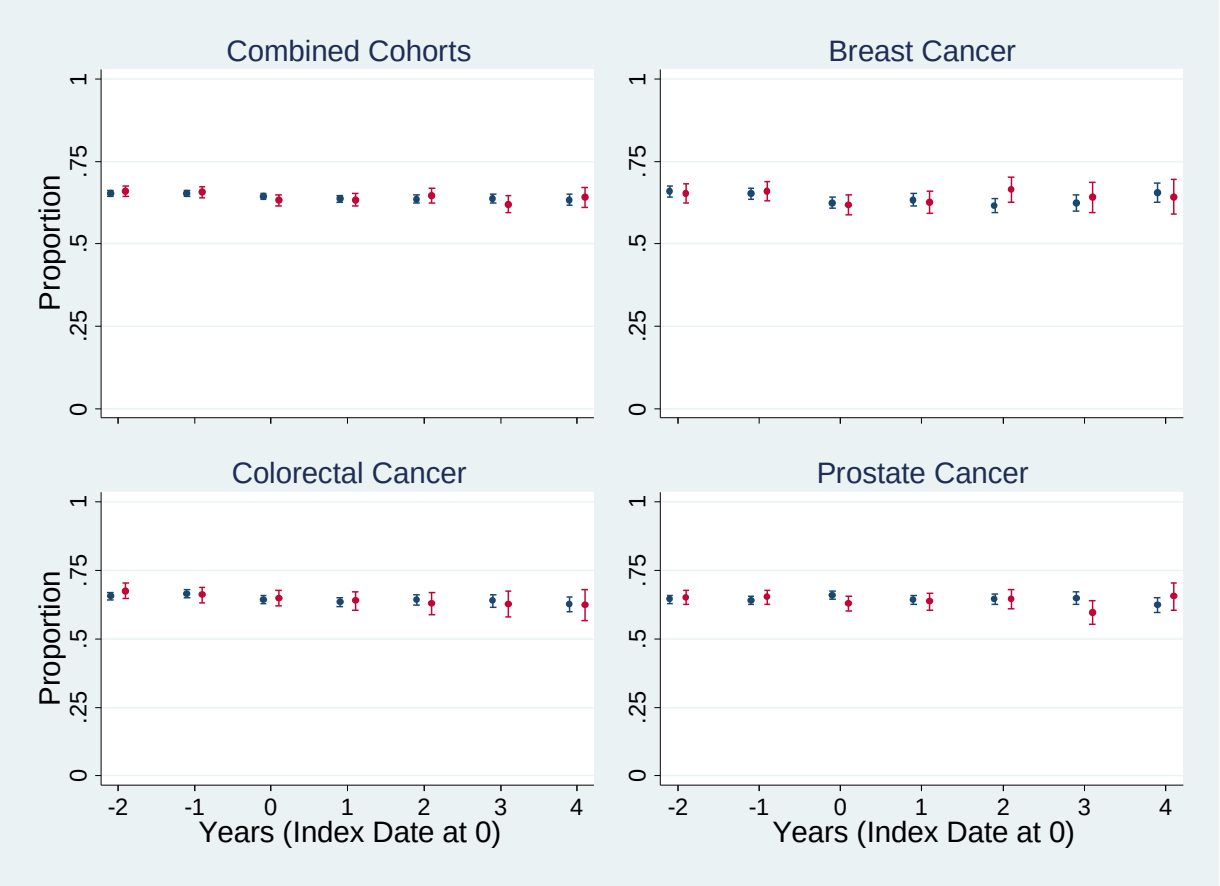
Figure 4.9: Influenza Immunisation



4.3.1.7 Retinal Screening

Proportions of patients meeting the quality measure for retinal screening (Figure 4.10) remained relatively stable over time at around 64% in both cancer patients (red) and controls (blue). Cancer was not associated with either a change in the proportion of patients meeting this quality measure during the index year (year=0) or a change in the proportion meeting the quality measure thereafter.

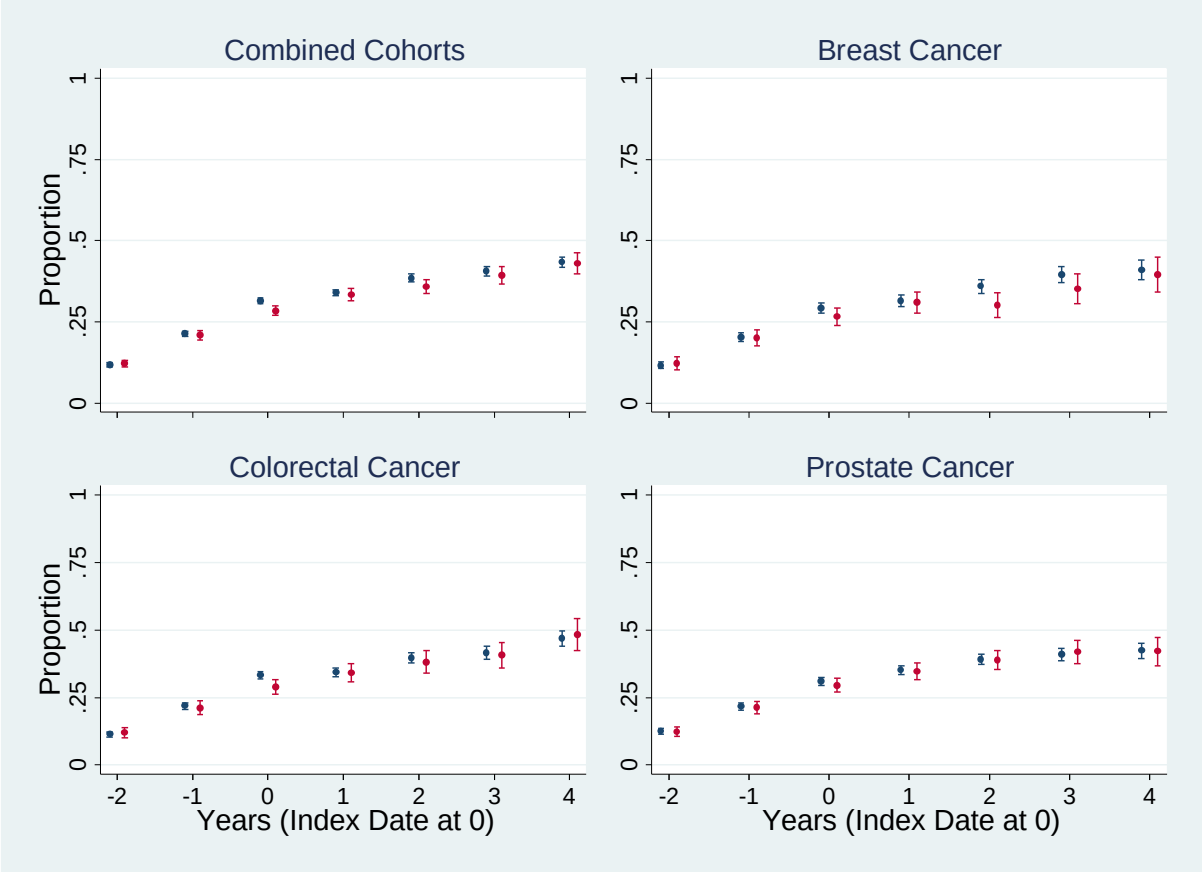
Figure 4.10: Retinal Screening



4.3.1.8 Foot Exam

Proportions of patients meeting the quality measure for foot exam (Figure 4.11) increased considerably from 12.2% (95% CI, 11.1%-13.3%) in cancer patients (red) and 11.9% (95% CI, 11.3%-12.5%) in controls (blue) two years before the index date to 43.0% (95% CI, 39.8%-46.2%) and 43.4% (95% CI, 41.7%-45.0%), respectively, five years after the index date. Colorectal cancer was associated with a slight decrease in the proportion of patients meeting this quality measure during the index year. However, there was no difference between cancer patients and controls by the end of the observation period.

Figure 4.11: Foot Exam



4.3.1.9 Dietary Review

Very few patients received dietary review (Figure 4.12). This likely reflects the fact that the QOF for this measure was introduced toward the end of the observation period.

Figure 4.12: Dietary Review

4.3.1.10 Erectile Dysfunction

Very few patients were asked about (Figure 4.13) or provided advice for (Figure 4.14) erectile dysfunction during the observation period. This too likely reflects the fact that the QOFs for these measures were introduced toward the end of the observation period.

Figure 4.13: Asked About Erectile Dysfunction

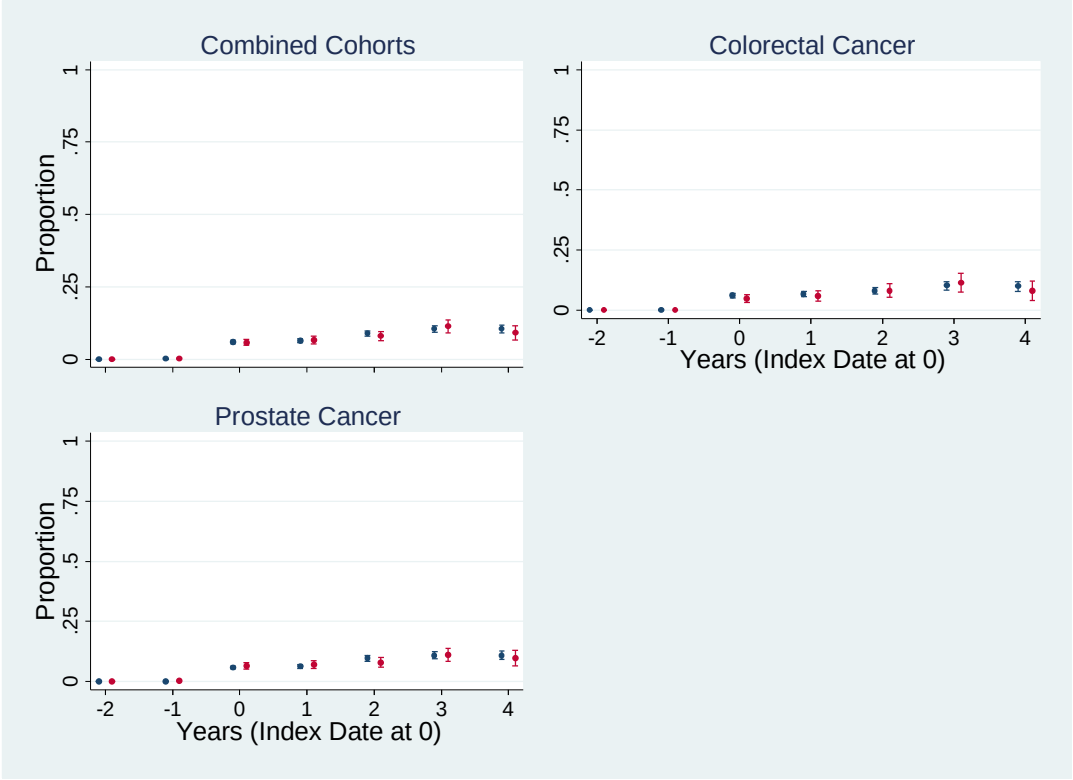
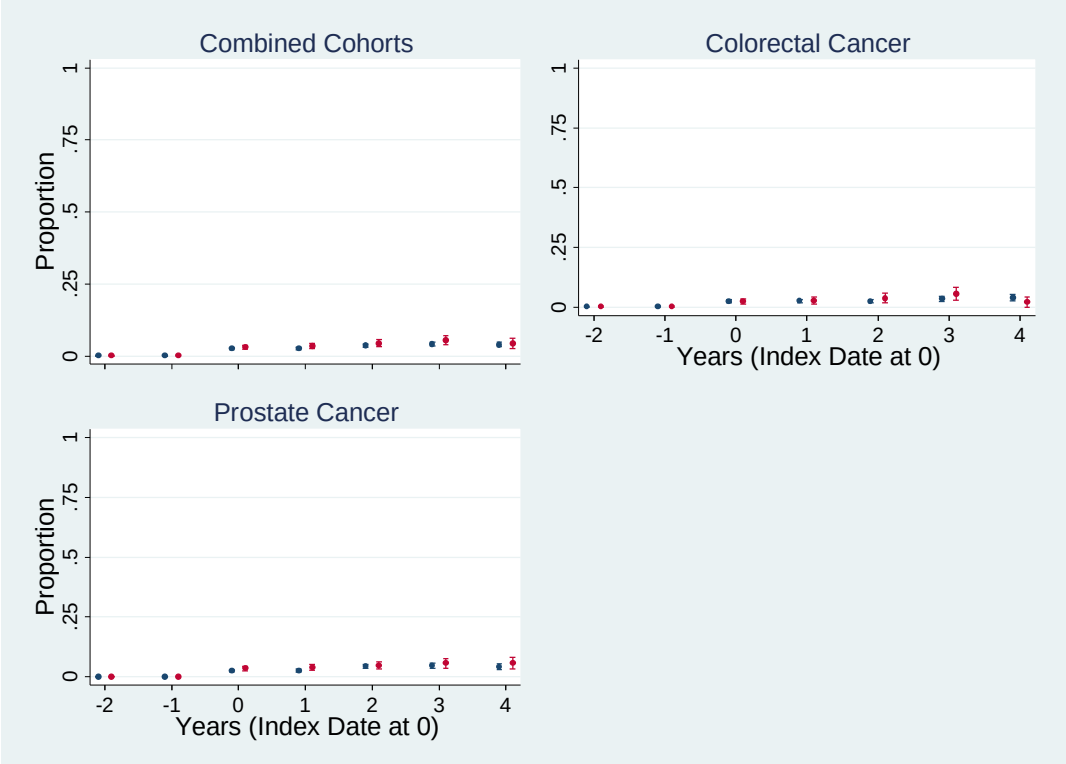


Figure 4.14: Received Advice/Assessment of Erectile Dysfunction



4.3.2 Primary Analyses of Quality Measures

The results of the primary multilevel logistic regression analyses (Table 4.1) show that in the combined cohort, after adjustment for baseline characteristics and for multiple comparisons, cancer patients were statistically significantly ($p \leq 0.05$) less likely than non-cancer controls to meet five of 14 quality measures examined, including: total cholesterol ≤5 mmol/L (adjusted OR=0.82; 95% CI, 0.75-0.90); HbA1c ≤59 mmol/mol (adjusted OR=0.77; 95% CI, 0.70-0.85); and albumin creatinine ratio testing (adjusted OR=0.83; 95% CI, 0.75-0.91). Cancer patients were statistically significantly more likely than non-cancer controls to receive influenza immunisation (adjusted OR=1.31; 95% CI, 1.07-1.59), and to get advice about erectile dysfunction. (Table 4.1) Cancer patients were as likely as their matched controls to meet quality measures for other diabetes services, including retinal screening, foot examination, and dietary review. (Table 4.1)

In some instances, the impact of cancer on the quality of diabetes primary care differed across the three individual cancer cohorts. For instance, in the breast cancer cohort the adjusted OR for total cholesterol ≤5 mmol/L was 1.03 (95% CI, 0.88-1.21), but in prostate cancer it was 0.66 (95% CI, 0.57-0.76). In the breast cancer cohort, the adjusted OR for influenza immunisation was 0.95 (95% CI, 0.68-1.34), but in prostate cancer it was 2.18 (95% CI, 1.56-3.06). In other instances, findings were consistent across the cohorts. For example, cancer patients in all four cohorts were less likely than the non-cancer controls to achieve adequate HbA1c control. Full tabular results of the adjusted analyses, which include coefficients for all predictor variables in the models, are provided in the Appendix.

Table 4.1: Primary Analyses of Quality Measures [continued on the following page]

Quality Measure	Cohort							
	Combined		Breast Cancer		Colorectal Cancer		Prostate Cancer	
	Unadjusted[1]	Adjusted[2]	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Blood Pressure ≤150/90 mm Hg								
Odds Ratio[3]	1.02	1.05	0.96	1.00	0.96	0.96	1.14	1.16*
95% CI	(0.93-1.13)	(0.96-1.16)	(0.81-1.14)	(0.85-1.18)	(0.81-1.14)	(0.81-1.13)	(0.97-1.13)	(1.00-1.35)
Blood Pressure ≤140/80 mm Hg								
Odds Ratio	1.02	1.04	1.00	1.06	1.00	0.99	1.04	1.06
95% CI	(0.94-1.10)	(0.97-1.12)	(0.87-1.15)	(0.93-1.20)	(0.88-1.14)	(0.87-1.11)	(0.92-1.18)	(0.95-1.19)
Total Cholesterol ≤5mmol/L								
Odds Ratio	0.81***†	0.82***†	0.95	1.03	0.85	0.80**†	0.66***†	0.66***†
95% CI	(0.73-0.89)	(0.75-0.90)	(0.80-1.15)	(0.88-1.21)	(0.72-1.01)	(0.68-0.93)	(0.57-0.77)	(0.57-0.76)
Albumin Creatinine Ratio Test								
Odds Ratio	0.81***†	0.83***†	0.78**†	0.80**	0.81*	0.81*	0.84*	0.86
95% CI	(0.73-0.89)	(0.75-0.91)	(0.65-0.92)	(0.68-0.95	0.67-0.97)	(0.68-0.97)	(0.72-0.99)	(0.73-1.01)
ACE-I or ARB[4]								
Odds Ratio	0.64	0.48	0.85	0.57	0.81	0.76	0.44	0.33
95% CI	(0.30-1.35)	(0.21-1.10)	(0.13-5.75)	(0.05-5.98)	(0.26-2.60)	(0.23-2.56)	(0.14-1.43)	(0.09-1.14)
HbA1c ≤59 mmol/mol								
Odds Ratio	0.80***†	0.77***†	0.74**	0.72***†	0.79*	0.80*	0.86	0.79**†
95% CI	(0.72-0.89)	(0.70-0.85)	(0.60-0.90)	(0.61-0.85)	(0.65-0.97)	(0.68-0.95)	(0.72-1.02)	(0.68-0.92)
HbA1c ≤64 mmol/mol								
Odds Ratio	0.78***†	0.75***†	0.76**†	0.74***†	0.76**	0.77**†	0.80*	0.73**†
95% CI	(0.70-0.87)	(0.68-0.82)	(0.62-0.93)	(0.63-0.88)	(0.63-0.93)	(0.65-0.91)	(0.67-0.95)	(0.63-0.85)

Quality Measure	Cohort							
	Combined		Breast Cancer		Colorectal Cancer		Prostate Cancer	
	Unadjusted[1]	Adjusted[2]	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
HbA1c ≤75 mmol/mol								
Odds Ratio	0.81***†	0.80***†	0.86	0.86	0.74**	0.76**	0.83*	0.79**†
95% CI	(0.73-0.91)	(0.73-0.89)	(0.70-1.05)	(0.72-1.03)	(0.60-0.90)	(0.63-0.91)	(0.70-1.00)	(0.67-0.93)
Influenza Immunisation								
Odds Ratio	1.26*	1.31**†	0.93	0.95	0.98	0.96	2.04***†	2.18***†
95% CI	(1.03-1.53)	(1.07-1.59)	(0.66-1.31)	(0.68-1.34)	(0.69-1.39)	(0.67-1.36)	(1.46-2.86)	(1.56-3.06)
Retinal Screening								
Odds Ratio	0.96	0.99	1.01	1.03	1.00	1.03	0.89	0.91
95% CI	(0.88-1.05)	(0.91-1.08)	(0.87-1.18)	(0.88-1.19)	(0.85-1.18)	(0.88-1.20)	(0.77-1.03)	(0.79-1.05)
Foot Exam								
Odds Ratio	0.79**†	0.94	0.75*	0.88	0.76*	0.92	0.93	1.03
95% CI	(0.68-0.92)	(0.85-1.04)	(0.57-0.98)	(0.74-1.04)	(0.58-0.99)	(0.78-1.09)	(0.71-1.21)	(0.87-1.21)
Dietary Review								
Odds Ratio	0.85	1.01	0.77	0.89	0.87	1.02	0.98	1.08
95% CI	(0.70-1.03)	(0.87-1.16)	(0.53-1.13)	(0.66-1.21)	(0.66-1.14)	(0.80-1.28)	(0.69-1.39)	(0.83-1.41)
Asked About Erectile Dysfunction								
Odds Ratio	0.94	1.06	NA	NA	0.86	1.00	1.02	1.08
95% CI	(0.77-1.16)	(0.89-1.26)	NA	NA	(0.64-1.15)	(0.75-1.32)	(0.78-1.34)	(0.86-1.35)
Advice About Erectile Dysfunction								
Odds Ratio	1.55*	1.60**	NA	NA	1.17	1.26	1.68**	1.71**†
95% CI	(1.09-2.19)	(1.18-2.18)	NA	NA	(0.65-2.11)	(0.71-2.26)	(1.14-2.48)	(1.21-2.41)

Notes for Table 1

[1]The multilevel logistic regression models for the unadjusted odds ratios also included time (years) as a factor variable and a random effect for the patient.

[2]The regression models for the adjusted odds ratios also included age, sex (combined cohorts, colorectal cancer), year of index date, smoking status, drinking status, body mass index, Charlson Comorbidity Index, Index of Multiple Deprivation score, baseline blood pressure, baseline total cholesterol, baseline HbA1c, history of one or more microvascular complications of diabetes, history of one or more macrovascular complications of diabetes, and history of diabetes medications.

[3]Odds Ratios: Cancer compared to control.

[4]In patients diagnosed with nephropathy or microalbuminuria.

*p <0.05, **p <0.01, ***p <0.001.

[†]Remained statistically significant after Benjamini-Hochberg adjustment for multiple comparisons.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HbA1c, glycosylated haemoglobin, NA, not applicable.

4.3.3 Partitioned Plots of Quality Measures for Control

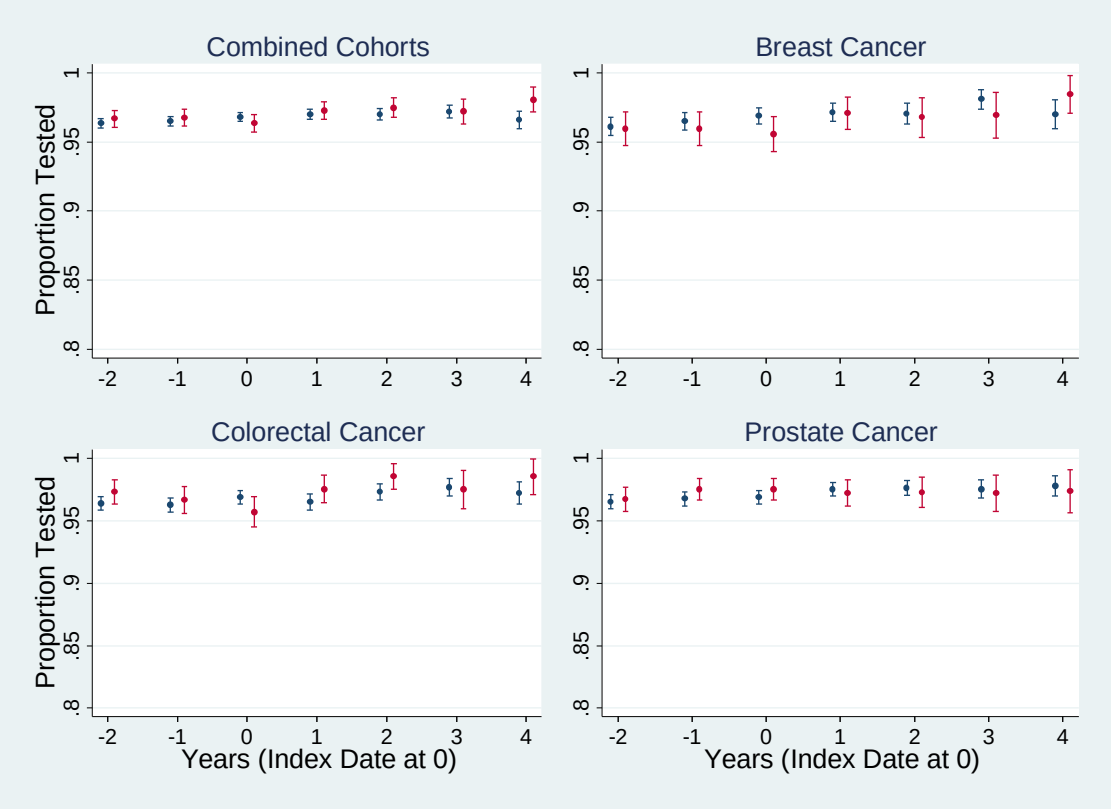
Partitioned[m] plots of the unadjusted annual proportions (dots) and 95% CIs (bars) of cancer patients (red) and controls (blue) who met the quality measures for blood pressure, cholesterol, and HbA1c control are presented in Figures 4.15-4.23. The text of this section describes the plots for the combined cohort, with additional information on the individual cancer cohorts if those plots differed substantially from the combined cohort.

4.3.3.1 Hypertension

Proportions of patients who had an annual blood pressure reading fluctuated between 96% and 98% in cancer patients (red) and controls (blue) throughout the observation period, with no discernable temporal trend. (Figure 4.15) Cancer was not associated with either a change in the proportion of patients with a blood pressure reading during the index year (year=0), or a change in the proportion with a reading thereafter (years 1-4).

[m] Partitioned into A) the probability of having a reading/test result indicating that the patient was assessed in that year, and (B) the conditional (upon having had a reading/test result) probability that the last result in the year was at or below the established threshold for the quality measure.

Figure 4.15: Proportions of Patients Who Had a Blood Pressure Reading



Proportions of patients with a blood pressure reading who also met the threshold of ≤150/90 mm Hg for this quality measure (Figure 4.16) increased slightly from 84.9% (95% CI, 83.7%-86.1%) in cancer patients (red) and 83.7% (95% CI, 83.0%-84.4%) in controls (blue) two years before the index date to 88.2% (95% CI, 86.4%-90.0%) and 88.2% (95% CI, 87.3%-89.1%), respectively, five years after the index date. Cancer was not associated with either a change in the proportion of patients meeting the blood pressure threshold during the index year (year=0), or a change in the proportion meeting the threshold thereafter (years 1-4). Proportions of patients who also met the threshold of ≤140/80 mm Hg (Figure 4.17) were lower, and increased at a higher rate than for the threshold of ≤150/90 mm Hg.

Figure 4.16: Patients with a Blood Pressure Reading Who Also Had a Result ≤150/90 mm Hg

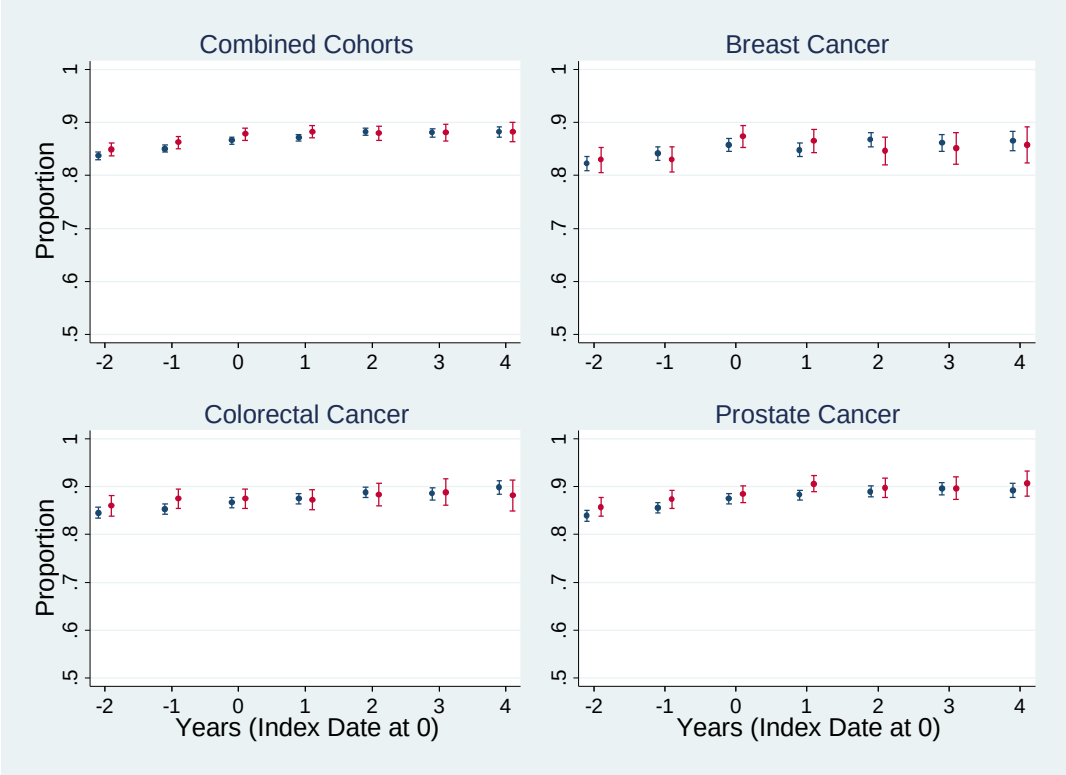
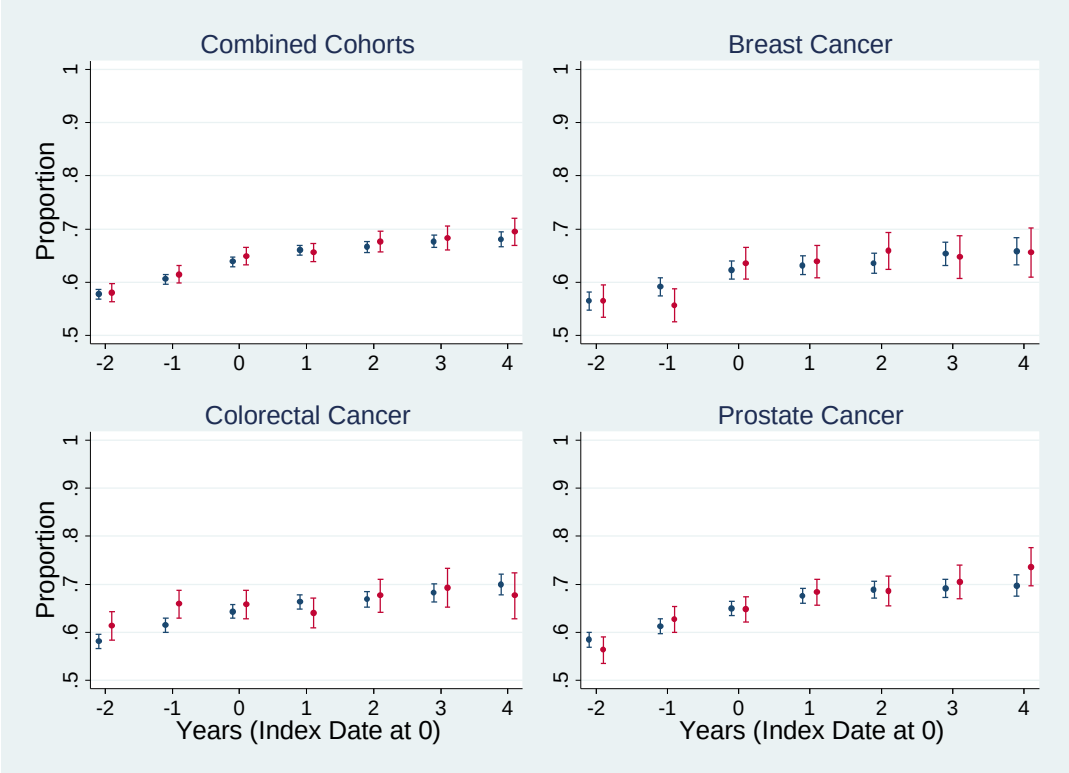


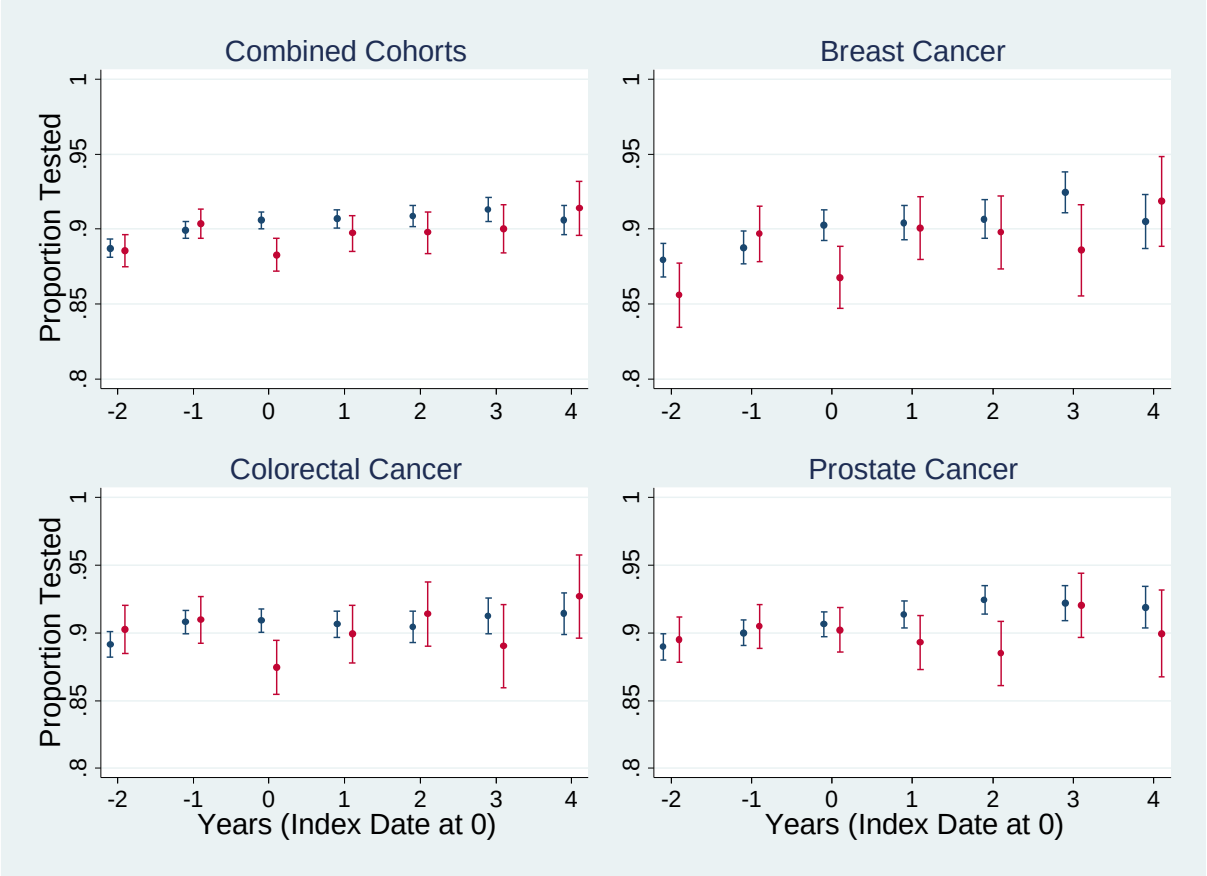
Figure 4.17: Patients with a Blood Pressure Reading Who Also Had a Result ≤140/80 mm Hg



4.3.3.2 Cholesterol

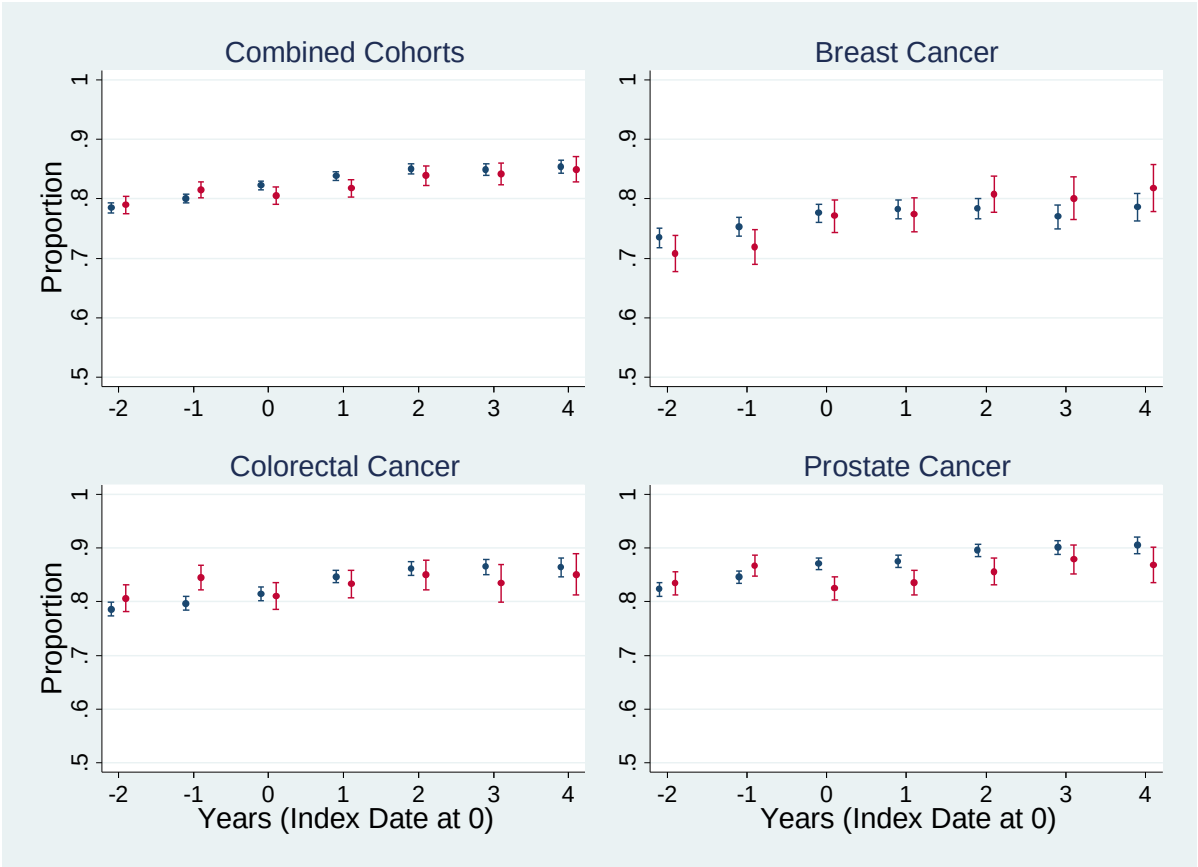
Proportions of patients who had an annual cholesterol test were between 88% and 91% in cancer patients (red) and controls (blue), with small increases in both groups during the observation period. (Figure 4.18) Cancer was associated with a slight decrease in the proportion of patients with a cholesterol test during the index year (year -1 = 90.4% [95% CI, 89.4%-91.4%] versus year 0 = 88.3% [95% CI, 87.2%-89.4%]). This association also was present in both the breast and colorectal cancer cohorts.

Figure 4.18: Proportions of Patients Who Had a Cholesterol Test



Proportions of patients with a cholesterol test that also met the threshold of ≤5 mmol/L for the quality measure (Figure 4.19) increased from 78.6% (95% CI, 77.2%-80.1%) in cancer patients (red) and 78.4% (95% CI, 77.5%-79.2%) in controls (blue) two years before the index date to 84.9% (95% CI, 82.8%-87.1%) and 85.3% (95% CI, 84.2%-86.4%), respectively, five years after the index date. Prostate cancer was associated with a slight decrease in the proportion of patients meeting the test threshold during both the index year and the year after. However, there was no difference between cancer patients and controls by the end of the observation period. Colorectal cancer was associated with a slight increase in the proportion of patients meeting the test threshold in the year before cancer.

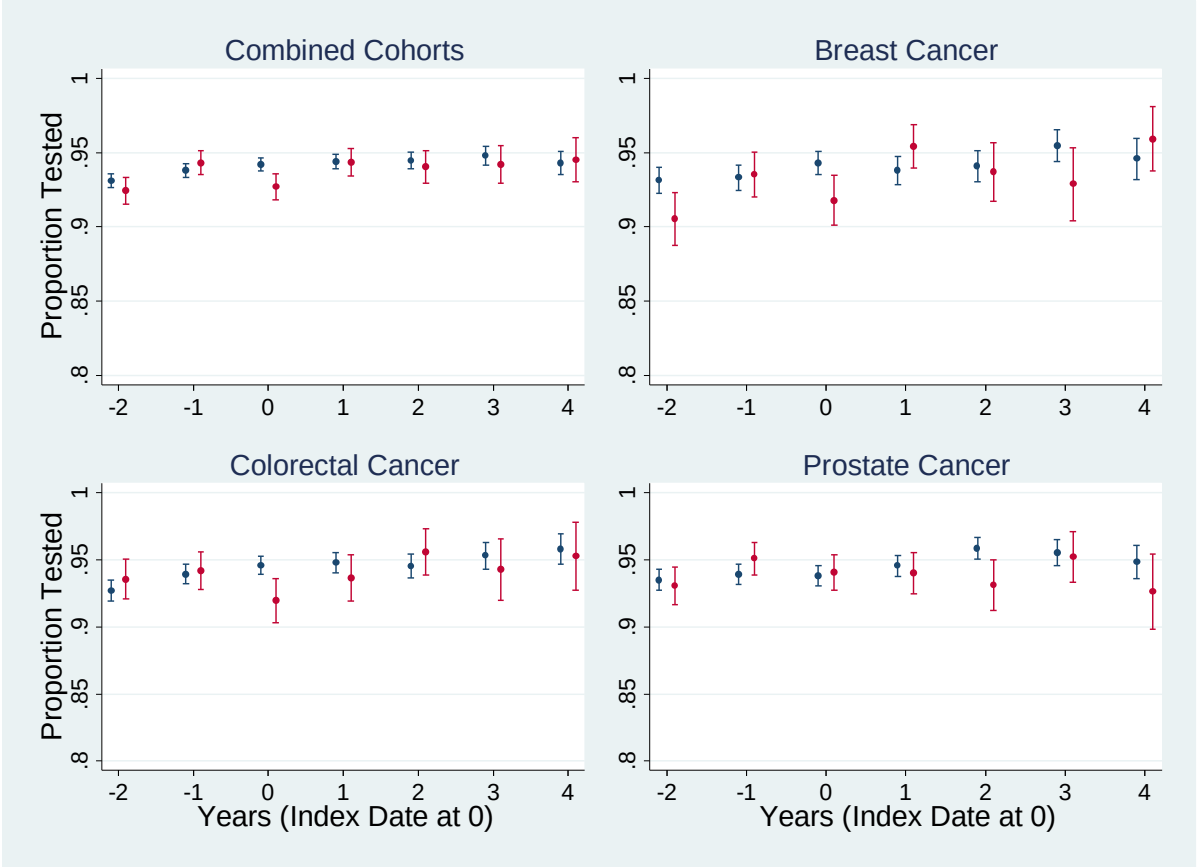
Figure 4.19: Patients with a Cholesterol Test Who Also Had a Test Result ≤5 mmol/L



4.3.3.3 Glycosylated Haemoglobin

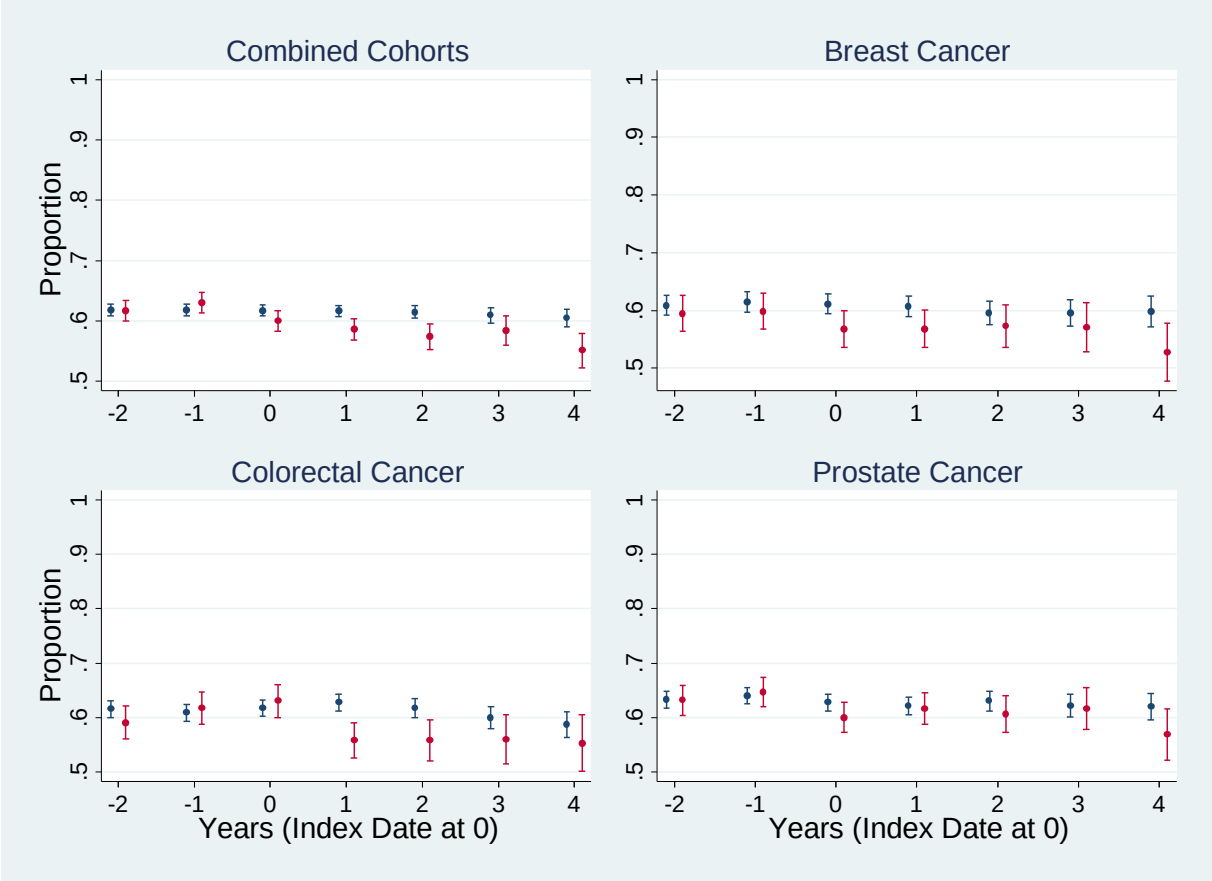
Proportions of patients who had an annual HbA1c test were between 92% and 95% in cancer patients (red) and controls (blue), with small increases in both groups during the observation period. (Figure 4.20) Cancer was associated with a slight decrease in the proportion of patients with an HbA1c test during the index year (year -1 = 94.3% [95% CI, 93.5%-95.1%] versus year 0 = 92.7% [95% CI, 91.8%-93.6%]). This association also was present in both the breast and colorectal cancer cohorts.

Figure 4.20: Proportions of Patients Who Had a Glycosylated Haemoglobin Test



Proportions of patients with an HbA1c test who also met the threshold of ≤59 mmol/mol for the quality measure (Figure 4.21) decreased from 61.4% (95% CI, 59.7%-63.1%) in cancer patients (red) and 61.9% (95% CI, 61.0%-62.9%) in controls (blue) two years before the index date to 55.4% (95% CI, 52.6%-58.3%) and 60.6% (95% CI, 59.2%-62.1%), respectively, five years after the index date. Colorectal cancer was associated with a decrease in the proportion of patients who met the HbA1c threshold after the index year (year 0 = 62.9% [95% CI, 59.8%-65.9%] versus year 1 = 55.5% [95% CI, 52.5%-58.8%]).

Figure 4.21: Patients with a Glycosylated Haemoglobin Test and a Test Result ≤59 mmol/mol



Proportions of patients who also met the threshold of ≤64 mmol/mol (Figure 4.22) and ≤75 mmol/mol (Figure 4.23) were higher (approximately 10% per threshold level), but followed a similar pattern to ≤59 mmol/mol.

Figure 4.22: Patients with a Glycosylated Haemoglobin Test and a Test Result ≤64 mmol/mol

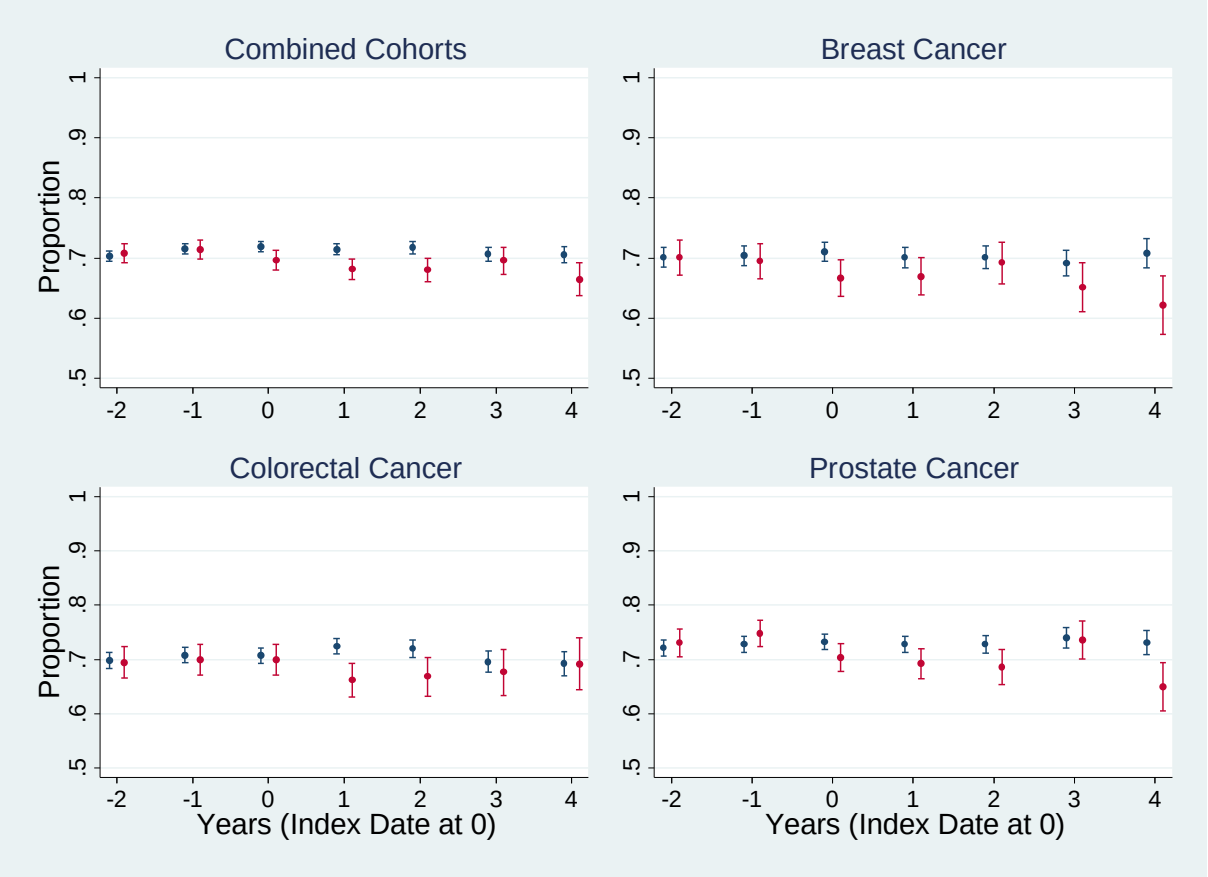
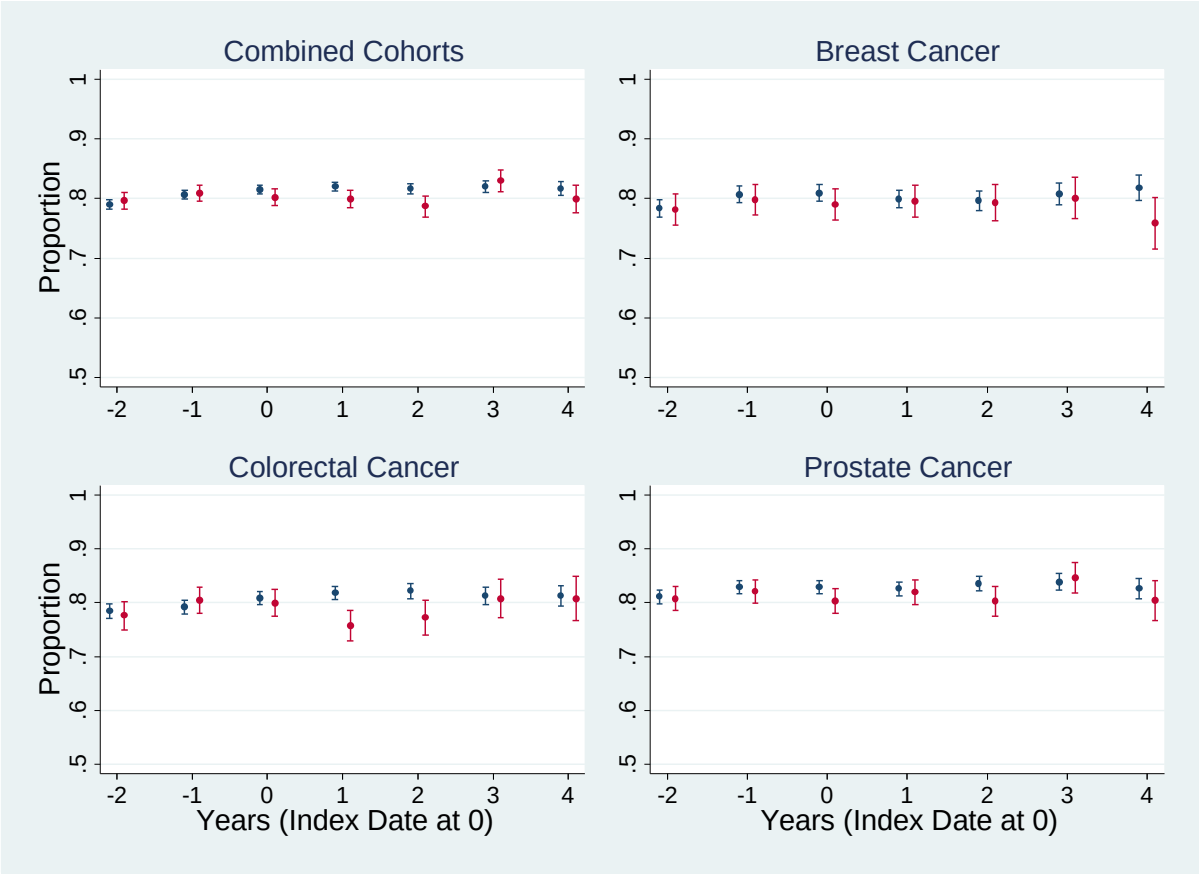


Figure 4.23: Patients with a Glycosylated Haemoglobin Test and a Test Result ≤75 mmol/mol

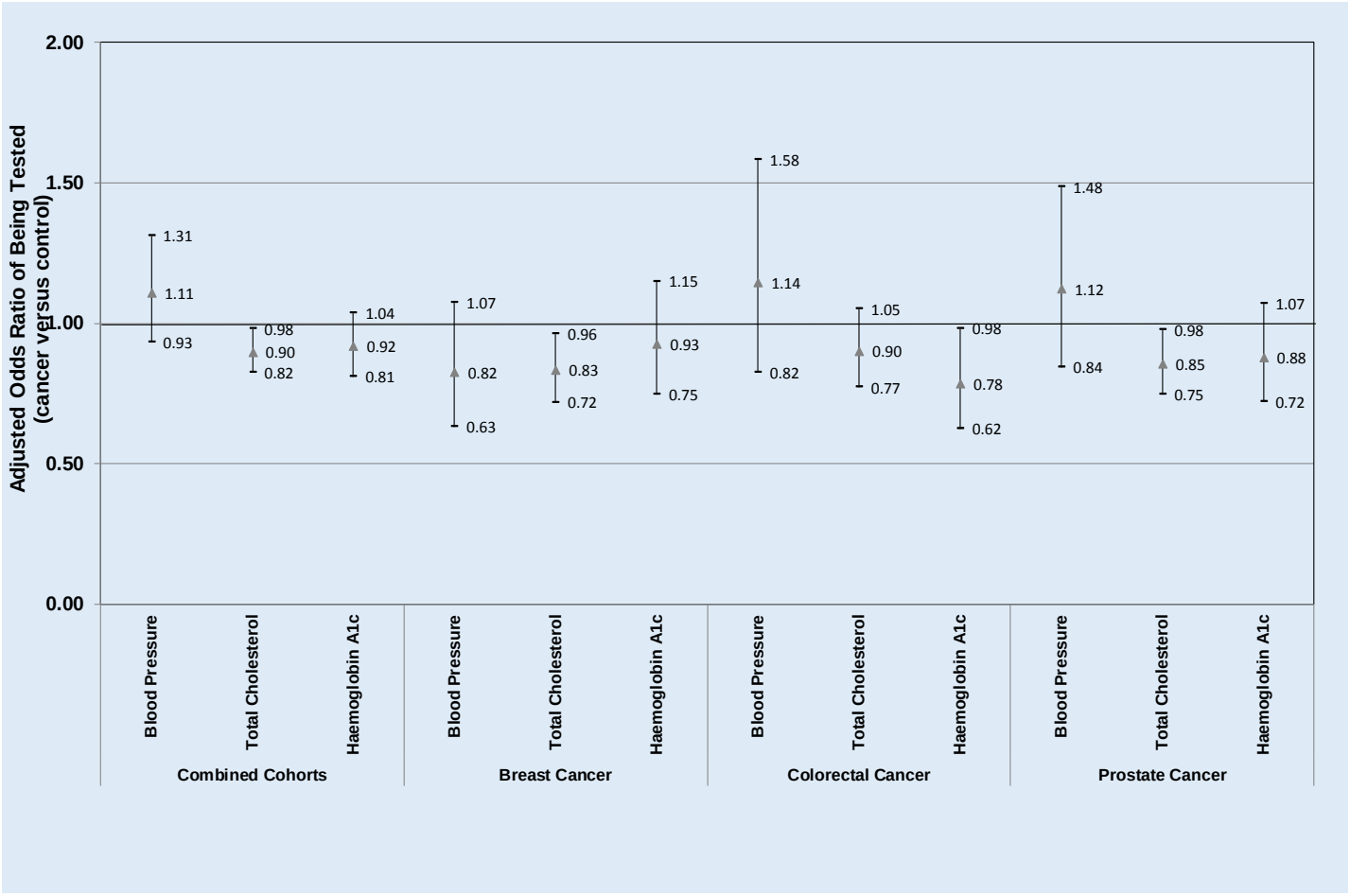


4.3.4 Primary Analyses of Partitioned Quality Measures

4.3.4.1 Odds of Being Measured and Tested

In multilevel logistic regression analyses of partitioned quality measures, cancer was associated with statistically significantly ($p \leq 0.05$) lower adjusted odds of having an annual cholesterol test (combined cohort, breast cancer, and prostate cancer), and statistically significantly lower adjusted odds of having an annual HbA1c test (colorectal cancer). (Figure 4.24) Cancer was not associated with lower odds of having a blood pressure reading.

Figure 4.24. Adjusted Odds (Cancer Compared to Control) of Being Measured and Tested

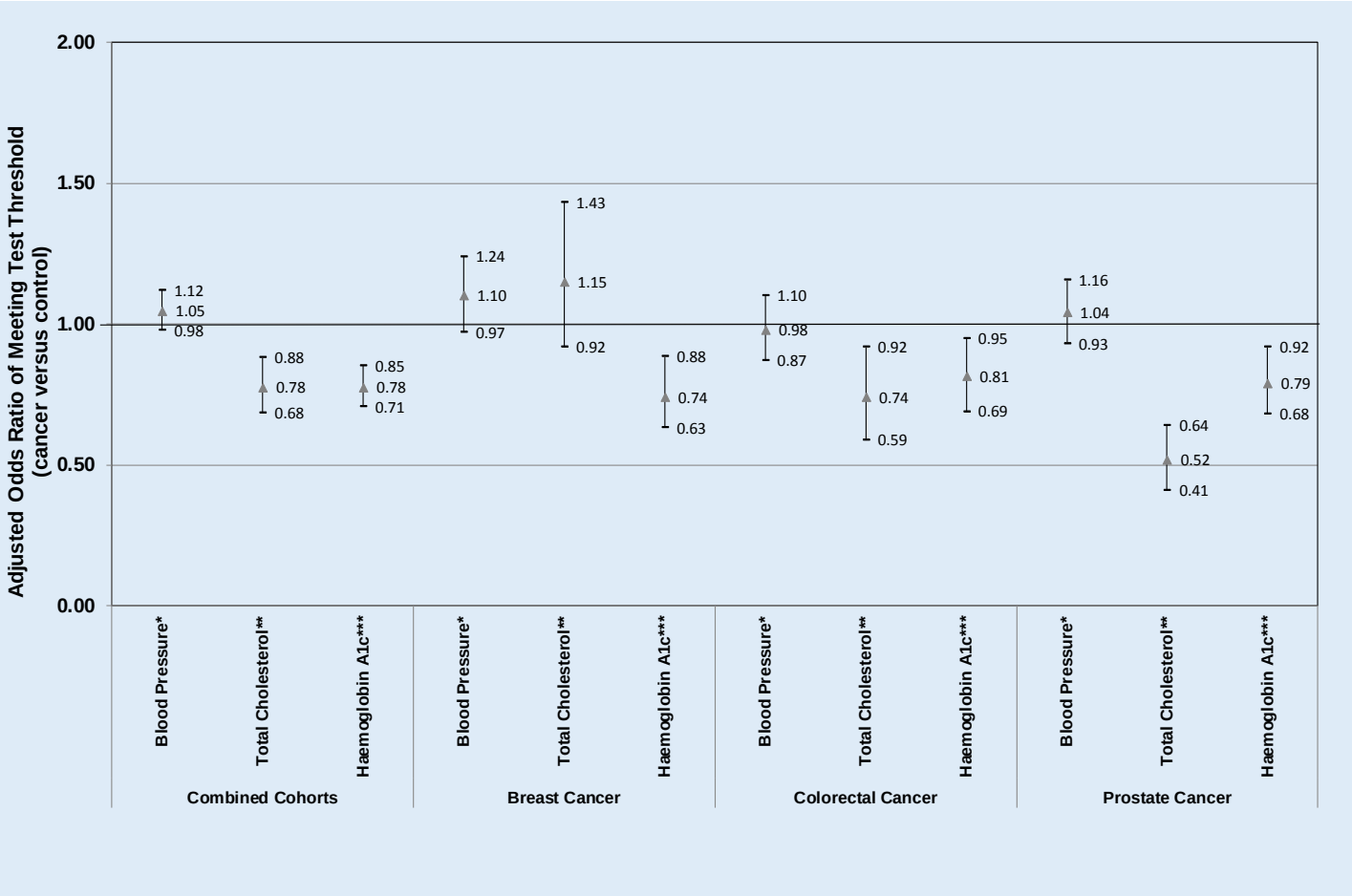


Legend: Figure 4.24. Adjusted odds ratios and 95% confidence intervals (CI) (cancer compared with controls) of testing during five years after cancer diagnosis or matched date in controls. An upper bound of the 95% CI <1.0 indicates that cancer patients had lower adjusted odds of being measured/tested than controls. A lower bound of the 95% CI >1.0 indicates that cancer patients had higher adjusted odds of being measured/tested.

4.3.4.2 Odds of Meeting Measurement and Test Thresholds

In multivariate analysis, cancer was associated with statistically significantly ($p \leq 0.05$) lower adjusted odds of meeting test thresholds for total cholesterol (combined cohort, colorectal cancer, and prostate cancer), and for HbA1c (combined cohort, breast cancer, colorectal cancer, and prostate cancer). (Figure 4.25) Cancer was not associated with lower odds of meeting the threshold for blood pressure.

Figure 4.25. Adjusted Odds (Cancer Compared to Control) of Meeting Thresholds



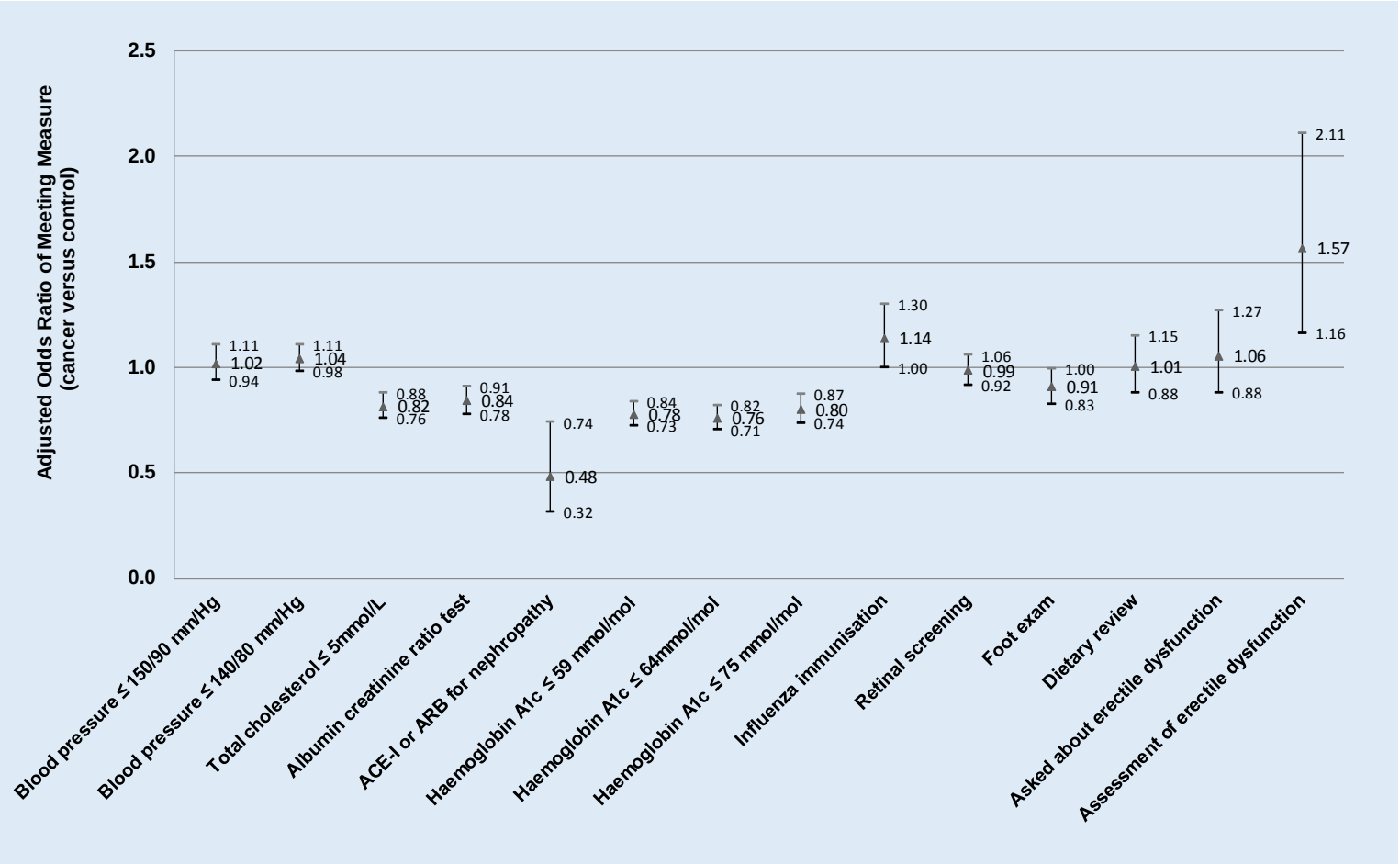
Legend: Figure 4.25. Adjusted odds ratios and 95% confidence intervals (CI) (cancer compared with controls) of meeting the test threshold during five years after cancer diagnosis or matched date in controls. An upper bound of the 95% CI <1.0 indicates that cancer patients had lower adjusted odds of meeting the threshold than controls. A lower bound of the 95% CI >1.0 indicates that cancer patients had higher adjusted odds of meeting the threshold than controls. *blood pressure ≤140/80 mm Hg; **total cholesterol ≤5 mmol/L; ***Haemoglobin A1c ≤59 mmol/mol.

4.3.5 Results of the Secondary Analyses

4.3.5.1 Extended Follow Up

In secondary multilevel logistic regression analyses based on seven years of (extended) follow-up, in the combined cohort cancer was associated with statistically significantly lower adjusted odds of meeting quality measures based on total cholesterol, albumin creatinine ratio testing, use of ACE-I or ARB among patients with nephropathy or microalbuminuria, HbA1c (at all three thresholds), and foot examination. (Figure 4.26)

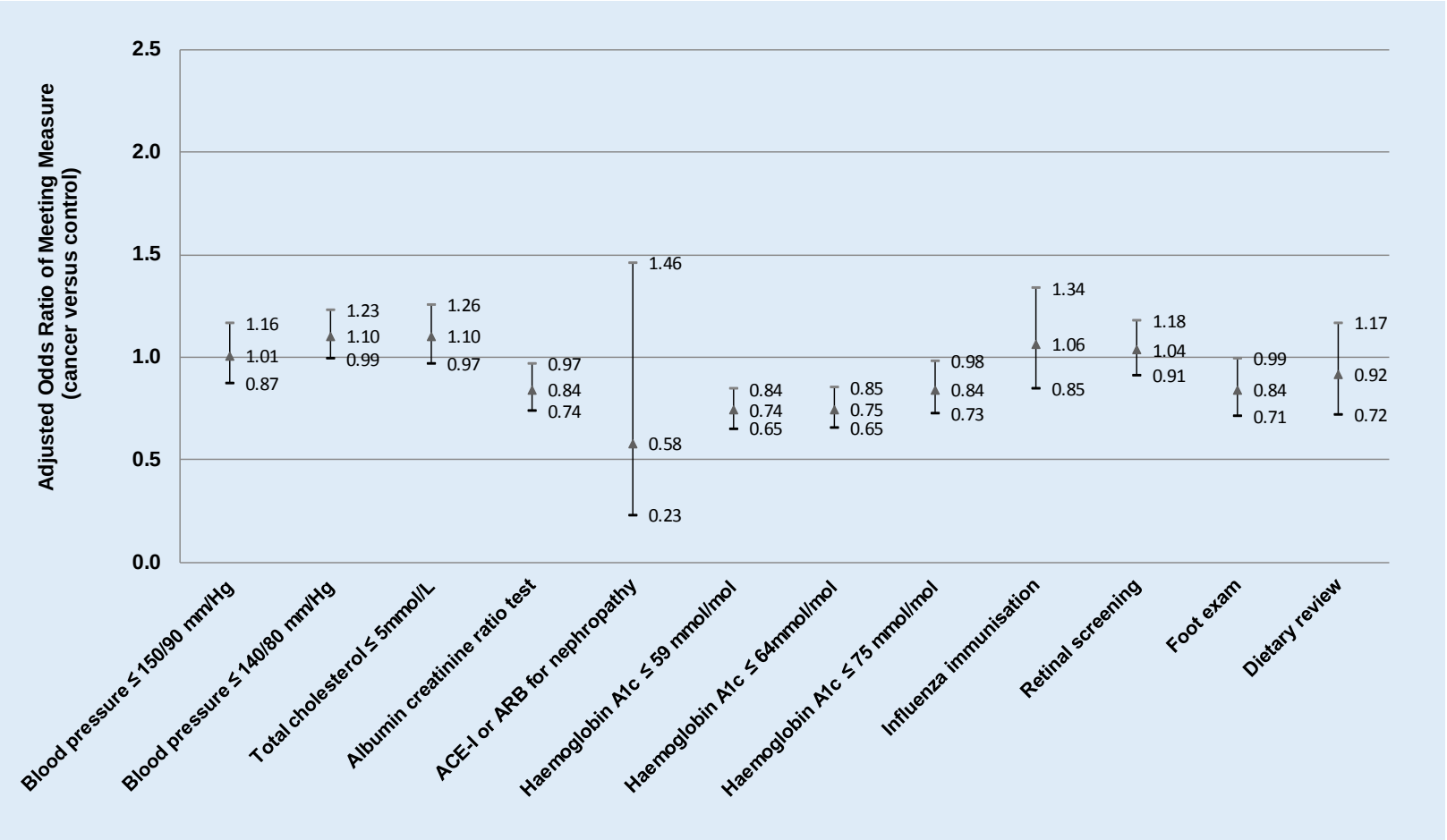
Figure 4.26. Adjusted Odds of Meeting Quality Measures- Combined Cohort, Seven Years



Legend: Figure 4.26. Adjusted odds ratios and 95% confidence intervals (CI) (cancer compared with controls) of meeting the corresponding quality measure (shown on x-axis). Results are from the multivariate mixed-effects logistic regression analyses of the full cohorts during seven years of follow up. An upper bound of the 95% CI <1.0 indicates that cancer patients had lower adjusted odds of meeting the threshold than controls. A lower bound of the 95% CI >1.0 indicates that cancer patients had higher adjusted odds of meeting the threshold than controls.

In the breast cancer cohort, cancer was associated with significantly lower adjusted odds of meeting quality measures based on albumin creatinine ratio testing, HbA1c (at all three thresholds), and foot examination. (Figure 4.27)

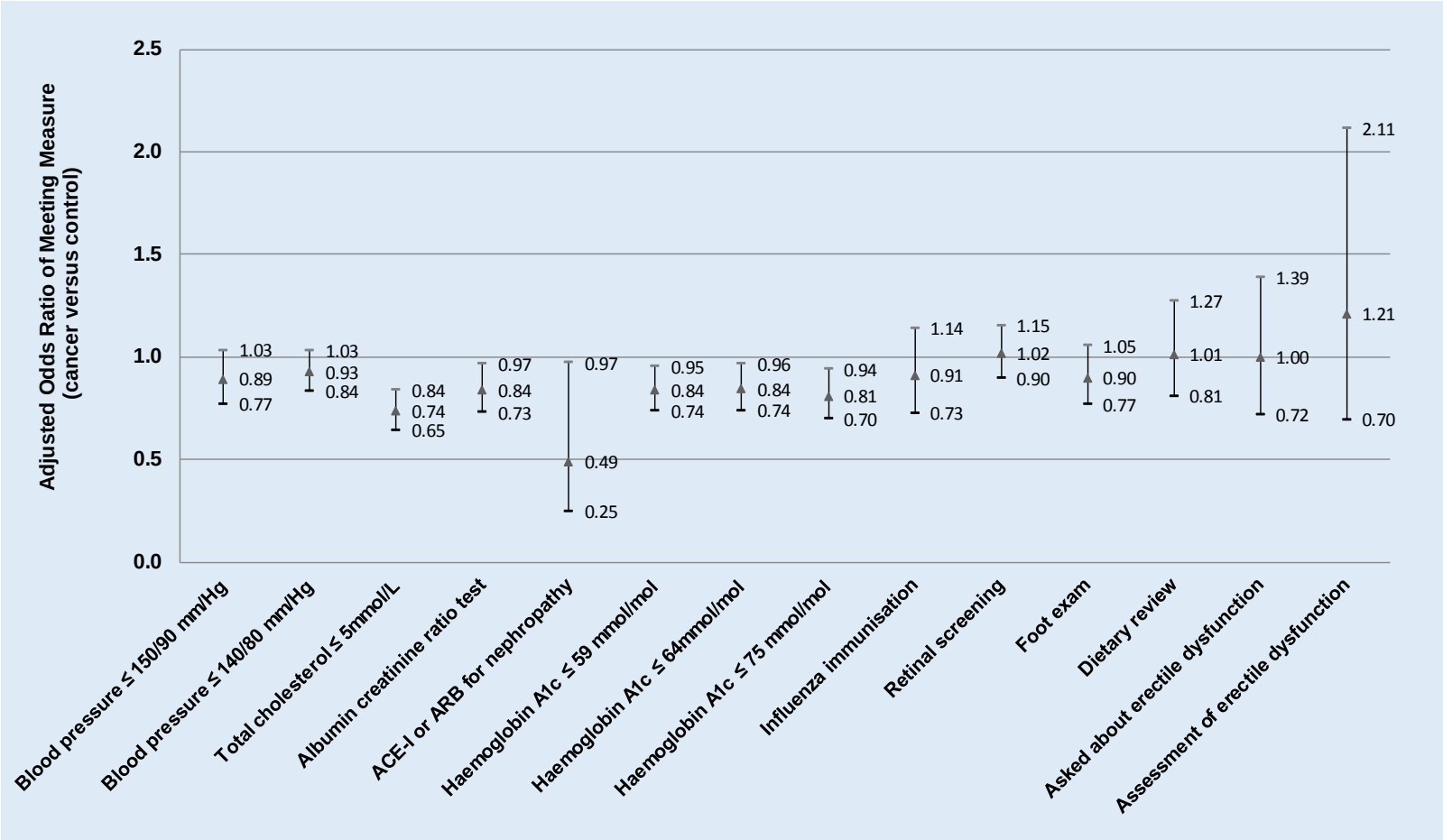
Figure 4.27. Adjusted Odds of Meeting Quality Measures- Breast Cancer, Seven Years



Legend: Figure 4.27. Adjusted odds ratios and 95% confidence intervals (CI) (cancer compared with controls) of meeting the corresponding quality measure (shown on x-axis). Results are from the multivariate mixed-effects logistic regression analyses of the full cohorts during seven years of follow up. An upper bound of the 95% CI <1.0 indicates that cancer patients had lower adjusted odds of meeting the threshold than controls. A lower bound of the 95% CI >1.0 indicates that cancer patients had higher adjusted odds of meeting the threshold than controls.

In the colorectal cancer cohort, cancer was associated with significantly lower adjusted odds of meeting quality measures based on cholesterol, albumin creatinine ratio testing, use of ACE-I or ARB among patients with nephropathy or microalbuminuria, and HbA1c (at all three thresholds). (Figure 4.28)

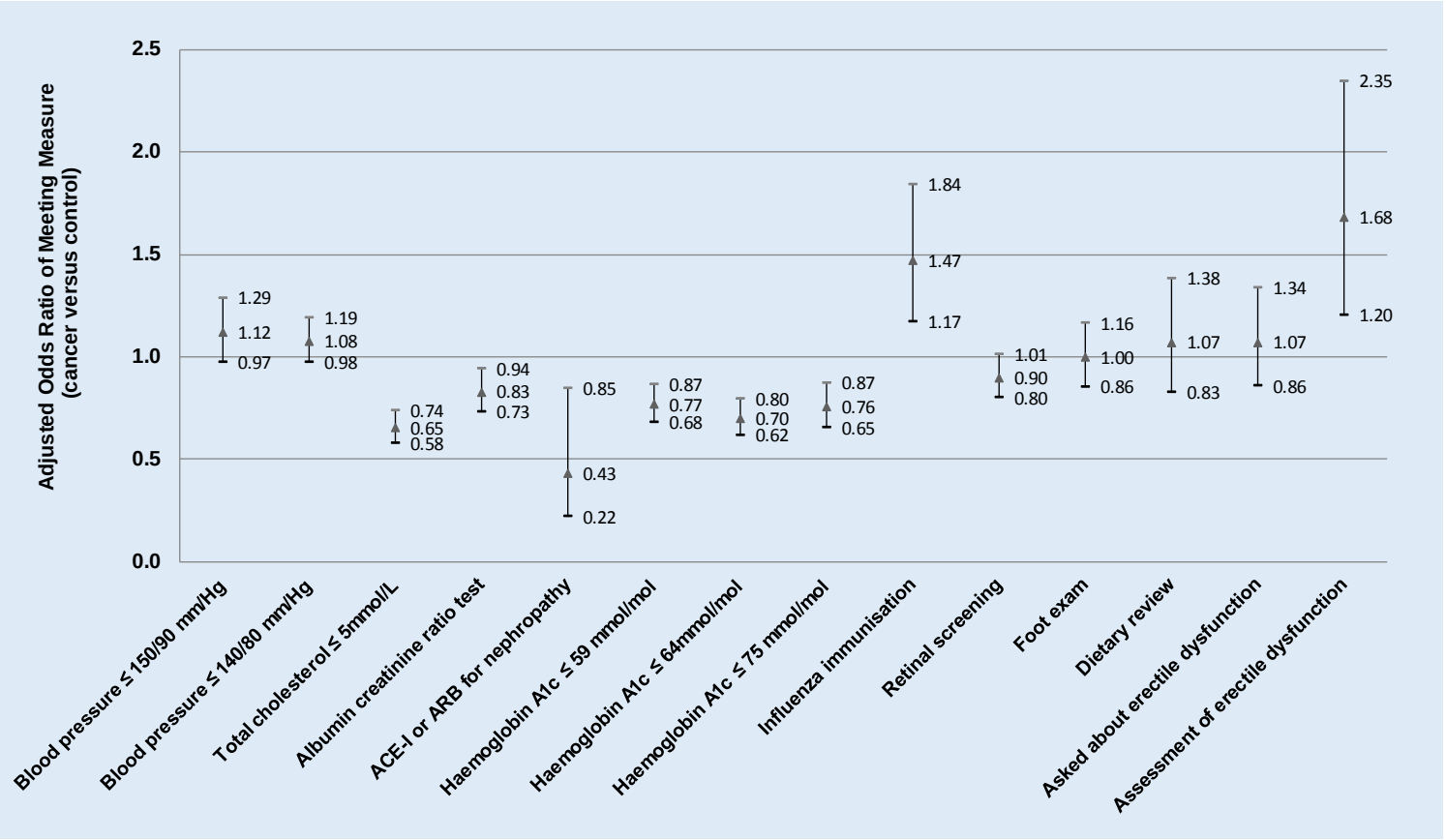
Figure 4.28. Adjusted Odds of Meeting Quality Measures- Colorectal Cancer, Seven Years



Legend: Figure 4.28. Adjusted odds ratios and 95% confidence intervals (CI) (cancer compared with controls) of meeting the corresponding quality measure (shown on x-axis). Results are from the multivariate mixed-effects logistic regression analyses of the full cohorts during seven years of follow up. An upper bound of the 95% CI <1.0 indicates that cancer patients had lower adjusted odds of meeting the threshold than controls. A lower bound of the 95% CI >1.0 indicates that cancer patients had higher adjusted odds of meeting the threshold than controls.

In the prostate cancer cohort, cancer was associated with significantly lower odds of meeting quality measures based on cholesterol, albumin creatinine ratio testing, use of ACE-I or ARB among patients with nephropathy or microalbuminuria, and HbA1c (at all three thresholds). (Figure 4.29)

Figure 4.29. Adjusted Odds of Meeting Quality Measures- Prostate Cancer, Seven Years



Legend: Figure 4.29. Adjusted odds ratios and 95% confidence intervals (CI) (cancer compared with controls) of meeting the corresponding quality measure (shown on x-axis). Results are from the multivariate mixed-effects logistic regression analyses of the full cohorts during seven years of follow up. An upper bound of the 95% CI <1.0 indicates that cancer patients had lower adjusted odds of meeting the threshold than controls. A lower bound of the 95% CI >1.0 indicates that cancer patients had higher adjusted odds of meeting the threshold than control.

4.3.5.2 Propensity Matched Cohort – Five Years of Follow-Up

The results of the secondary multilevel logistic regression analyses in the propensity matched combined cohort based on five years of follow-up after the index date (Table 4.2: "Propensity Matched" columns) were very similar to the results of the primary adjusted analyses which were reported in Table 1 and are reproduced in Table 4.2 "Primary" columns. There was no instance in which the OR from *only one* of the two analyses was statistically significant (95% CI, did not overlap 1.0). However, for the majority of measures, the propensity matched ORs were slightly smaller than the ones from the primary adjusted analyses.

Table 4.2: Secondary Analyses of Quality Measures – Propensity Matched, Combined Cohort

	Combined Cohort						
	Propensity Matched			Primary			Δ Odds Ratios
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Blood pressure ≤150/90	1.04	0.92	1.16	1.05	0.96	1.16	-0.01
Blood pressure ≤140/80	1.04	0.95	1.14	1.04	0.97	1.12	0.00
Total cholesterol ≤5mmol/L	0.76	0.67	0.86	0.82	0.75	0.90	-0.06
Albumin creatinine ratio test	0.81	0.71	0.91	0.83	0.75	0.91	-0.02
ACE-I or ARB for nephropathy	0.72	0.29	1.78	0.48	0.21	1.10	0.23
Haemoglobin A1c ≤59	0.76	0.66	0.87	0.77	0.70	0.85	-0.01
Haemoglobin A1c ≤64	0.74	0.65	0.85	0.75	0.68	0.82	-0.01
Haemoglobin A1c ≤75	0.75	0.66	0.86	0.80	0.73	0.89	-0.05
Influenza immunisation	1.28	1.01	1.63	1.30	1.07	1.59	-0.02
Retinal screening	0.97	0.87	1.08	0.99	0.91	1.08	-0.02
Foot exam	0.86	0.71	1.05	0.94	0.85	1.04	-0.08
Dietary review	0.96	0.78	1.20	1.01	0.87	1.16	-0.04
Asked about erectile dysfunction	1.13	0.89	1.45	1.06	0.89	1.26	0.07
Assessment of erectile dysfunction	1.65	1.14	2.37	1.60	1.18	2.17	0.05

Odds Ratio of meeting the quality measure in cancer patients compared to controls. "Primary" results duplicated from Table 4.1, and presented here for comparison to propensity-matched results

The results of the secondary analyses in the propensity matched breast cancer cohort based on five years of follow up (Table 4.3) also were very similar to the original primary adjusted analyses, except for ACE-I or ARB for nephropathy or microalbuminuria, where the OR was 0.58 lower in the primary adjusted compared to the propensity matched

analysis. Again, there was no instance in which the OR from only one of the two analyses was statistically significant; and, for the majority of measures the propensity matched ORs were smaller than the ones from the primary adjusted analyses.

Table 4.3: Secondary Analyses of Quality Measures – Propensity Matched, Breast Cancer

	Breast Cancer						
	Propensity Matched			Primary			Δ Odds Ratios
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Blood pressure ≤150/90	0.93	0.76	1.15	1.00	0.85	1.18	-0.07
Blood pressure ≤140/80	0.98	0.83	1.16	1.06	0.93	1.20	-0.07
Total cholesterol ≤5mmol/L	1.02	0.82	1.27	1.03	0.88	1.21	-0.01
Albumin creatinine ratio test	0.78	0.63	0.96	0.80	0.68	0.95	-0.02
ACE-I or ARB for nephropathy	1.15	0.10	13.09	0.57	0.05	5.98	0.58
Haemoglobin A1c ≤59	0.69	0.54	0.89	0.72	0.61	0.85	-0.03
Haemoglobin A1c ≤64	0.75	0.58	0.96	0.74	0.63	0.88	0.01
Haemoglobin A1c ≤75	0.92	0.72	1.18	0.86	0.72	1.03	0.06
Influenza immunisation	1.04	0.68	1.58	0.95	0.68	1.34	0.09
Retinal screening	1.02	0.85	1.23	1.03	0.88	1.19	-0.01
Foot exam	0.84	0.61	1.16	0.88	0.74	1.04	-0.04
Dietary review	0.76	0.49	1.19	0.89	0.66	1.21	-0.13

Odds Ratio of meeting the quality measure in cancer patients compared to controls. "Primary" results duplicated from Table 4.1, and presented here for comparison to propensity-matched results

Several results from the secondary analyses of the propensity matched colorectal cancer cohort (Table 4.4) were different from those of the primary adjusted analyses, including foot examination, dietary review, asked about erectile dysfunction, and assessment of erectile dysfunction. Also, there were two instances (shaded in the table) in which the OR from one analysis, but not the other, was statistically significantly different from 1.0: total cholesterol (significant in the primary adjusted analysis but not the propensity matched); and foot examination (significant in the propensity matched analysis but not the primary adjusted one). Again, most ORs were lower in the propensity matched analyses than in the primary adjusted.

Table 4.4: Secondary Analyses of Quality Measures – Propensity Matched, Colorectal Cancer

	Colorectal Cancer						
	Propensity Matched			Primary			Δ Odds Ratios
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Blood pressure ≤150/90	0.99	0.80	1.24	0.96	0.81	1.13	0.03
Blood pressure ≤140/80	0.95	0.81	1.13	0.99	0.87	1.11	-0.03
Total cholesterol ≤5mmol/L	0.82	0.66	1.03	0.80	0.68	0.93	0.02
Albumin creatinine ratio test	0.76	0.60	0.95	0.81	0.68	0.97	-0.05
ACE-I or ARB for nephropathy	0.69	0.16	2.95	0.77	0.23	2.58	-0.08
Haemoglobin A1c ≤59	0.73	0.57	0.93	0.80	0.67	0.95	-0.07
Haemoglobin A1c ≤64	0.73	0.57	0.94	0.77	0.65	0.91	-0.04
Haemoglobin A1c ≤75	0.71	0.55	0.91	0.76	0.63	0.91	-0.05
Influenza immunisation	0.84	0.51	1.38	0.96	0.67	1.36	-0.12
Retinal screening	1.01	0.84	1.23	1.03	0.88	1.20	-0.01
Foot exam	0.64	0.45	0.90	0.92	0.78	1.09	-0.29
Dietary review	0.78	0.53	1.17	1.02	0.80	1.28	-0.23
Asked about erectile dysfunction	0.72	0.49	1.07	0.99	0.75	1.32	-0.27
Assessment of erectile dysfunction	1.04	0.49	2.22	1.26	0.71	2.25	-0.22

Odds Ratio of meeting the quality measure in cancer patients compared to controls. "Primary" results duplicated from Table 4.1, and presented here for comparison to propensity-matched results.

Several results from the secondary analyses of the propensity matched prostate cancer cohort (Table 4.5) were different from those of the primary adjusted analyses, including foot examination, dietary review, asked about erectile dysfunction, and assessment of erectile dysfunction. Also, there were two instances (shaded in the table) in which the

OR from one analysis, but not the other, was statistically significantly different from 1.0: blood pressure ≤150/90 mm Hg and HbA1c ≤59 mmol/mol (significant in the primary adjusted analysis but not the propensity matched analysis).

Table 4.5: Secondary Analyses of Quality Measures – Propensity Matched, Prostate Cancer

	Prostate Cancer						
	Propensity Matched			Primary			Δ Odds Ratios
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Blood pressure ≤150/90	1.08	0.90	1.31	1.16	1.00	1.35	-0.08
Blood pressure ≤140/80	1.05	0.90	1.22	1.06	0.95	1.19	-0.01
Total cholesterol ≤5mmol/L	0.66	0.54	0.80	0.66	0.57	0.76	0.00
Albumin creatinine ratio test	0.86	0.70	1.05	0.86	0.73	1.01	0.00
ACE-I or ARB for nephropathy	0.29	0.06	1.31	0.33	0.09	1.14	-0.03
Haemoglobin A1c ≤59	0.83	0.67	1.03	0.79	0.68	0.92	0.04
Haemoglobin A1c ≤64	0.77	0.62	0.95	0.73	0.63	0.85	0.04
Haemoglobin A1c ≤75	0.81	0.65	1.00	0.79	0.67	0.93	0.02
Influenza immunisation	2.35	1.53	3.61	2.18	1.56	3.05	0.17
Retinal screening	0.93	0.78	1.12	0.91	0.79	1.05	0.02
Foot exam	0.87	0.63	1.20	1.03	0.87	1.21	-0.15
Dietary review	0.80	0.51	1.24	1.08	0.83	1.41	-0.29
Asked about erectile dysfunction	0.91	0.60	1.39	1.08	0.86	1.35	-0.17
Assessment of erectile dysfunction	1.44	1.01	2.05	1.71	1.21	2.41	-0.27

Odds Ratio of meeting the quality measure in cancer patients compared to controls. "Primary" results duplicated from Table 4.1, and presented here for comparison to propensity-matched results.

4.3.5.3 Propensity Matched Cohort – Extended Follow-Up

The results of the secondary analyses in the propensity matched combined cohort with extended follow-up (Table 4.6: "Propensity Matched" columns) were very similar to results of the corresponding analyses on the full cohorts presented in Section 4.3.4.1 above (Table 4.6: "Full Cohort" columns). There was one instance in which the OR from only one of the two analyses was statistically significant: influenza immunisation, which was statistically significantly higher in the full cohort. For the majority of measures, the propensity matched ORs were smaller than the ones from the primary adjusted analyses.

Table 4.6: Secondary Analyses – Propensity Matched, Extended Follow-Up, Combined Cohort

	Combined Cohort						
	Propensity Matched			Full Cohort			Δ Odds Ratios
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Blood pressure ≤150/90	0.99	0.89	1.10	1.02	0.94	1.11	-0.03
Blood pressure ≤140/80	1.04	0.95	1.12	1.04	0.98	1.11	-0.01
Total cholesterol ≤5mmol/L	0.76	0.69	0.85	0.82	0.76	0.88	-0.05
Albumin creatinine ratio test	0.86	0.77	0.94	0.84	0.78	0.91	0.01
ACE-I or ARB for nephropathy	0.55	0.33	0.90	0.48	0.32	0.74	0.06
Haemoglobin A1c ≤59	0.79	0.71	0.87	0.78	0.73	0.84	0.00
Haemoglobin A1c ≤64	0.75	0.67	0.83	0.76	0.71	0.82	-0.02
Haemoglobin A1c ≤75	0.74	0.66	0.83	0.80	0.74	0.87	-0.06
Influenza immunisation	1.08	0.92	1.26	1.14	1.00	1.30	-0.06
Retinal screening	1.00	0.91	1.09	0.99	0.92	1.06	0.01
Foot exam	0.84	0.73	0.97	0.91	0.83	1.00	-0.07
Dietary review	0.96	0.79	1.18	1.01	0.88	1.15	-0.04
Asked about erectile dysfunction	1.16	0.86	1.57	1.06	0.88	1.27	0.11
Assessment of erectile dysfunction	1.75	1.20	2.56	1.57	1.16	2.11	0.18

Odds Ratio of meeting the quality measure in cancer patients compared to controls. "Full Cohort" results duplicated from Figure 4.26, and presented here for comparison to propensity-matched results

The results of the secondary analyses in the propensity matched breast cancer cohort with extended follow-up (Table 4.7: "Propensity Matched" columns) were very similar to results of the corresponding analyses on the full cohorts presented in Section 4.3.4.1 above (Table 4.7: "Full Cohort" columns). There were only two instances in which the OR

from only one of the two analyses was statistically significant; and, for the majority of measures the propensity matched ORs were smaller than the ones from the primary adjusted analyses.

Table 4.7: Secondary Analyses – Propensity Matched, Extended Follow-Up, Breast Cancer

	Breast Cancer						
	Propensity Matched			Full Cohort			Δ Odds Ratios
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Blood pressure ≤150/90	0.94	0.78	1.13	1.01	0.87	1.16	-0.07
Blood pressure ≤140/80	1.04	0.90	1.20	1.10	0.99	1.23	-0.07
Total cholesterol ≤5mmol/L	1.08	0.90	1.30	1.10	0.97	1.26	-0.02
Albumin creatinine ratio test	0.79	0.67	0.94	0.84	0.74	0.97	-0.05
ACE-I or ARB for nephropathy	0.82	0.26	2.58	0.58	0.23	1.46	0.24
Haemoglobin A1c ≤59	0.73	0.60	0.87	0.74	0.65	0.84	-0.02
Haemoglobin A1c ≤64	0.76	0.63	0.92	0.75	0.65	0.85	0.02
Haemoglobin A1c ≤75	0.89	0.72	1.10	0.84	0.73	0.98	0.05
Influenza immunisation	1.11	0.84	1.47	1.06	0.85	1.34	0.05
Retinal screening	1.01	0.87	1.19	1.04	0.91	1.18	-0.02
Foot exam	0.82	0.64	1.05	0.84	0.71	0.99	-0.03
Dietary review	0.82	0.62	1.09	0.92	0.72	1.17	-0.10

Odds Ratio of meeting the quality measure in cancer patients compared to controls. "Full Cohort" results duplicated from Figure 4.27, and presented here for comparison to propensity-matched results.

Several results from secondary analyses in the propensity matched colorectal cancer cohort with extended follow-up (Table 4.8: "Propensity Matched" columns) were

different from the results of the corresponding analyses on the full cohorts presented in Section 4.3.4.1 above (Table 4.8: “Full Cohort” columns), including foot examination, dietary review, asked about erectile dysfunction, and assessment of erectile dysfunction. There were only two instances in which the OR from only one of the two analyses was statistically significant different from 1.0: ACE-I or ARB for nephropathy or microalbuminuria (significant in the full cohort but not the propensity matched cohort); and foot examination (significant in the propensity matched cohort but not the full cohort). Again, most ORs were lower in the propensity matched analyses than in the full cohort analyses.

Table 4.8: Secondary Analyses – Propensity Matched, Extended Follow-Up, Colorectal Cancer

	Colorectal Cancer						
	Propensity Matched			Full Cohort			Δ Odds Ratios
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Blood pressure ≤150/90	0.94	0.77	1.15	0.89	0.77	1.03	0.05
Blood pressure ≤140/80	0.94	0.81	1.08	0.93	0.84	1.03	0.01
Total cholesterol ≤5mmol/L	0.79	0.65	0.96	0.74	0.65	0.84	0.06
Albumin creatinine ratio test	0.80	0.66	0.96	0.84	0.73	0.97	-0.04
ACE-I or ARB for nephropathy	0.43	0.18	1.05	0.49	0.25	0.97	-0.06
Haemoglobin A1c ≤59	0.80	0.66	0.96	0.84	0.74	0.95	-0.04
Haemoglobin A1c ≤64	0.76	0.63	0.93	0.84	0.74	0.96	-0.08
Haemoglobin A1c ≤75	0.74	0.60	0.91	0.81	0.70	0.94	-0.07
Influenza immunisation	0.86	0.64	1.16	0.91	0.73	1.14	-0.05
Retinal screening	0.97	0.82	1.13	1.02	0.90	1.15	-0.05
Foot exam	0.78	0.61	1.00	0.90	0.77	1.05	-0.12
Dietary review	0.79	0.55	1.13	1.01	0.81	1.27	-0.23
Asked about erectile dysfunction	0.72	0.49	1.07	1.00	0.72	1.39	-0.28
Assessment of erectile dysfunction	1.07	0.53	2.17	1.21	0.70	2.11	-0.14

Odds Ratio of meeting the quality measure in cancer patients compared to controls. "Full Cohort" results duplicated from Figure 4.28, and presented here for comparison to propensity-matched results.

Several results from secondary analyses in the propensity matched prostate cancer cohort with extended follow-up (Table 4.9: “Propensity Matched” columns) were different from the results of the corresponding analyses on the full cohorts presented in Section 4.3.4.1 above (Table 4.9: “Full Cohort” columns), including dietary review, asked about erectile dysfunction, and assessment of erectile dysfunction. There was only one instance in which the OR from only one of the two analyses was statistically significant different from 1.0: ACE-I or ARB for nephropathy or microalbuminuria (significant in the full cohort but not the propensity matched cohort).

Table 4.9: Secondary Analyses – Propensity Matched, Extended Follow-Up, Prostate Cancer

	Prostate Cancer						
	Propensity Matched			Full Cohort			Δ Odds Ratios
	Odds Ratio	95% CI		Odds Ratio	95% CI		
Blood pressure ≤150/90	1.01	0.84	1.21	1.12	0.97	1.29	-0.11
Blood pressure ≤140/80	1.05	0.92	1.21	1.08	0.98	1.19	-0.02
Total cholesterol ≤5mmol/L	0.66	0.55	0.78	0.65	0.58	0.74	0.01
Albumin creatinine ratio test	0.85	0.72	1.00	0.83	0.73	0.94	0.02
ACE-I or ARB for nephropathy	0.52	0.22	1.25	0.43	0.22	0.85	0.09
Haemoglobin A1c ≤59	0.79	0.67	0.93	0.77	0.68	0.87	0.02
Haemoglobin A1c ≤64	0.73	0.61	0.87	0.70	0.62	0.80	0.03
Haemoglobin A1c ≤75	0.76	0.62	0.93	0.76	0.65	0.87	0.00
Influenza immunisation	1.48	1.12	1.96	1.47	1.17	1.84	0.01
Retinal screening	0.89	0.76	1.03	0.90	0.80	1.01	-0.01
Foot exam	0.99	0.79	1.24	1.00	0.86	1.16	-0.01
Dietary review	0.81	0.57	1.17	1.07	0.83	1.38	-0.26
Asked about erectile dysfunction	0.93	0.65	1.33	1.07	0.86	1.34	-0.14
Assessment of erectile dysfunction	1.53	1.03	2.27	1.68	1.20	2.35	-0.15

Odds Ratio of meeting the quality measure in cancer patients compared to controls. "Full Cohort" results duplicated from Figure 4.29, and presented here for comparison to propensity-matched results.

4.4 DISCUSSION AND CONCLUSIONS

4.4.1 Summary of Findings

This chapter has presented the methods and results of the primary research in which changes in the quality of diabetes care over time were compared between cancer patients and controls. In all, 216 multilevel logistic regression analyses were performed based on the four full cohorts and the four propensity-matched cohorts, using both five years and seven years of follow-up. The ORs for the cancer variable from all of the adjusted analyses are presented in Table 4.10.

Cancer was associated with statistically significantly lower adjusted odds (red coefficients) of meeting the quality measure in 78/216 (36%) of the analyses, most notably for those measures based on HbA1c (44/48)[n] or cholesterol control (11/16 total), and albumin creatinine ratio testing (15/16). In general, effect sizes ranged from 20%-30% reduction in the odds of meeting these measures in cancer patients. There was no evidence breast cancer was associated with lower odds of cholesterol control. Otherwise, the findings were remarkably consistent across all four cancer cohorts, and also across the four analyses within each cohort and quality measure. There was no evidence that cancer was associated with lower adjusted odds of blood pressure control, or with receiving any of the other services in the Diabetes Mellitus Indicator Set[1] (Box 4.1) except perhaps foot examination.

[n] The three HbA1c measures are "nested" in the sense that if the patient met the threshold of ≤ 59 mmol/mol they also met the thresholds of ≤ 64 mmol/mol and of ≤ 75 mmol/mol.

Table 4.10: Summary of All Adjusted Analyses (continued following page)

Quality Measure	Cohort							
	Combined Cohorts				Breast Cancer			
	Full Cohorts		PSM Cohorts		Full Cohorts		PSM Cohorts	
	5 Years	7 Years	5 Years	7 Years	5 Years	7 Years	5 Years	7 Years
Blood Pressure ≤150/90 mm/Hg	1.05	1.02	1.04	0.99	1.00	1.01	0.93	0.94
Blood Pressure ≤140/80 mm/Hg	1.04	1.04	1.04	1.04	1.06	1.10	0.98	1.04
Total Cholesterol ≤5mmol/L	**0.82**	**0.82**	**0.76**	**0.76**	1.03	1.10	1.02	1.08
Albumin Creatinine Ratio Test	**0.83**	**0.84**	**0.81**	**0.86**	**0.80**	**0.84**	**0.78**	**0.79**
ACE Inhibitor or ARB	0.48	**0.48**	0.72	**0.55**	0.57	0.58	1.15	0.82
HbA1c ≤59 mmol/mol	**0.77**	**0.78**	**0.76**	**0.79**	**0.72**	**0.74**	**0.69**	**0.73**
HbA1c ≤64 mmol/mol	**0.75**	**0.76**	**0.74**	**0.75**	**0.74**	**0.75**	**0.75**	**0.76**
HbA1c ≤75 mmol/mol	**0.80**	**0.80**	**0.75**	**0.74**	0.86	**0.84**	0.92	0.89
Influenza Immunisation	**1.31**	**1.14**	**1.28**	1.08	0.95	1.06	1.04	1.11
Retinal Screening	0.99	0.99	0.97	1.00	1.03	1.04	1.02	1.01
Foot Exam	0.94	**0.91**	0.86	**0.84**	0.88	**0.84**	0.84	0.82
Dietary Review	1.01	1.01	0.96	0.96	0.89	0.92	0.76	0.82
Asked About Erectile Dysfunction	1.06	1.06	1.13	1.16	Not Applicable			
Advice About Erectile Dysfunction	**1.60**	**1.57**	**1.65**	**1.75**				

Quality Measure	Cohort							
	Colorectal Cancer				Prostate Cancer			
	Full Cohorts		PSM Cohorts		Full Cohorts		PSM Cohorts	
	5 Years	7 Years	5 Years	7 Years	5 Years	7 Years	5 Years	7 Years
Blood Pressure ≤150/90 mm/Hg	0.96	0.89	0.99	0.94	1.16	1.12	1.08	1.01
Blood Pressure ≤140/80 mm/Hg	0.99	0.93	0.95	0.94	1.06	1.08	1.05	1.05
Total Cholesterol ≤5mmol/L	**0.80**	**0.74**	0.82	**0.79**	**0.66**	**0.65**	**0.66**	**0.66**
Albumin Creatinine Ratio Test	**0.81**	**0.84**	**0.76**	**0.80**	**0.86**	**0.83**	0.86	**0.85**
ACE Inhibitor or ARB	0.76	**0.49**	0.69	0.43	0.33	**0.43**	0.29	0.52
HbA1c ≤59 mmol/mol	**0.80**	**0.84**	**0.73**	**0.80**	**0.79**	**0.77**	0.83	**0.79**
HbA1c ≤64 mmol/mol	**0.77**	**0.84**	**0.73**	**0.76**	**0.73**	**0.70**	**0.77**	**0.73**
HbA1c ≤75 mmol/mol	**0.76**	**0.81**	**0.71**	**0.74**	**0.79**	**0.76**	**0.81**	**0.76**
Influenza Immunisation	0.96	0.91	0.84	0.86	**2.18**	**1.47**	**2.35**	**1.48**
Retinal Screening	1.03	1.02	1.01	0.97	0.91	0.90	0.93	0.89
Foot Exam	0.92	0.90	**0.64**	0.78	1.03	1.00	0.87	0.99
Dietary Review	1.02	1.01	0.78	0.79	1.08	1.07	0.80	0.81
Asked About Erectile Dysfunction	1.00	1.00	0.72	0.72	1.08	1.07	0.91	0.93
Advice About Erectile Dysfunction	1.26	1.21	1.04	1.07	**1.71**	**1.68**	**1.44**	**1.53**

Note: This table summarizes the results from 216 multivariate, multilevel logistic regression analyses performed to examine adjusted associations between cancer and the odds (cells in table) of meeting diabetes quality measures over time. Red indicates adjusted odds of meeting the measure were statistically significantly lower in cancer patients than non-cancer controls. Green indicates odds of meeting the measure were statistically significantly higher in cancer patients than non-cancer controls. PSM Propensity Score Matched; ACE Angiotensin Converting Enzyme; ARB Angiotensin Receptor Blocker; HbA1c Glycosylated Haemoglobin.

Prostate cancer was associated with statistically significantly higher adjusted odds (green coefficients) of receiving influenza immunisation. Prostate cancer also was associated with statistically significantly higher adjusted odds of receiving advice for erectile dysfunction, which could be due to the fact that treatment modalities for prostate cancer, including prostatectomy and radiation therapy, are associated with erectile dysfunction.

One possible explanation for these findings is that follow-up of prostate cancer, with the aims of checking how cancer has responded to treatment, and helping patients manage any side effects of treatment,[10] increases the frequency of appointments at the patient's GP surgery, which in turn provides more opportunities for providing routine primary care, such as influenza immunisation, to these patients. In particular, regular prostate specific antigen testing may be performed at the GP surgery,[10] with subsequent appointments to review the results. Also, since GPs will be aware that erectile dysfunction is a side-effect of treatment for prostate cancer, and patients are encouraged to discuss symptoms or treatment side-effects during their follow-up visits,[10] prostate cancer patients are more likely to receive advice about erectile dysfunction.

4.4.2 Strengths and Limitations

The strengths and limitations of this research have been assessed with the same instrument used to assess the quality of studies in the systematic review (Chapter 2), the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (Box 4.2).[11]

Box 4.2: Criteria for Assessing the Quality of Cohort Studies[11]

- **Representativeness of the exposed cohort[o]**
- **Selection of the non-exposed cohort[o]**
- **Ascertainment of exposure[o]**
- **Comparability of cohorts**

  Study controls for age

  Study controls for additional factors
- **Assessment of outcome**
- **Follow-up long enough for outcomes to occur**
- **Adequacy of follow-up of cohorts**

4.4.2.1 Comparability of the Cohorts

Since the primary analyses were based on the full cohorts, multivariate statistical methods were used to adjust for differences in baseline characteristics between cancer patients and controls that were not accounted for in the matching process, and which otherwise could have confounded associations between cancer and the quality of diabetes primary care. These included baseline BMI, smoking status, blood pressure, cholesterol, and HbA1c, which were all well-populated (see Chapter 3). As most of the differences observed between cancer patients and controls occurred in the test result–based quality measures, controlling for baseline test values (at the same cutoffs as in the

[o] Assessed in the corresponding section of Chapter 3.

quality measures) in the multivariate analyses removed an important source of potential confounding in those comparisons.

4.4.2.2 Assessment of Outcome

All of the quality measures were based on QOF performance indicators,[1] and there are considerable incentives for primary care practices to record the delivery of all services and test results pertaining to these indicators. In this research, the same Read codes used for the QOF indicators were used to identify the quality measures. Therefore, it is likely this approach was highly sensitive and specific. Also, during follow-up patients were required to have survived for the full year to be "at risk" for meeting the outcomes during that year. This was designed to minimize the chance that any observed differences in the probabilities of meeting the quality measures might be due to differences in person-time at risk between cancer patients and controls, the most likely source of which would have been excess mortality in the cancer cohort.

As described above, differences were observed in quality measures based on testing and control of cholesterol and HbA1c between cancer patients and controls. One limitation is that the research may have failed to identify services, including testing, that were provided by a specialist during cancer treatment and follow-up, but not recorded in the primary care data. However, HES[12] inpatient data, which are part of the CPRD linkage, do not contain the level of detail required to reliably identify the quality measures analyzed in this chapter, and are available for only approximately two-thirds of the CPRD population. Therefore, HES data were not used to supplement information from the primary care data in CPRD. Another limitation is that CPRD does not contain

comprehensive data on patient adherence to diabetes self-management activities, such as diet, exercise, and therapy regimens, which are important components of high quality diabetes care.

4.4.2.3 Length of Follow-Up

The length of follow-up was established to capture differences in quality of diabetes care throughout the continuum of cancer care, from initial treatment through to long-term survivorship. However, the study was not designed to assess quality in long-term survivors of cancer, as others have previously done.[13] Consequently, it would not capture the impact of long-term cancer recurrence on the quality of diabetes care, for instance.

4.4.2.4 Adequacy of Follow-Up of the Cohorts

As described in Chapter 3, the median length of follow-up for these analyses was 3.5 years after the index date, with a minimum of one year and a maximum of five. Reasons for attrition before the maximum were death or administrative (right) censoring. In order to maximize the size of the cohort, all patients with at least one year of follow-up before the end of their data (described in Chapter 3) were eligible for inclusion, which meant patients with an index date later in the calendar window, e.g. 2013, had shorter follow-up. Nevertheless, the combined cohort for these analyses accounted for 44,507 patient-years of follow-up, and unadjusted plots of the proportions of patients meeting the quality of care indicators (Figure 4.1-4.11) show that, in almost all instances, the CIs remained quite narrow, suggesting sufficient power to detect even small differences was retained throughout the observation period.

4.4.3 Conclusions and Implications

Overall, diabetic patients with cancer were less likely to achieve target thresholds for cholesterol and HbA1c. Potential reasons, including the effects of cancer treatment and changes in patient health behaviors in response to cancer diagnosis, should be investigated further. Options to improve achievement of target thresholds could include the development of specific indicators and incentives to promote greater coordination of care between oncologists and general practitioners, especially to identify and address instances in which cancer treatment may cause blood sugar and/or cholesterol concentrations to rise, and the widespread development of diabetes programs that are tailored specifically to cancer patients.

4.5 CHAPTER REFERENCES

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CHAPTER FIVE

Clinical and Laboratory Values Over Time

V CLINICAL AND LABORATORY VALUES OVER TIME

5.1 CHAPTER AIM

Results presented in the previous chapter show that cancer was associated with lower adjusted odds of meeting binary quality measures for cholesterol and HbA1c control based on test result thresholds specified in the QOF Diabetes Indicator Set.[1] The aim of this chapter is to present the methods and results of primary research in which changes in actual blood pressure, cholesterol, and HbA1c levels over time were compared between cancer patients and controls.

5.2 METHODS OF RESEARCH

5.2.1 Construction of a Period Prevalent Dataset

Since the research in this chapter entailed comparing changes in clinical and laboratory values between cancer patients and controls over time, patient-period datasets were constructed from the patient-level datasets in Chapter 3. First one patient record was constructed for each full quarter that the patient was included in the study. These records were numbered from 1 up to 28, with the 9th record representing the quarter immediately after (and including) the index date. So, a patient followed for the minimum of one year after their index date had 12 records, including 8 for the two years prior to their index date, which was the minimum required in the study inclusion criteria.

Second, a variable was constructed for each of the clinical[p] and laboratory values. (Box 5.1) Third, clinical and laboratory results for each patient were retained, and each result was assigned to a patient-period record based on the date that the result was obtained. Forth, the average of those values was calculated, and then used to populate the corresponding clinical or laboratory variable constructed in step 2.

Box 5.1: Clinical and laboratory Values

- Systolic blood pressure (mm Hg)
- Diastolic blood pressure (mm Hg)
- Total cholesterol (mmol/L)
- Low density lipoprotein cholesterol (mmol/L)
- High density lipoprotein cholesterol (mmol/L)
- HbA1c (mmol/mol)
- Weight (Kg)

5.2.2 Statistical Methods

Multilevel regression analysis[2-4] was used to investigate changes in clinical and laboratory values over time, and more importantly for this research, *whether those patterns of change over time differed between cancer patients and controls.*

[p] Weight was added to the list after exploratory analysis showed changes in blood pressure, cholesterol, and HbA1c levels around the time of cancer were similar to changes in body weight, especially in colorectal cancer.

5.2.2.1 Primary Analyses

The primary multilevel analyses were performed on all seven clinical and laboratory values (Box 5.1) in each of the four cohorts (cancers combined, breast, colorectal, and prostate) using up to five years (20 quarters) of patient-period data after the index date. Unadjusted analyses included linear (time) and quadratic (time*time) predictors for time (in calendar quarters, and specified as continuous variables), a binary predictor for cancer, and linear (time*cancer) and quadratic (time*time*cancer) interaction predictors.

In these models, the coefficients for the *cancer* variables are interpreted as follows:

- the "cancer" coefficient is the estimated difference in the clinical or laboratory value between cancer patients and controls *during the first quarter after (and including) the index date*;
- the "time*cancer" coefficient is the linear component of the difference in the rate of change in the clinical or laboratory value over time between cancer patients and controls; and
- the "time*time*cancer" coefficient is the quadratic component of the difference in the rate of change in the clinical or laboratory value over time between cancer patients and controls.

Adjusted analyses also included patient demographic and clinical characteristics, consisting of age, sex (combined and colorectal cancer cohorts), year of cancer diagnosis, smoking status, BMI, IMD,[5] Charlson Comorbidity Index,[6,7] history of microvascular and macrovascular complications of diabetes, blood pressure, total

cholesterol, and HbA1c (based on the most recent test result within one year before the index date), and history of diabetes medications.

5.2.2.2 Secondary Analyses

Secondary adjusted analyses were conducted on the four full cohorts using all seven years of patient-period data (including two years before the index date). In this instance, several of the unadjusted plots (see Results below) showed abrupt reversals in the direction of the clinical and laboratory values in cancer patients around the time of diagnosis. Therefore, the models for extended follow-up included a cancer predictor to account for within-patient changes at the time of cancer diagnosis, as well as several cancer*time interaction terms, both before and after cancer, to account for changes in the directions of the clinical and laboratory values around the time of cancer. A full explanation of the development of these models, as well as interpretation of the individual coefficients, is provided in the Appendix. Since interpretation of the individual cancer coefficients from these models is quite challenging (and not very informative), the results of these analyses are presented as plots of the marginal predicted clinical and laboratory values (with 95% CIs), which were generated using the actual patient data and coefficients from the models.[3] Secondary analyses also were conducted in the propensity-matched cohorts using both five and seven years of data. All statistical analyses were performed in STATA 14[8] using the xtmixed command.[3,4]

5.3 RESULTS

5.3.1 Unadjusted Plots of Clinical and Laboratory Values

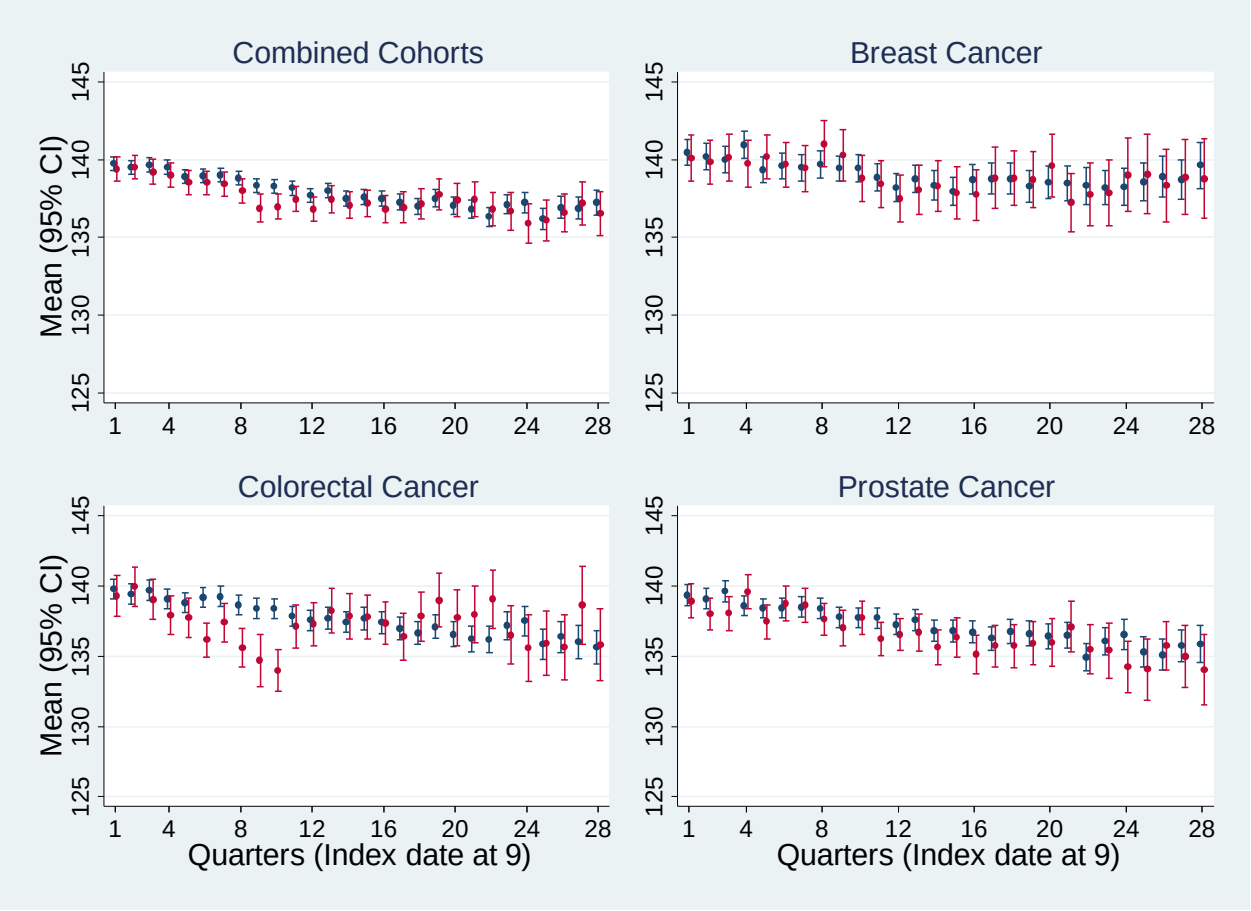
Plots of the unadjusted clinical and laboratory values (means [dots] and 95% CIs[q] [bars]) for cancer patients (red) and controls (blue), quarterly from two years before (quarters 1-8), up to five years after (quarters 9-28), the index date (quarter of index date=9) are shown in figures 5.1-5.7. The text in this section describes the plots for the combined cohorts, with additional information on the individual cancer cohorts also provided if those plots differed substantially from the combined cohort.

5.3.1.1 Blood Pressure

Mean systolic blood pressure (Figure 5.1) decreased in both groups from 139 mm Hg (95% CI, 139-140) in cancer patients (red) and 140 mm Hg (95% CI, 139-140) in controls (blue) in the first quarter (beginning two years before the index date), to 136 mm Hg (95% CI, 135-138) and 137 mm Hg (95% CI, 136-138) respectively in the 28th quarter (last before the end of the five-year follow-up). Colorectal cancer was associated with a decline from 139 mm Hg (95% CI, 138-141) in the first quarter to 134 mm Hg (95% CI, 132-136) in the index quarter (quarter=9), and was statistically significantly ($p \leq 0.05$) lower than in controls for several quarters around the index date, before returning to levels comparable to the control group thereafter.

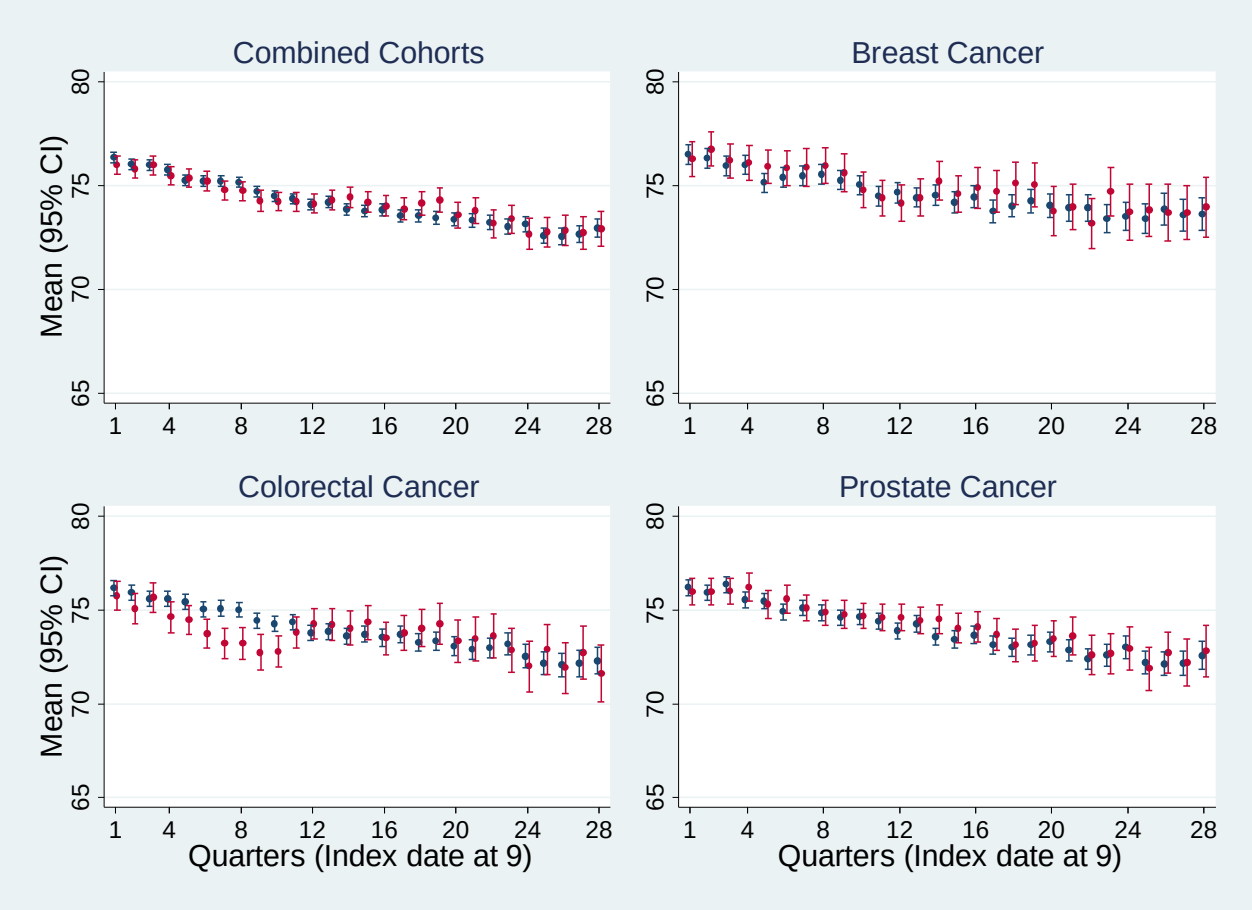
[q] Confidence intervals reported in this section may not be symmetrical due to rounding.

Figure 5.1: Unadjusted Systolic Blood Pressure (mm Hg)



Diastolic blood pressure (Figure 5.2) followed a similar pattern, with similar differences between colorectal cancer patients and controls around the time of cancer diagnosis.

Figure 5.2: Unadjusted Diastolic Blood Pressure (mm Hg)

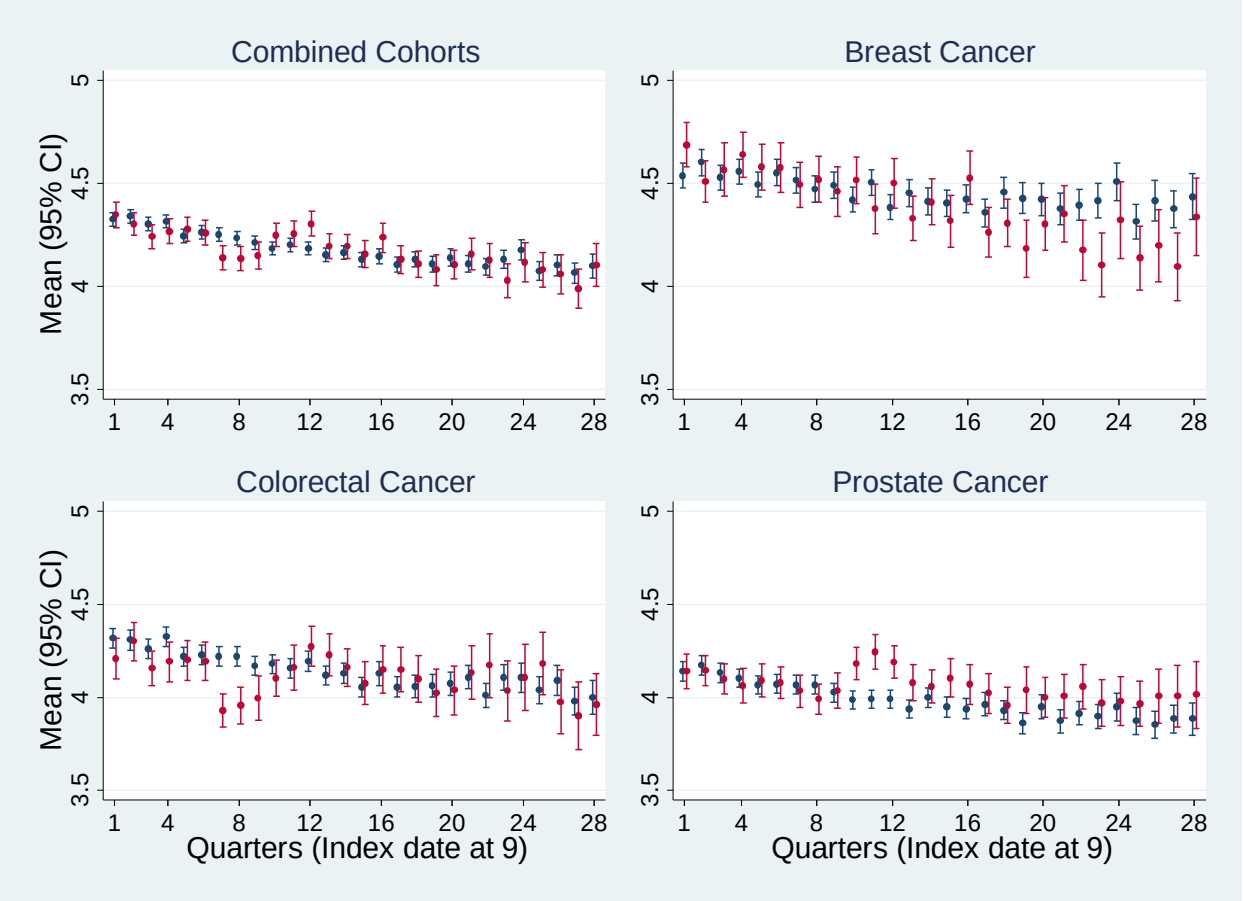


5.3.1.2 Cholesterol

Mean total cholesterol (Figure 5.3) decreased in both groups from 4.3 mmol/L (95% CI, 4.3-4.4) in cancer patients (red) and 4.3 mmol/L (95% CI, 4.3-4.4) in controls (blue) in the first quarter, to 4.1 mmol/L (95% CI, 4.0-4.2) in both groups in the 28th quarter. Colorectal cancer was associated with a decrease from 4.2 mmol/L (95% CI, 4.1-4.3) in the first quarter to 3.9 mmol/L (95% CI, 3.8-4.0) two quarters before the index date, and was statistically significantly lower than in controls for several quarters around the index

date, before returning to levels comparable to the control group thereafter. Prostate cancer was associated with an increase (and reversal in the direction of the longitudinal trajectory) in total cholesterol for several quarters after cancer diagnosis, before returning to levels comparable to the control group thereafter.

Figure 5.3: Unadjusted Total Cholesterol (mmol/L)



Overall trajectories of low density lipoprotein (Figure 5.4) and high-density lipoprotein (Figure 5.5) cholesterol were similar to total cholesterol.

Figure 5.4: Unadjusted Low-Density Lipoprotein Cholesterol (mmol/L)

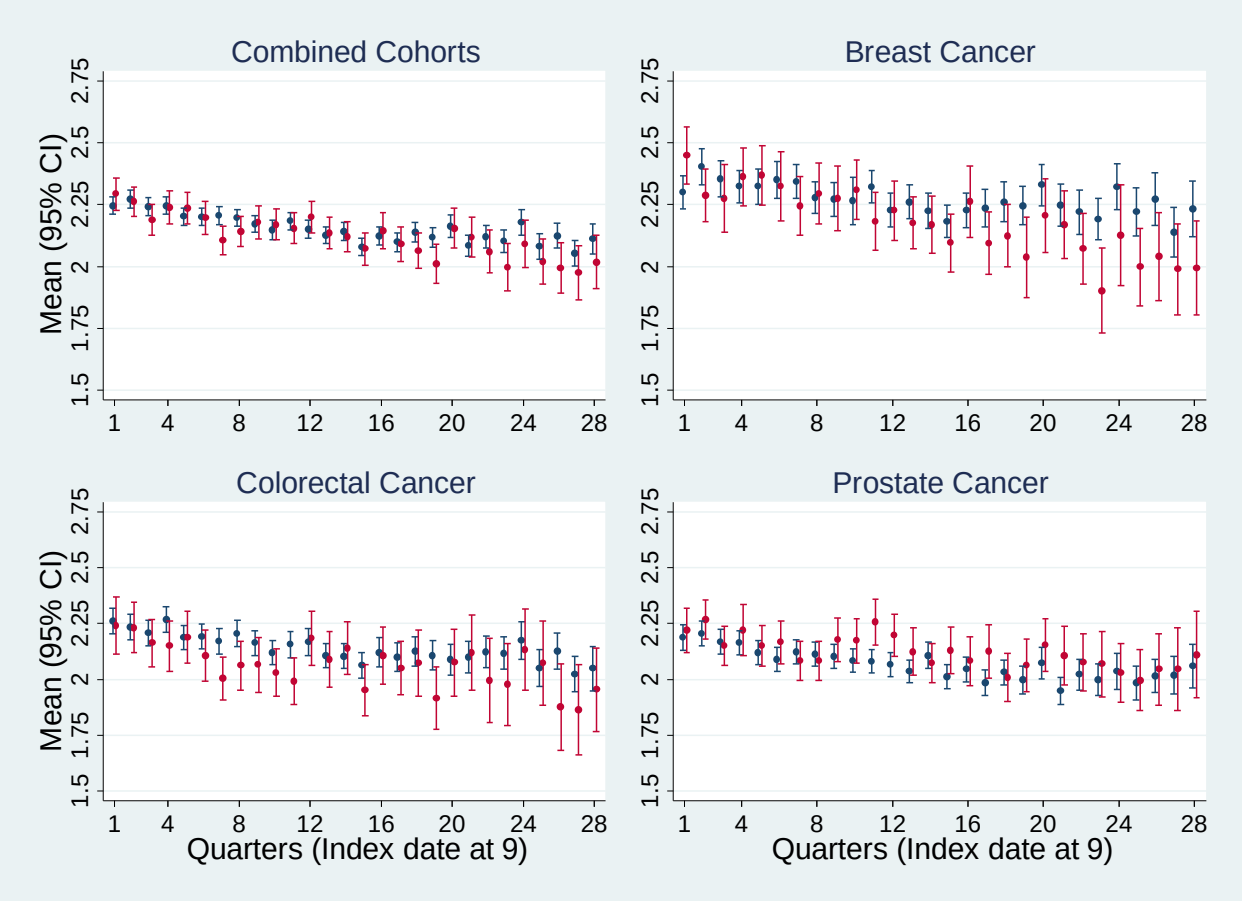
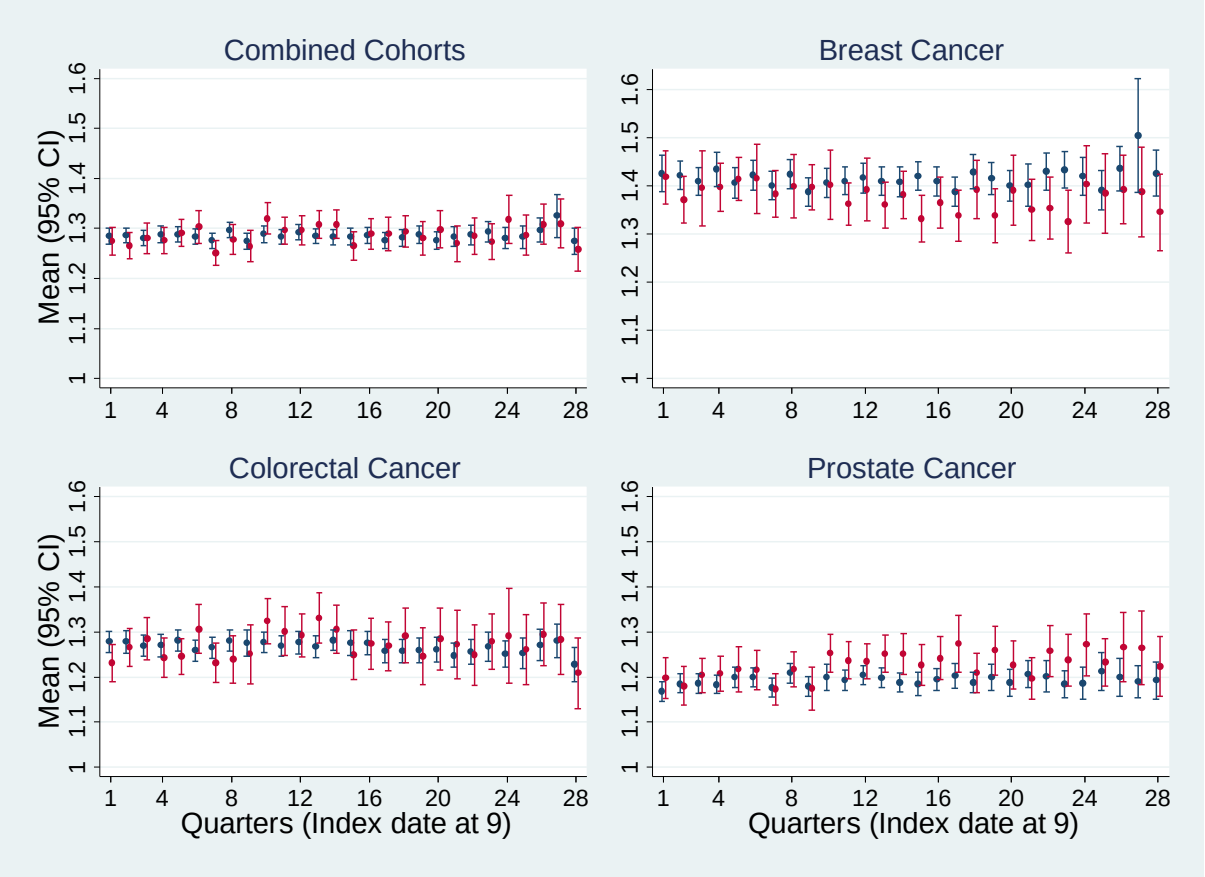


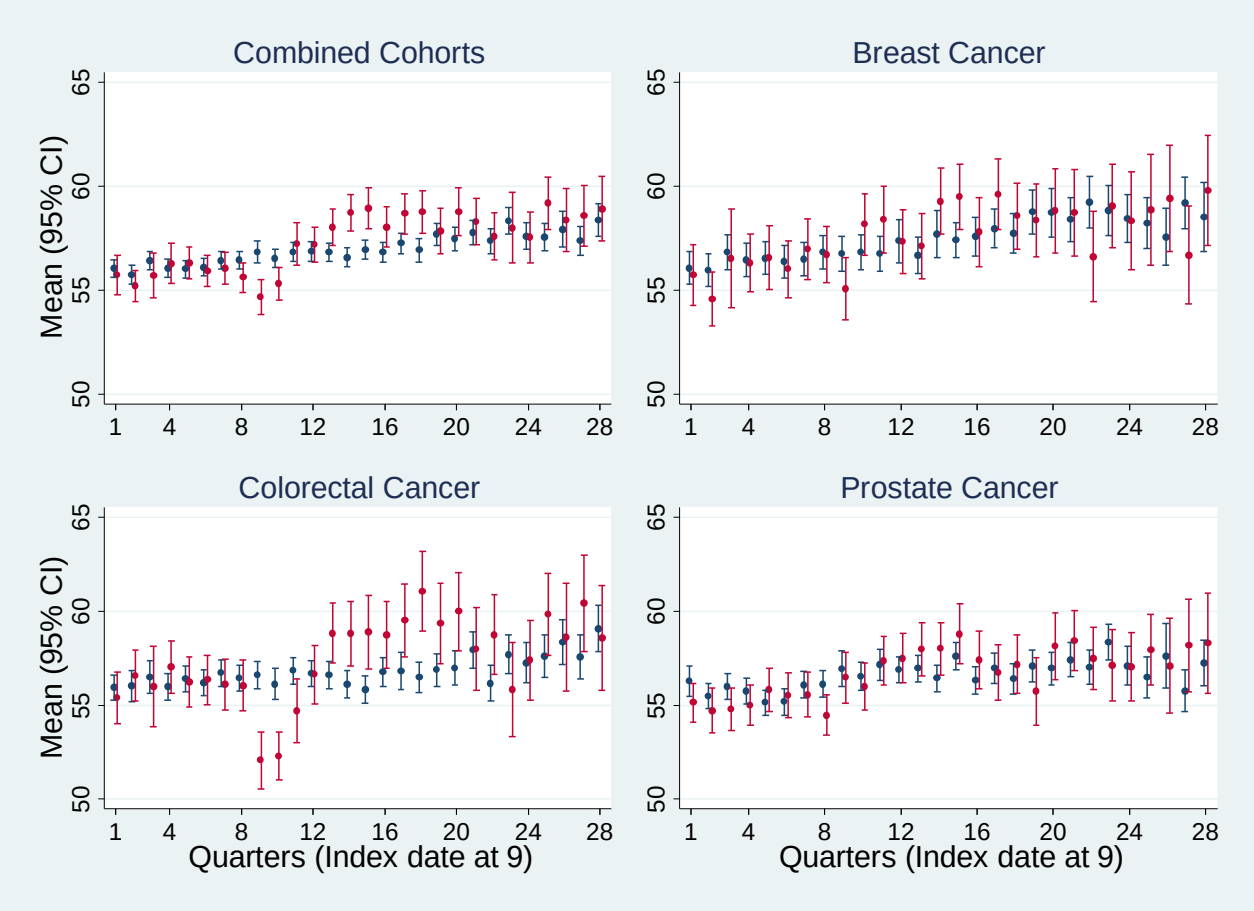
Figure 5.5: Unadjusted High-Density Lipoprotein Cholesterol (mmol/L)



5.3.1.3 Glycosylated Haemoglobin

Mean HbA1c (Figure 5.6) increased in both groups from 55.8 mmol/mol (95% CI, 54.9-56.7) in cancer patients (red) and 56.0 mmol/mol (95% CI, 55.6-56.5) in controls (blue) in the first quarter, to 58.8 mmol/mol (95% CI, 57.2-60.4) and 58.3 mmol/mol (95% CI, 57.5-59.1) respectively in the 28th quarter. Colorectal cancer was associated with a decrease from 55.5 mmol/mol (95% CI, 54.1-56.9) in the first quarter to 52.0 mmol/mol (95% CI, 50.5-53.5) during the index quarter, and was statistically significantly lower than in controls for several quarters around the index date. Thereafter, HbA1c increased to levels that were higher than in controls for two years, before returning to levels comparable to the control group.

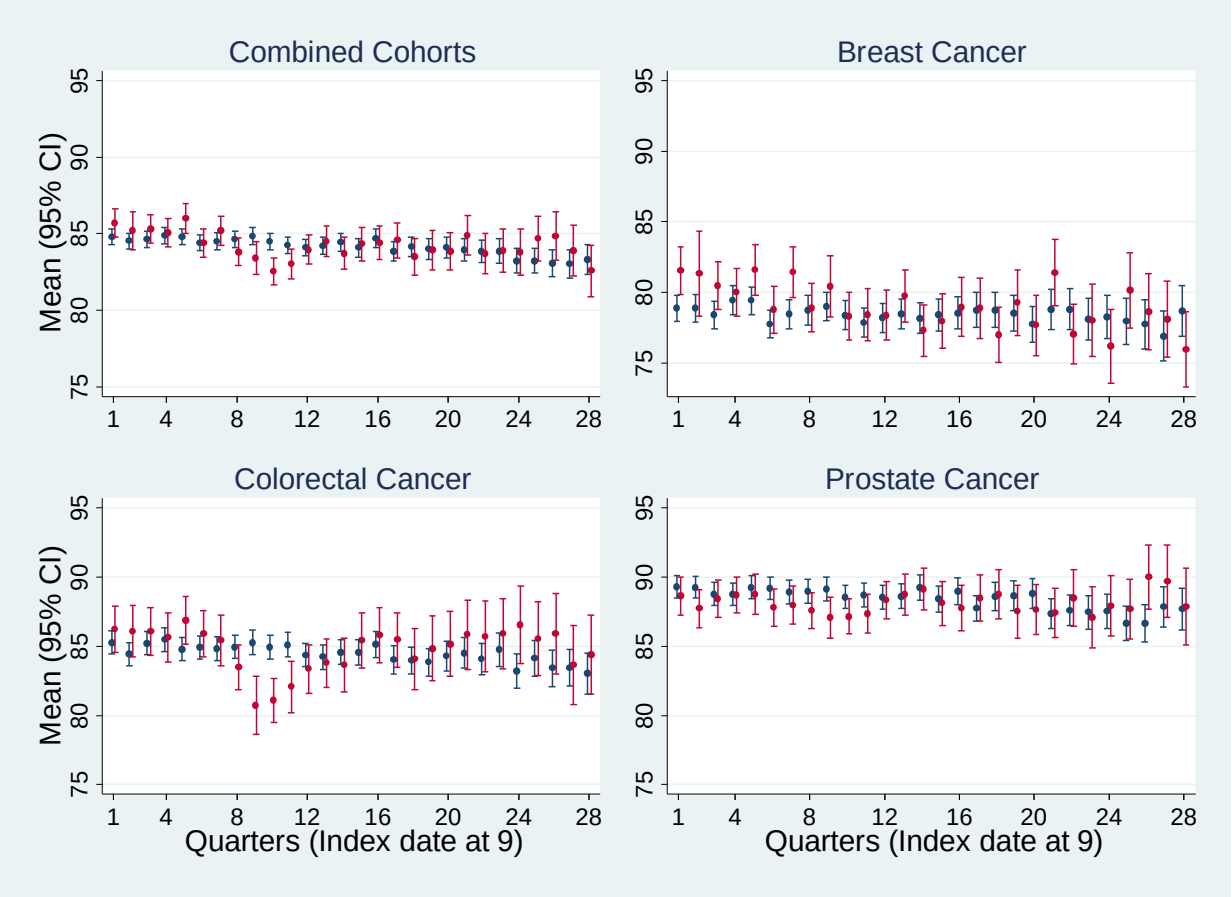
Figure 5.6: Unadjusted Glycosylated Haemoglobin (mmol/mol)



5.3.1.4 Weight

Mean patient weight (Figure 5.7) decreased slightly over time in both groups from 85.7 kg (95% CI, 84.8-86.6) in cancer patients (red) and 84.8 kg (95% CI, 84.3-85.3) in controls (blue) in the first quarter, to 82.6 kg (95% CI, 80.9-84.2) and 83.3 kg (95% CI, 82.4-84.3) respectively in the 28th quarter. Colorectal cancer was associated with a decrease from 86.2 kg (95% CI, 84.6-87.9) in the first quarter to 80.7 kg (95% CI, 78.6-82.7) in the index quarter, and was statistically significantly lower in cancer patients than controls for several quarters around the index date, before returning to levels comparable to the control group thereafter.

Figure 5.7: Unadjusted Weight (kg)



5.3.2 Primary Analyses

The results of the primary unadjusted and adjusted analyses are summarized in Tables 5.1 and 5.2 respectively. Overall, findings were similar between the unadjusted and adjusted analyses. Therefore, the text of this section reports on only the adjusted ones.

In the primary adjusted analyses (Table 5.2) of the combined cohort, cancer patients had statistically significantly ($p \leq 0.05$) lower systolic (-1.6 mm Hg; 95% CI[r]= -2.4- -0.9) and diastolic blood pressure (-0.5 mm Hg; 95% CI, -0.9- -0.1), HbA1c (-1.5 mmol/mol; 95% CI, -2.5- -0.5), and body weight (-1.6 kg; 95% CI, -2.1- -1.1), but significantly higher

[r] *Ibid.*

cholesterol (0.1 mmol/L; 95% CI, 0.0-0.1), than controls during the first quarter after their index date. However, blood pressure (systolic=0.2 mm Hg/quarter; 95% CI, 0.1-0.4: diastolic=0.1 mm Hg/quarter; 95% CI, 0.0-0.2), HbA1c (0.5 mmol/mol/quarter; 95% CI, 0.3-0.7), and body weight (0.4 kg/quarter; 95% CI, 0.3-0.4) all then increased relative to controls after the first quarter. In the combined cohort, there was no difference in the rate of cholesterol change over time between cancer patients and non-cancer controls.

Findings differed considerably by type of cancer. In breast cancer, there were no differences between cancer patients and controls in the first quarter after the index date, and total cholesterol decreased relative to controls thereafter. Colorectal cancer patients had significantly lower systolic (-3.8 mm Hg; 95% CI, -5.1- -2.5) and diastolic blood pressure (-1.4 mm Hg; 95% CI, -2.1- -0.7), HbA1c (-3.6 mmol/mol; 95% CI, -5.4- -1.8), and body weight (-4.2 kg; 95% CI, -5.1- -3.4) than controls during the first quarter following their index date. However, blood pressure (systolic=0.8 mm Hg/quarter; 95% CI, 0.5-1.0: diastolic=0.3 mm Hg/quarter; 95% CI, 0.2-0.5), HbA1c (1.2 mmol/mol/quarter; 95% CI, 0.8-1.6), and body weight (0.9 Kg/quarter; 95% CI, 0.8-1.0) all then increased relative to controls after the first quarter, and by one year after the index date these values were comparable to those in the non-cancer group. Prostate cancer patients had significantly higher total cholesterol (0.2 mmol/L; 95% CI, 0.1-0.3) during the first quarter after diagnosis, with no significant changes thereafter.

Table 5.1: Primary Unadjusted Analyses of Clinical and Laboratory Values [continued on the following page]

	Clinical or Laboratory Value						
	Systolic BP (mm Hg)	**Diastolic BP (mm Hg)**	**Total Cholesterol (mmol/L)**	**LDL Cholesterol (mmol/L)**	**HDL Cholesterol (mmol/L)**	**Hemoglobin A1C (mmol/mol)**	**Weight (kg)**
	Coefficient (95% CI)	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**
Combined Cohorts							
Cancer	-1.554***	-0.529*	0.055*	0.022	0.02	-1.474**	-1.976***
	(-2.322,-0.785)	(-0.962,-0.095)	(0.006-0.104)	(-0.029-0.073)	(-0.001-0.042)	(-2.443,-0.506)	(-2.691,-1.262)
Time*Cancer	0.201**	0.165***	0	-0.004	-0.002	0.451***	0.386***
	(0.051-0.351)	(0.079-0.252)	(-0.008-0.009)	(-0.013-0.006)	(-0.005-0.001)	(0.268-0.634)	(0.337-0.435)
Time^2*Cancer	-0.007	-0.008***	0	0	0	-0.020***	-0.014***
	(-0.015-0.000)	(-0.012,-0.004)	(-0.001-0.000)	(-0.000-0.001)	(-0.000-0.000)	(-0.029,-0.011)	(-0.016,-0.011)
Breast Cancer							
Cancer	-0.402	-0.332	0.062	0.053	-0.001	0.43	0.525
	(-1.863-1.058)	(-1.142-0.477)	(-0.032-0.155)	(-0.047-0.153)	(-0.045-0.042)	(-1.459-2.319)	(-0.794-1.845)
Time*Cancer	-0.067	0.105	-0.019*	-0.023*	-0.007	0.031	0.045
	(-0.348-0.215)	(-0.054-0.264)	(-0.035,-0.002)	(-0.041,-0.004)	(-0.014-0.001)	(-0.309-0.371)	(-0.048-0.137)
Time^2*Cancer	0.005	-0.004	0.001	0.001	0	-0.003	-0.001
	(-0.009-0.019)	(-0.012-0.004)	(-0.000-0.001)	(-0.000-0.002)	(-0.000-0.001)	(-0.020-0.013)	(-0.005-0.003)

	Clinical or Laboratory Value						
	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Total Cholesterol (mmol/L)	LDL Cholesterol (mmol/L)	HDL Cholesterol (mmol/L)	Hemoglobin A1C (mmol/mol)	Weight (kg)
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Colorectal Cancer							
Cancer	-3.707***	-1.662***	-0.115**	-0.124**	0.034	-3.871***	-4.879***
	(-5.063,-2.351)	(-2.424,-0.900)	(-0.200,-0.031)	(-0.214,-0.034)	(-0.002-0.070)	(-5.531,-2.212)	(-6.110,-3.648)
Time*Cancer	0.711***	0.349***	0.032***	0.016	-0.003	1.102***	0.894***
	(0.447-0.976)	(0.196-0.502)	(0.017-0.047)	(-0.001-0.032)	(-0.008-0.002)	(0.760-1.444)	(0.807-0.980)
Time^2*Cancer	-0.029***	-0.016***	-0.001***	-0.001	0	-0.047***	-0.034***
	(-0.042,-0.016)	(-0.023,-0.008)	(-0.002,-0.001)	(-0.001-0.000)	(-0.000-0.000)	(-0.064,-0.030)	(-0.038,-0.029)
Prostate Cancer							
Cancer	-1.016	-0.155	0.180***	0.108**	0.033*	-0.085	-1.565**
	(-2.209-0.177)	(-0.840-0.530)	(0.105-0.256)	(0.032-0.184)	(0.002-0.064)	(-1.495-1.325)	(-2.645,-0.485)
Time*Cancer	0.064	0.097	-0.006	-0.002	0.001	0.107	0.257***
	(-0.174-0.302)	(-0.040-0.234)	(-0.019-0.007)	(-0.016-0.012)	(-0.004-0.006)	(-0.162-0.376)	(0.179-0.336)
Time^2*Cancer	-0.002	-0.005	0	0	0	-0.006	-0.008***
	(-0.014-0.010)	(-0.012-0.001)	(-0.000-0.001)	(-0.001-0.001)	(-0.000-0.000)	(-0.019-0.008)	(-0.012,-0.005)

Notes for Table 5.1

The unadjusted longitudinal models for the primary analyses included as predictors linear and quadratic variables for time (in calendar quarters, and specified as continuous variables; not shown in the table as they do not pertain directly to the effect of cancer), a binary variable for cancer, and linear and quadratic interaction terms for time*cancer. "**Cancer",** the binary variable, is the estimated difference in the value between cancer patients and non-cancer controls during the first quarter after the index date; "**Time*Cancer"** is an interaction term for time*cancer, which indicates whether values rise faster (statistically significant positive coefficient) or slower (statistically significant negative coefficient) in cancer patients than non-cancer controls; and **Time^2*Cancer** is a quadratic interaction for time*cancer.

Random effects were included for patient and time, which equates to a random slopes and intercepts model.

* p <0.05, ** p <0.01, *** p <0.001

Table 5.2: Primary Adjusted Analyses of Clinical and Laboratory Values [continued on the following page]

	Clinical or Laboratory Value						
	Systolic BP (mm Hg)	**Diastolic BP (mm Hg)**	**Total Cholesterol (mmol/L)**	**LDL Cholesterol (mmol/L)**	**HDL Cholesterol (mmol/L)**	**Hemoglobin A1C (mmol/mol)**	**Weight (kg)**
	Coefficient (95% CI)	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**	**Coefficient (95% CI)**
Combined Cohorts							
Cancer	-1.645***	-0.484*	0.058*	0.031	0.017	-1.476**	-1.596***
	(-2.380,-0.910)	(-0.901,-0.067)	(0.014-0.103)	(-0.017-0.079)	(-0.004-0.038)	(-2.454,-0.497)	(-2.080,-1.111)
Time*Cancer	0.237**	0.135**	0	-0.005	-0.002	0.538***	0.379***
	(0.087-0.388)	(0.049-0.221)	(-0.009-0.008)	(-0.015-0.004)	(-0.006-0.001)	(0.339-0.737)	(0.330-0.428)
Time^2*Cancer	-0.009*	-0.007**	0	0	0	-0.025***	-0.013***
	(-0.017,-0.002)	(-0.011,-0.002)	(-0.000-0.000)	(-0.000-0.001)	(-0.000-0.000)	(-0.035,-0.015)	(-0.016,-0.011)
Breast Cancer							
Cancer	-0.936	-0.283	0.023	0.017	0.001	0.498	-0.064
	(-2.331-0.458)	(-1.060-0.494)	(-0.062-0.108)	(-0.077-0.111)	(-0.042-0.043)	(-1.122-2.117)	(-0.987-0.858)
Time*Cancer	0.054	0.047	-0.017*	-0.022*	-0.007	0.089	0.035
	(-0.228-0.335)	(-0.111-0.205)	(-0.034,-0.001)	(-0.040,-0.003)	(-0.015-0.001)	(-0.248-0.426)	(-0.057-0.127)
Time2*Cancer	-0.001	-0.002	0	0.001	0	-0.006	-0.001
	(-0.015-0.013)	(-0.010-0.006)	(-0.000-0.001)	(-0.000-0.002)	(-0.000-0.001)	(-0.023-0.010)	(-0.005-0.004)

	Clinical or Laboratory Value						
	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Total Cholesterol (mmol/L)	LDL Cholesterol (mmol/L)	HDL Cholesterol (mmol/L)	Hemoglobin A1C (mmol/mol)	Weight (kg)
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Colorectal Cancer							
Cancer	-3.827***	-1.397***	-0.069	-0.08	0.031	-3.633***	-4.234***
	(-5.128,-2.526)	(-2.131,-0.663)	(-0.146,0.008)	(-0.163,0.004)	(-0.004,0.066)	(-5.429,-1.837)	(-5.056,-3.412)
Time*Cancer	0.760***	0.326***	0.031***	0.016	-0.004	1.202***	0.907***
	(0.496,1.024)	(0.173,0.479)	(0.015,0.046)	(-0.000,0.032)	(-0.009,0.001)	(0.817,1.587)	(0.823,0.992)
Time^2*Cancer	-0.030***	-0.016***	-0.001***	-0.001	0	-0.054***	-0.035***
	(-0.043,-0.016)	(-0.023,-0.008)	(-0.002,-0.001)	(-0.001,0.000)	(-0.000,0.000)	(-0.073,-0.035)	(-0.039,-0.030)
Prostate Cancer							
Cancer	-0.79	0.054	0.192***	0.111**	0.025	0.057	-0.778*
	(-1.936,0.356)	(-0.606,0.715)	(0.122,0.263)	(0.039,0.183)	(-0.005,0.056)	(-1.287,1.400)	(-1.554,-0.002)
Time*Cancer	0.061	0.061	-0.008	-0.003	0.001	0.125	0.269***
	(-0.176,0.298)	(-0.076,0.198)	(-0.022,0.005)	(-0.016,0.011)	(-0.004,0.006)	(-0.162,0.411)	(0.192,0.347)
Time^2*Cancer	-0.003	-0.004	0	0	0	-0.005	-0.009***
	(-0.015,0.009)	(-0.011,0.003)	(-0.000,0.001)	(-0.001,0.001)	(-0.000,0.000)	(-0.019,0.009)	(-0.013,-0.005)

Notes for Table 5.2

The adjusted longitudinal models for the primary analyses included as predictors linear and quadratic variables for time (in calendar quarters, and specified as continuous variables; not shown in the table as they do not pertain directly to the effect of cancer), a binary variable for cancer, and linear and quadratic interaction terms for time*cancer. "**Cancer",** the binary variable, is the estimated difference in the value between cancer patients and non-cancer controls during the first quarter after the index date; "**Time*Cancer"** is an interaction term for time*cancer, which indicates whether values rise faster (statistically significant positive coefficient) or slower (statistically significant negative coefficient) in cancer patients than non-cancer controls; and **Time^2*Cancer** is a quadratic interaction for time*cancer.

The adjusted models also included patient demographic and clinical characteristics, consisting of age, sex (combined and colorectal cancer cohorts), year of cancer diagnosis, smoking status, body mass index, Index of Multiple Deprivation, Charlson Comorbidity Index, history of microvascular and macrovascular complications of diabetes, blood pressure, total cholesterol, and glycosylated haemoglobin (based on the most recent test result within one year before the index date), and history of diabetes medications.

Random effects were included for patient and time, which equates to a random slopes and intercepts model.

* p <0.05, ** p <0.01, *** p <0.001

5.3.3 Secondary Analyses – Extended Follow-Up

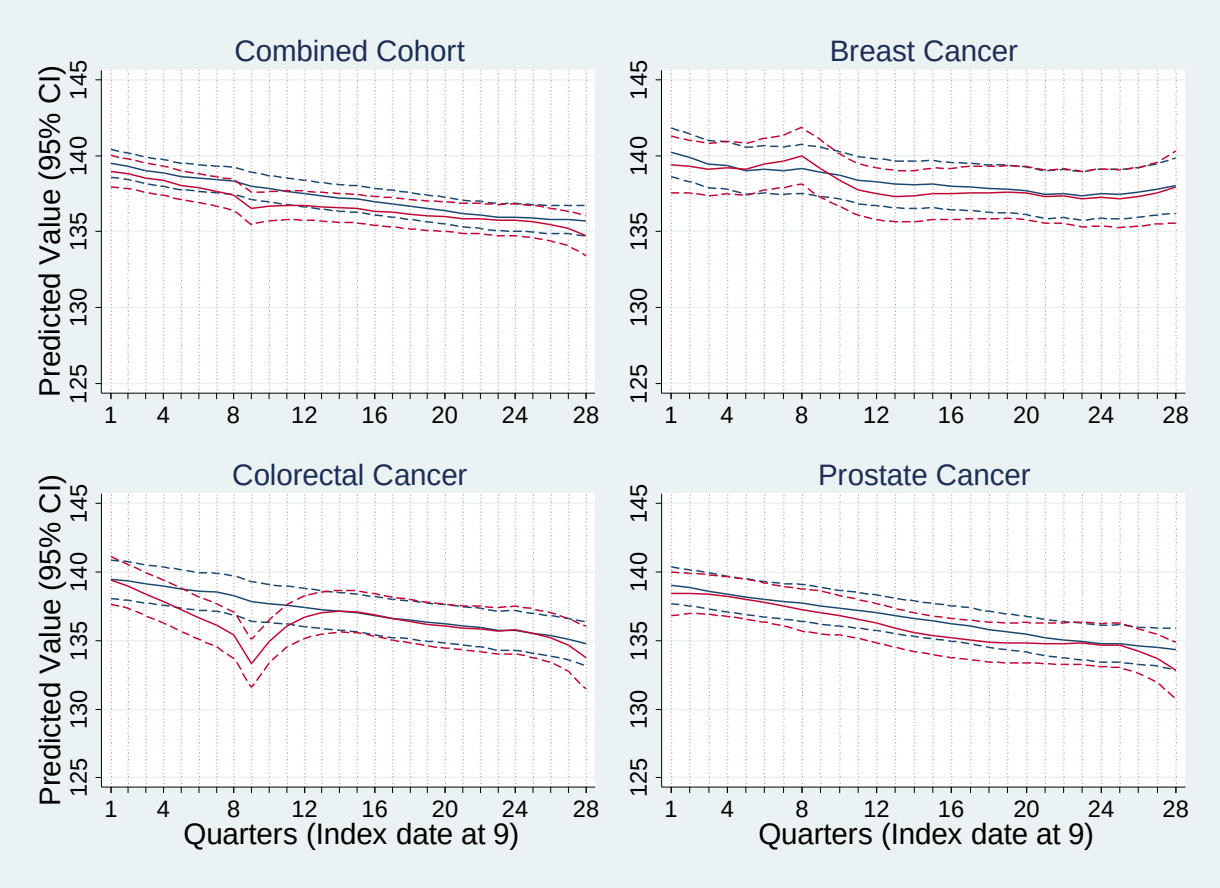
As described above, the multivariate statistical models constructed to estimate the longitudinal trajectories of values over *seven years* included multiple interaction terms for cancer and time. Therefore, the optimal way to present these findings is to plot the marginal predicted trajectories (means [solid line] and 95% CIs[s] [dashed lines]) for cancer patients (red) and controls (blue) based on the combined effects of these terms, and adjusting for baseline patient characteristics, quarterly from two years before (quarters 1-8), up to five years after (quarters 9-28), the index date (quarter of index date=9). (Figures 5.8-5.14) The text in this section describes the plots of the combined cohort, with additional information on the individual cancer cohorts also provided if those plots differed substantially from the combined cohort.

5.3.3.1 Blood Pressure

Predicted mean systolic blood pressure (Figure 5.8) decreased in both groups from 139 mm Hg (95% CI, 138-140) in cancer patients (red) and 140 mm Hg (95% CI, 139-140) in controls (blue) in the first quarter (beginning two years before the index date), to 135 mm Hg (95% CI, 134-137) and 136 mm Hg (95% CI, 135-137) respectively in the 28th quarter (last before the end of the five-year follow-up). Colorectal cancer was associated with a decline from 139 mm Hg (95% CI, 138-141) in the first quarter to 133 mm Hg (95% CI, 132-135) in the index quarter (quarter=9), and was statistically significantly lower than in controls in the index quarter, before returning to levels comparable to the control group thereafter.

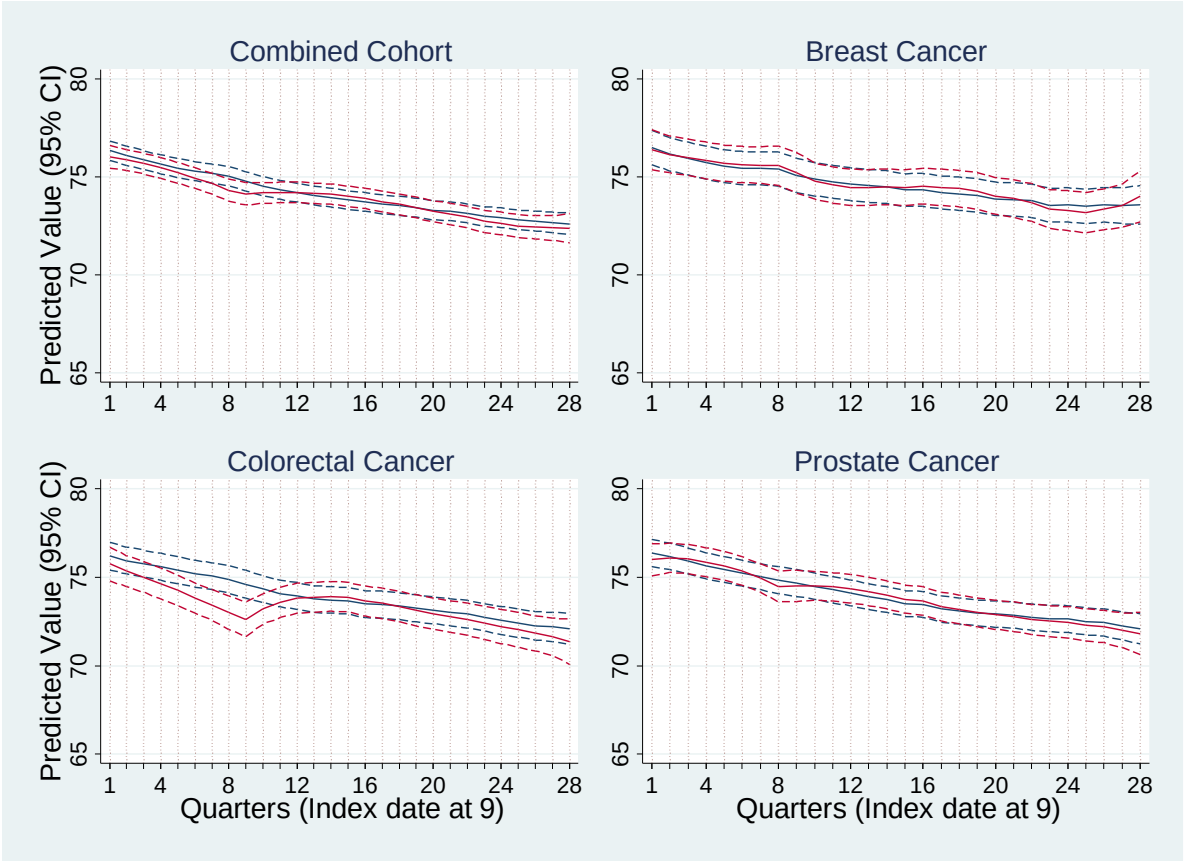
[s] *Ibid.*

Figure 5.8: Adjusted Systolic Blood Pressure (mm Hg)



Predicted mean diastolic blood pressure (Figure 5.9) followed a similar pattern, with similar differences between colorectal cancer patients and controls.

Figure 5.9: Adjusted Diastolic Blood Pressure (mm Hg)



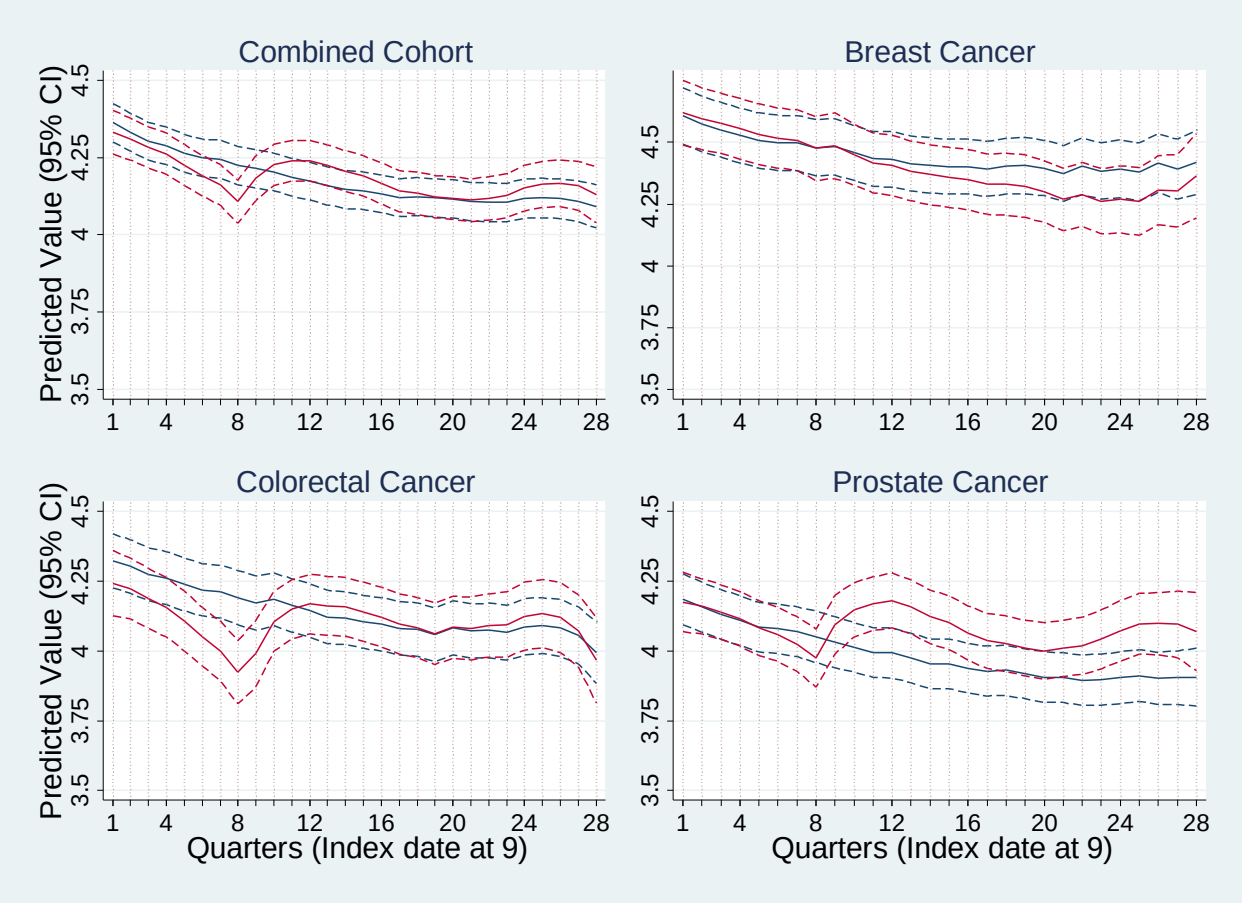
5.3.3.2 Cholesterol

Predicted mean total cholesterol (Figure 5.10) decreased in both groups from 4.3 mmol/L (95% CI[t] 4.3-4.4) in cancer patients (red) and 4.4 mmol/L (95% CI, 4.3-4.4) in controls (blue) in the first quarter, to 4.1 mmol/L (95% CI, 4.0-4.2) in both groups in the 28th quarter. Colorectal cancer was associated with a decrease from 4.2 mmol/L (95% CI, 4.1-4.4) in the first quarter to 3.9 mmol/L (95% CI, 3.8-4.0) in the quarter before the index date, and was statistically significantly lower than in controls during the two quarters (7,8) immediately preceding the index quarter (=9), before returning to levels comparable to the control group thereafter. Prostate cancer was associated with an

[t] Confidence intervals may not be symmetrical due to rounding.

increase (and reversal in the direction of the longitudinal trajectory) in total cholesterol for several quarters after cancer diagnosis, before returning to levels more comparable to the control group thereafter. However, at no time during the observation period was total cholesterol significantly higher in prostate cancer patients than controls.

Figure 5.10: Adjusted Total Cholesterol (mmol/L)



Patterns of predicted mean low-density lipoprotein (Figure 5.11) and high-density lipoprotein (Figure 5.12) cholesterol were similar to total cholesterol.

Figure 5.11: Adjusted Low Density Lipoprotein Cholesterol (mmol/L)

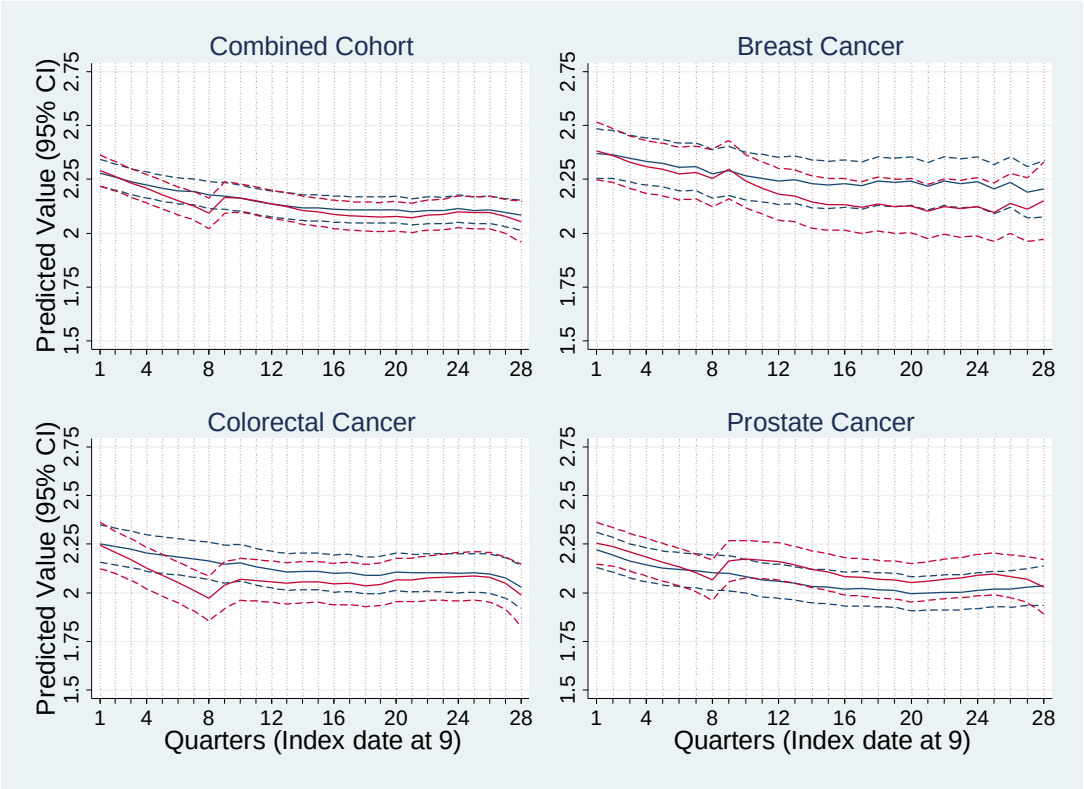
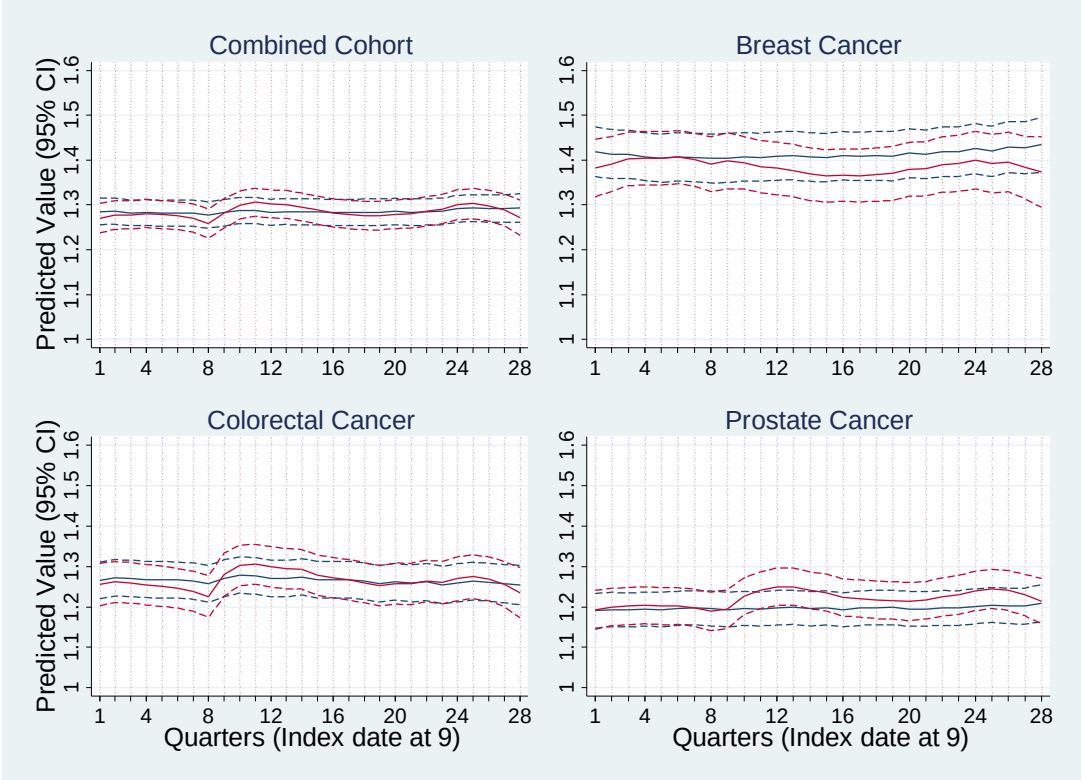


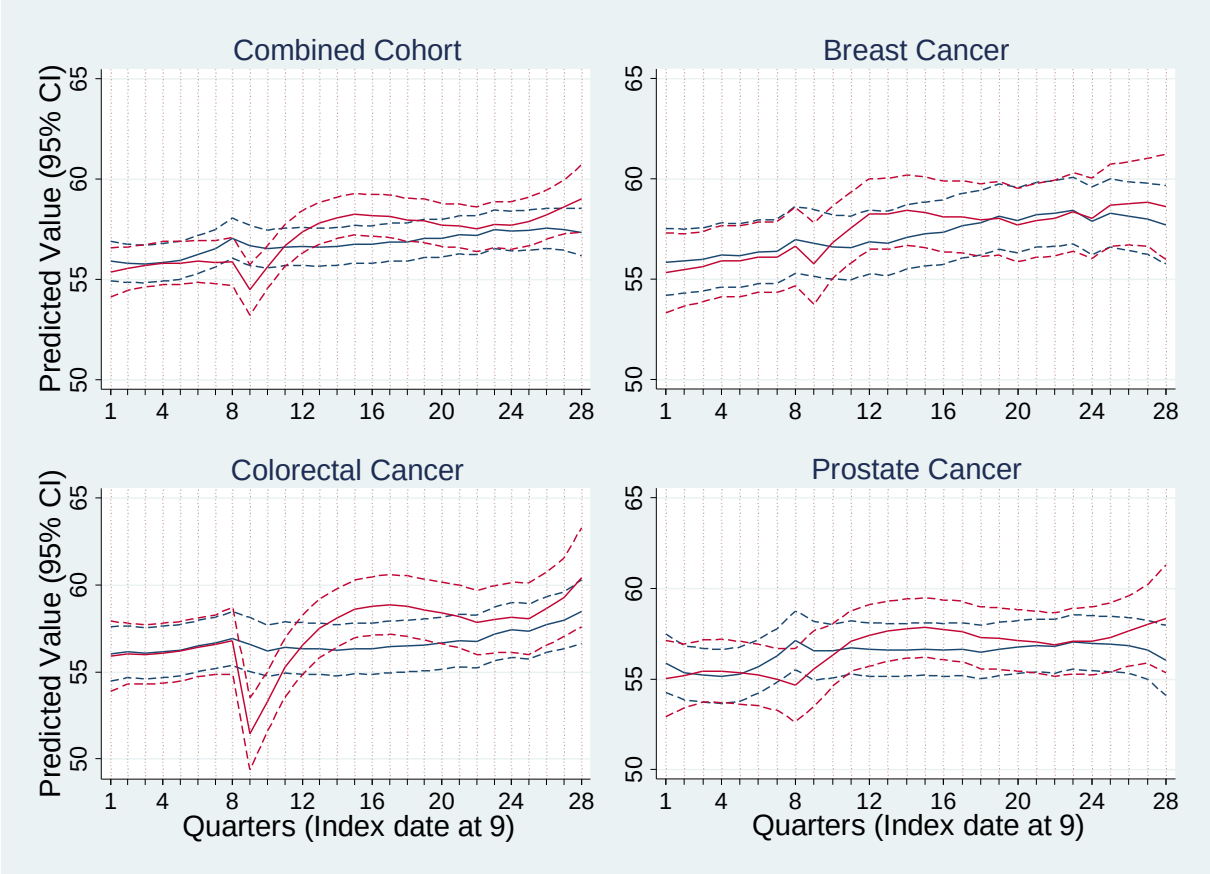
Figure 5.12: High Density Lipoprotein Cholesterol (mmol/L)



5.3.3.3 Glycosylated Haemoglobin

Predicted mean HbA1c (Figure 5.13) increased in both groups from 55.4 mmol/mol (95% CI, 54.1-56.6) in cancer patients (red) and 55.9 mmol/mol (95% CI, 54.9-56.9) in controls (blue) in the first quarter, to 59.0 mmol/mol (95% CI, 57.3-60.7) and 57.3 mmol/mol (95% CI, 56.2-58.5) respectively in the 28th quarter. Colorectal cancer was associated with a decrease from 55.9 mmol/mol (95% CI, 53.9-57.9) in the first quarter to 51.4 mmol/mol (95% CI, 49.4-53.5) during the index quarter, and was statistically significantly lower than in controls during the quarter of the index date. Thereafter, HbA1c increased to levels that were higher than in controls for two years, before returning to levels comparable to the control group.

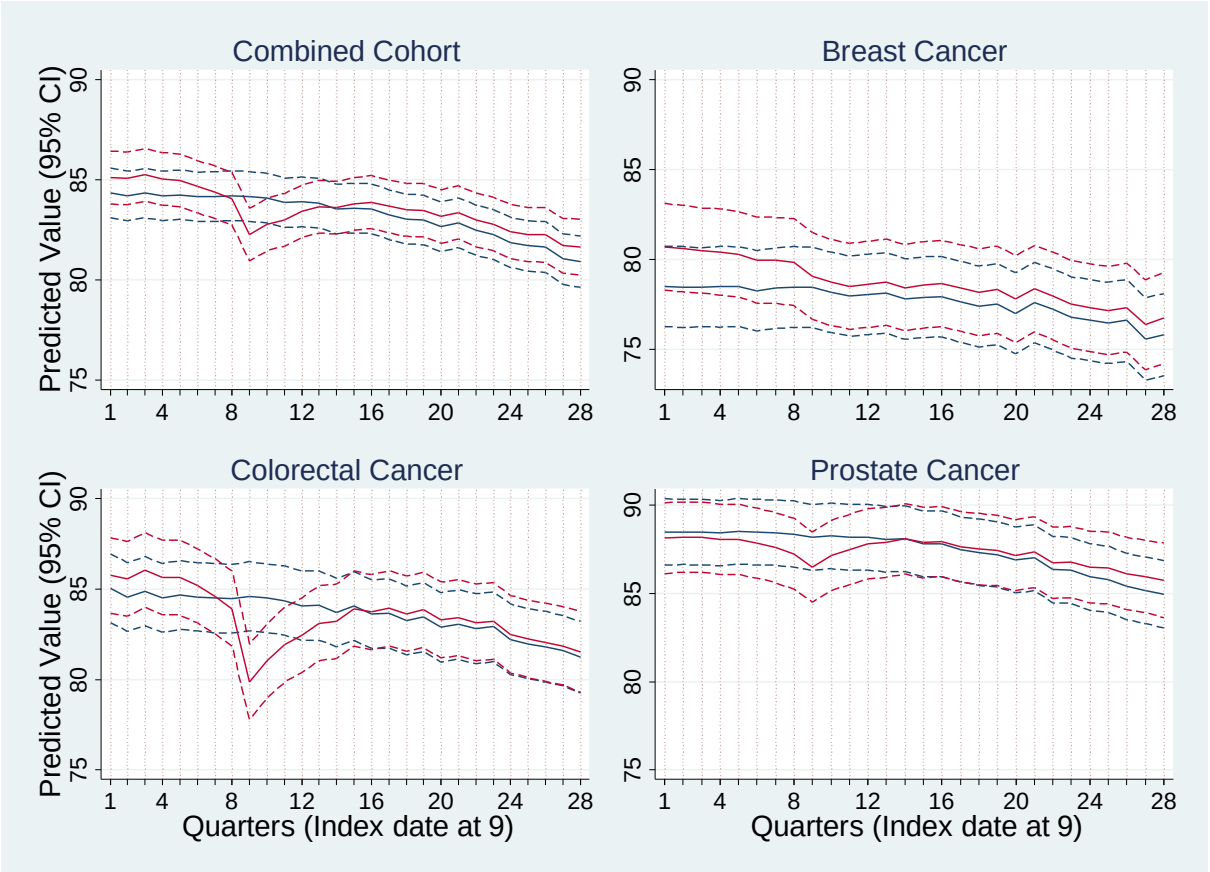
Figure 5.13: Adjusted Glycosylated Haemoglobin (mmol/mol)



5.3.3.4 Weight

Predicted mean patient weight (Figure 5.14) decreased over time in both groups from 85.1 kg (95% CI, 83.8-86.4) in cancer patients (red) and 84.3 kg (95% CI, 83.1-85.6) in controls (blue) in the first quarter, to 81.6 kg (95% CI, 80.2-83.0) and 80.9 kg (95% CI, 79.6-82.2) respectively in the 28th quarter. Colorectal cancer was associated with a decrease from 85.7 kg (95% CI, 83.7-87.8) in the first quarter to 79.9 kg (95% CI, 77.8-82.0) in the index quarter, and was statistically significantly lower in cancer patients than controls during the index quarter, before returning to levels comparable to the control group thereafter.

Figure 5.14: Adjusted Weight (kg)



5.3.4 Secondary Analyses – Propensity Matched Cohorts

Results from the secondary analyses of the propensity-matched cohorts with five (Table 5.3) and seven years of observation (See plots in Appendix to this Chapter) were comparable to the results of the primary and secondary analyses with the full cohorts.

Table 5.3: Secondary Analyses of Clinical and Laboratory Values – Propensity-Matched Cohort [continued on the following page]

	Clinical or Laboratory Value						
	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Total Cholesterol (mmol/L)	LDL Cholesterol (mmol/L)	HDL Cholesterol (mmol/L)	Hemoglobin A1C (mmol/mol)	Weight (kg)
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Combined Cohorts							
Cancer	-1.124*	-0.559*	0.066*	0.035	0.017	0.111	-1.674***
	(-2.064,-0.185)	(-1.097,-0.022)	(0.005,0.127)	(-0.027,0.097)	(-0.009,0.043)	(-0.950,1.172)	(-2.551,-0.798)
Time*Cancer	0.242*	0.170**	-0.001	-0.005	-0.002	0.268*	0.383***
	(0.056,0.429)	(0.064,0.277)	(-0.012,0.009)	(-0.016,0.006)	(-0.006,0.002)	(0.057,0.479)	(0.321,0.445)
Time^2*Cancer	-0.011*	-0.009**	0	0	0	-0.012*	-0.014***
	(-0.020,-0.002)	(-0.014,-0.004)	(-0.001,0.000)	(-0.000,0.001)	(-0.000,0.000)	(-0.022,-0.001)	(-0.017,-0.011)
Breast Cancer							
Cancer	-0.492	-0.523	0.037	0.03	-0.009	-0.378	-0.345
	(-2.241,1.258)	(-1.519,0.473)	(-0.076,0.151)	(-0.085,0.146)	(-0.057,0.039)	(-2.496,1.739)	(-1.953,1.262)
Time*Cancer	-0.01	0.135	-0.015	-0.017	-0.006	0.142	0.058
	(-0.351,0.331)	(-0.058,0.328)	(-0.035,0.004)	(-0.038,0.004)	(-0.014,0.002)	(-0.268,0.552)	(-0.052,0.167)
Time^2*Cancer	0	-0.007	0	0.001	0	-0.008	-0.001
	(-0.016,0.017)	(-0.017,0.002)	(-0.001,0.001)	(-0.000,0.002)	(-0.000,0.001)	(-0.028,0.013)	(-0.006,0.004)

	Clinical or Laboratory Value						
	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	Total Cholesterol (mmol/L)	LDL Cholesterol (mmol/L)	HDL Cholesterol (mmol/L)	Hemoglobin A1C (mmol/mol)	Weight (kg)
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Colorectal Cancer							
Cancer	-3.462***	-1.827***	-0.046	-0.077	0.042	-3.462**	-4.491***
	(-5.219,-1.705)	(-2.815,-0.839)	(-0.150,0.057)	(-0.186,0.032)	(-0.003,0.087)	(-5.886,-1.039)	(-6.083,-2.899)
Time*Cancer	0.583***	0.429***	0.022*	0.015	-0.002	1.316***	0.899***
	(0.246,0.920)	(0.233,0.626)	(0.004,0.041)	(-0.005,0.035)	(-0.009,0.004)	(0.788,1.844)	(0.786,1.013)
Time^2*Cancer	-0.021*	-0.019***	-0.001*	-0.001	0	-0.057***	-0.034***
	(-0.038,-0.004)	(-0.029,-0.009)	(-0.002,-0.000)	(-0.002,0.000)	(-0.000,0.000)	(-0.083,-0.031)	(-0.040,-0.029)
Prostate Cancer							
Cancer	-1.024	-0.065	0.175***	0.086	0.053**	-0.084	-1.373*
	(-2.500,0.452)	(-0.926,0.795)	(0.081,0.270)	(-0.012,0.184)	(0.013,0.093)	(-1.645,1.478)	(-2.669,-0.076)
Time*Cancer	0.125	0.105	-0.003	0.001	-0.002	0.181	0.266***
	(-0.169,0.418)	(-0.067,0.276)	(-0.020,0.013)	(-0.017,0.018)	(-0.009,0.004)	(-0.110,0.472)	(0.171,0.362)
Time^2*Cancer	-0.004	-0.005	0	0	0	-0.009	-0.008***
	(-0.019,0.011)	(-0.014,0.004)	(-0.001,0.001)	(-0.001,0.001)	(-0.000,0.000)	(-0.024,0.005)	(-0.013,-0.004)

Notes to Table 5.3

The secondary analyses using the propensity-matched cohorts included as predictors linear and quadratic variables for time (in calendar quarters, and specified as continuous variables; not shown in the table as they do not pertain directly to the effect of cancer), a binary variable for cancer, and linear and quadratic interaction terms for time*cancer. "**Cancer",** the binary variable, is the estimated difference in the value between cancer patients and non-cancer controls during the first quarter after the index date; "**Time*Cancer"** is an interaction term for time*cancer, which indicates whether values rise faster (statistically significant positive coefficient) or slower (statistically significant negative coefficient) in cancer patients than non-cancer controls; and **Time^2*Cancer** is a quadratic interaction for time*cancer.

Random effects were included for patient and time, which equates to a random slopes and intercepts model.

* p <0.05, ** p <0.01, *** p <0.001

5.4 DISCUSSION AND CONCLUSIONS

5.4.1 Summary of Findings

This chapter has presented the methods and findings of the primary research in which changes in actual blood pressure, cholesterol, and HbA1c levels over time were compared between cancer patients and controls. Patient weight was added to these after exploratory analyses showed that in several instances patterns of change in the other levels were similar to those for weight.

Overall, the findings show that in most instances cancer was associated with, at most, very modest changes in levels of actual blood pressure, cholesterol, and HbA1c over time. The largest changes occurred in colorectal cancer, where blood pressure and HbA1c levels were slightly (albeit statistically significantly) lower during the quarter of cancer diagnosis, but then rebounded to levels similar to control patients soon thereafter. Patterns of change in blood pressure and HbA1c in colorectal cancer were similar to the pattern of weight loss and then regain to previous levels observed in these patients. Therefore, it is possible that temporary weight loss was the cause of observed changes in blood pressure and HbA1c in colorectal cancer. There was no evidence that cancer had a long-term impact on blood pressure, cholesterol, or HbA1c in any of the four cohorts.

In Chapter 1 (Section 1.1) of the thesis, the overall impact of cancer on diabetes outcomes was hypothesized to depend in part on the extent to which observed changes in biological parameters due to cancer were of sufficient size and duration to increase the risk of diabetes complications. Evidence from the UKPDS[10-13] indicates that

sustained reductions in HbA1c and SBP over the long-term (mean duration of 10 years) are associated with reductions in the risks of diabetes complications and deaths. For example, in UKPDS 35,[10] each 1% (approximately 11 mmol/mol) reduction in updated mean HbA1c[u] was associated with reductions in risk of 21% for any endpoint related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications. In UKPDS 36,[11] each 10mm Hg decrease in updated mean systolic blood pressure was associated with reductions in risk of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications. The findings from the primary research presented in this chapter suggest that the observed changes in biological parameters associated with cancer were neither of sufficient size nor of sufficient duration to substantially increase the risk of diabetes complications relative to non-cancer controls.

5.4.2 Strengths and Limitations

The strengths and limitations of the overall study design and methods for the primary research in this chapter are discussed in the corresponding section of Chapter 3. Those pertaining to the comparability of the cohorts and the length of follow-up for the primary research in this chapter are discussed in the corresponding section of Chapter 4.

In this research, clinical and laboratory values were obtained from the corresponding files of the CPRD. One limitation is that values and test results that were obtained in specialty care during cancer treatment and follow-up, but not subsequently recorded in

[u] Calculated for each individual from baseline to each year of follow-up (mean duration of 10 years)

the primary care data, were not included in the analyses. Hospital Episode Statistics (HES)[9] inpatient data, which are part of the CPRD linkage, do not contain the level of detail required to obtain clinical and laboratory values analyzed in this chapter, and are available for only approximately two-thirds of the CPRD population. Therefore, it was not possible to use the HES data to supplement information from the primary care data in CPRD.

5.4.3 Conclusions and Implications

In sum, there is no evidence cancer had a long-term impact on actual blood pressure, cholesterol, or HbA1c levels in any of the four cohorts. Colorectal and prostate cancer were associated with statistically significant changes in blood pressure, cholesterol, and HbA1c around the time of cancer diagnosis. However, even these were small and short-lived. There was no evidence breast cancer impacted blood pressure, cholesterol, or HbA1c at any time during follow-up. Observed changes in biological parameters associated cancer were neither of sufficient size nor of sufficient duration to increase the risk of diabetes complications.

5.5 CHAPTER REFERENCES

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CHAPTER SIX

Diabetes Complications and Mortality

VI DIABETES COMPLICATIONS AND MORTALITY

6.1 CHAPTER AIM

The aim of this chapter is to present the methods and results of the primary research in which diabetes complications and mortality were compared between cancer patients and controls. Excerpts from this chapter have been included in the following article submitted for peer-review publication:

Griffiths RI, Valderas JM, McFadden EC, Bankhead CR, Lavery BA, Khan NF, Stevens RJ, Keating NL. Outcomes of Pre-Existing Diabetes Mellitus in Breast, Colorectal, and Prostate Cancer.

6.2 METHODS OF RESEARCH

6.2.1 Construction of the Dataset

The research in this chapter entailed comparing the incidences of diabetes complications and mortality between cancer patients and controls using time-to-event analysis. Therefore, the patient-level datasets described in Chapter 3 were used as the basis for the research in this chapter. Variables were added for each of the complications and for mortality, as described in the following two sections.

6.2.2 Diabetes Complications

Diabetes complications, consisting of microvascular and macrovascular conditions[1] *newly diagnosed within 10 years after the patient's index date* (cancer diagnosis or matched date in non-cancer controls), were identified based on the same Read codes[2] in the electronic health records of the CPRD[3] used to determine whether these conditions

were present prior to the patient's index date (as described in Section 3.2.7 of Chapter 3). Microvascular complications consisted of chronic kidney disease (stage 4 or 5), nephropathy, neuropathy, and retinopathy. Macrovascular complications consisted of acute myocardial infarction or acute coronary syndrome, cerebrovascular accident, lower limb amputation, and peripheral arterial disease. Lists of Read codes used to identify these conditions during follow-up are provided in the Appendix to Chapter 3.

Construction of the time-to-event variables for each complication proceeded after determining the dataset requirements for conducting time-to-event analyses in the presence of competing risks[4] using the stcrreg command[5] in STATA.[6] Competing risks are events that prevent the event of primary interest in the analysis from occurring.[7] In this case, death was the competing risk in the time-to-event analysis of complications. Competing risks regression is common in biomedical research, especially cancer research, where often there are multiple "competing" outcomes of interest.[7]

Two variables were required for each complication: a time variable to indicate the number of days from the patient's index date until the earliest of (A) the date of the *first* Read code indicating the presence of that complication, (B) the date of death, (C) the date of the end of the patient's eligible data (both B and C were calculated as part of determining the length of the patient's observation period, as described in section 3.2.6 of Chapter 3), or (D) the maximum follow-up for the analyses, which was 10 years; and, a categorical variable to indicate which event among A-D was the soonest. The categorical variable was coded to 0 if the patient's observation period ended due to C or D, to indicate that the patient was censored, to 1 if it ended due to A, the specific

complication of interest in the analysis, and to 2 if it ended due to death, which was considered the competing risk in the analyses of complications.

6.2.3 Mortality

Diabetes complications and all-cause mortality were compared between cancer patients and controls using time-to-event analysis. Since death due to other causes was considered a competing risk for diabetes-related mortality, construction of the time-to-event variables for analyzing diabetes-related mortality followed the same approach described for diabetes complications (see previous section). Deaths that occurred between one[v] and 10 years after the index date were identified using ONS data,[8] which are part of the CPRD data linkage. Deaths were classified as diabetes-related (or not) based on ICD-10 codes indicating the cause of death in the ONS[8] data, as follows: ICD-10 codes used to classify deaths as diabetes-related consisted of those for diabetes (ICD-10 E10-14), hyperglycaemia (R73), hypoglycaemia (E16.1, E16.2), myocardial infarction (I21-I22), ischaemic heart disease (I20, I24, I25), stroke/sequelae (I60-I64, I69.0-I69.4), heart failure (I50), sudden death due to cardiac arrest (I46), peripheral vascular disease (I70-I74), and kidney disease (N00-N28);[9] all other causes of death were classified as other-cause, and these patients were considered to have had a competing risk event in the analysis of diabetes-related mortality. There were no patients in the ONS who did not have at least one cause of death assigned.

[v] All patients in the study had to have survived at least one year after their index date. Therefore, there were no deaths during the first year, and follow-up for the mortality analysis began at the start of year two after the index date.

6.2.4 Statistical Methods

Competing risks regression analyses, according to the approach proposed by Fine and Gray,[4,5] were performed to estimate the cumulative incidence of each diabetes complication in cancer patients and controls, as well as to estimate the HRs[w] (cancer compared to control) for each complication, using up to 10 years of follow-up after the index date. All analyses included death as the competing risk. Unadjusted analyses included a binary predictor for cancer. Adjusted analyses also included the following baseline demographic and clinical covariates: age, sex (combined cohorts, colorectal cancer), year of index date, smoking status, drinking status, BMI, type of cancer (in the analyses in which the three cancer types were combined), Charlson Comorbidity Index,[10,11] IMD[12] score, baseline blood pressure, baseline total cholesterol, baseline HbA1c, and history of diabetes medications. Patients who had a diabetes complication prior to their index date were excluded from the analyses of that complication.

Competing risks regression[4,5] also was used to estimate the cumulative incidence, as well as the unadjusted and adjusted HRs for overall and diabetes-related mortality. Only patients eligible for linkage to the ONS mortality data,[4] approximately two thirds of the cohort, were included in the mortality analyses. Also, since study inclusion criteria (see section 3.2.6. in Chapter 3) required patients to have survived at least one year after their index date, survival analyses included only years 2-10 of follow-up.

[w] The interpretation of the hazard ratios from competing risks regression is identical to that in conventional survival analysis.

Primary analyses were performed in each of the four full cohorts (cancers combined, breast, colorectal, and prostate). Secondary analyses were performed in the propensity-matched cohorts. All analyses of diabetes complications—but not mortality, since there were only two comparisons for each cohort—were adjusted for multiple comparisons using the Benjamini-Hochberg[13-15] approach. All analyses were performed in STATA[6] using the stcrreg command.[5]

6.3 RESULTS

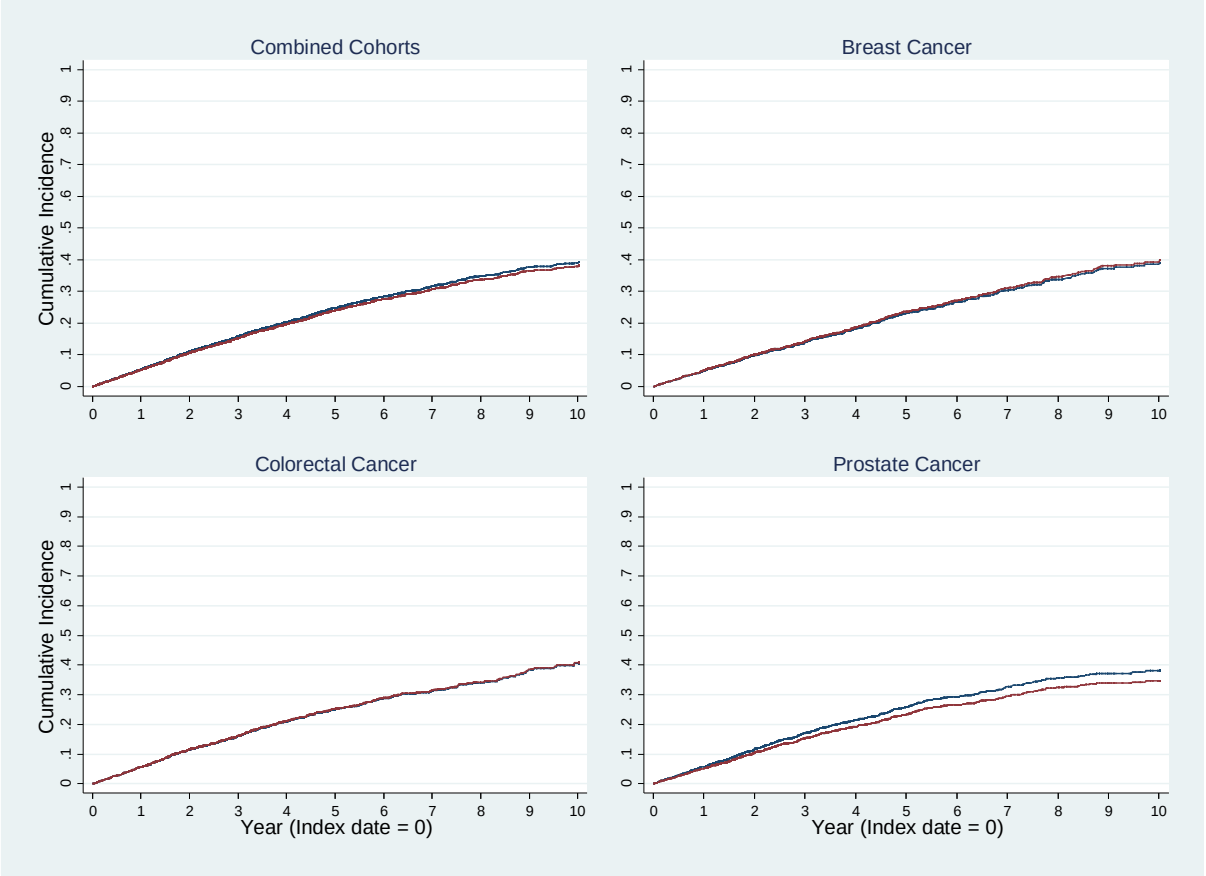
6.3.1 Plots of Diabetes Microvascular Complications

Plots of the cumulative incidences of microvascular complications in cancer patients (red) and controls (blue), which were generated from the unadjusted competing risks regression analyses, are presented in Figures 6.1-6.5. The text in this section describes the plots for the combined cohorts, with additional information on the individual cancer cohorts also provided if those plots differed substantially from the combined cohort.

6.3.1.1 Any Microvascular Complication

The unadjusted cumulative incidence of any microvascular complication (Figure 6.1) during 10 years of follow-up was 0.38 in cancer patients (red) and 0.39 in controls (blue) (HR=0.96; 95% CI, 0.87-1.06). Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

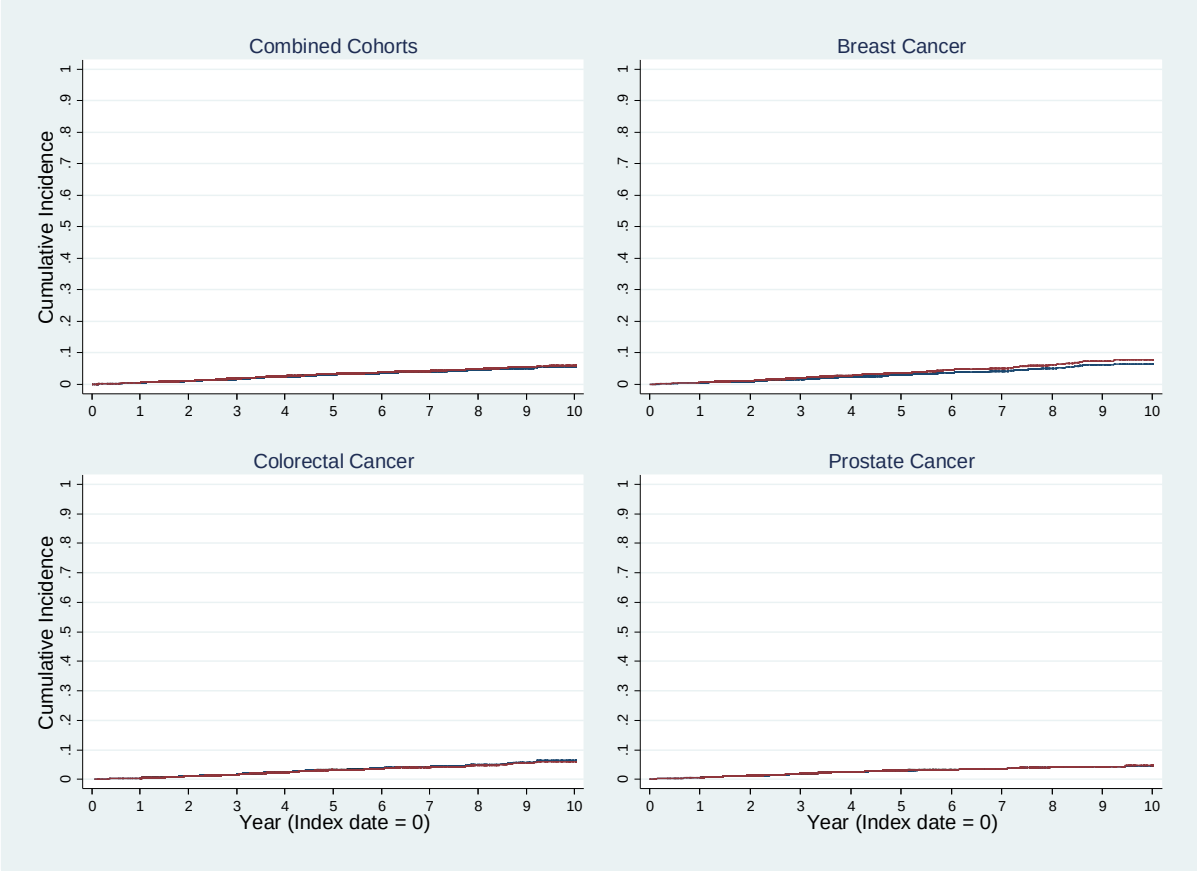
Figure 6.1: Unadjusted Cumulative Incidence of Any Microvascular Complication



6.3.1.2 Chronic Kidney Disease

The unadjusted cumulative incidence of chronic kidney disease (Figure 6.2) was less than 10%, and virtually identical in cancer patients (red) and controls (blue) (HR=1.08; 95% CI, 0.85-1.36). Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

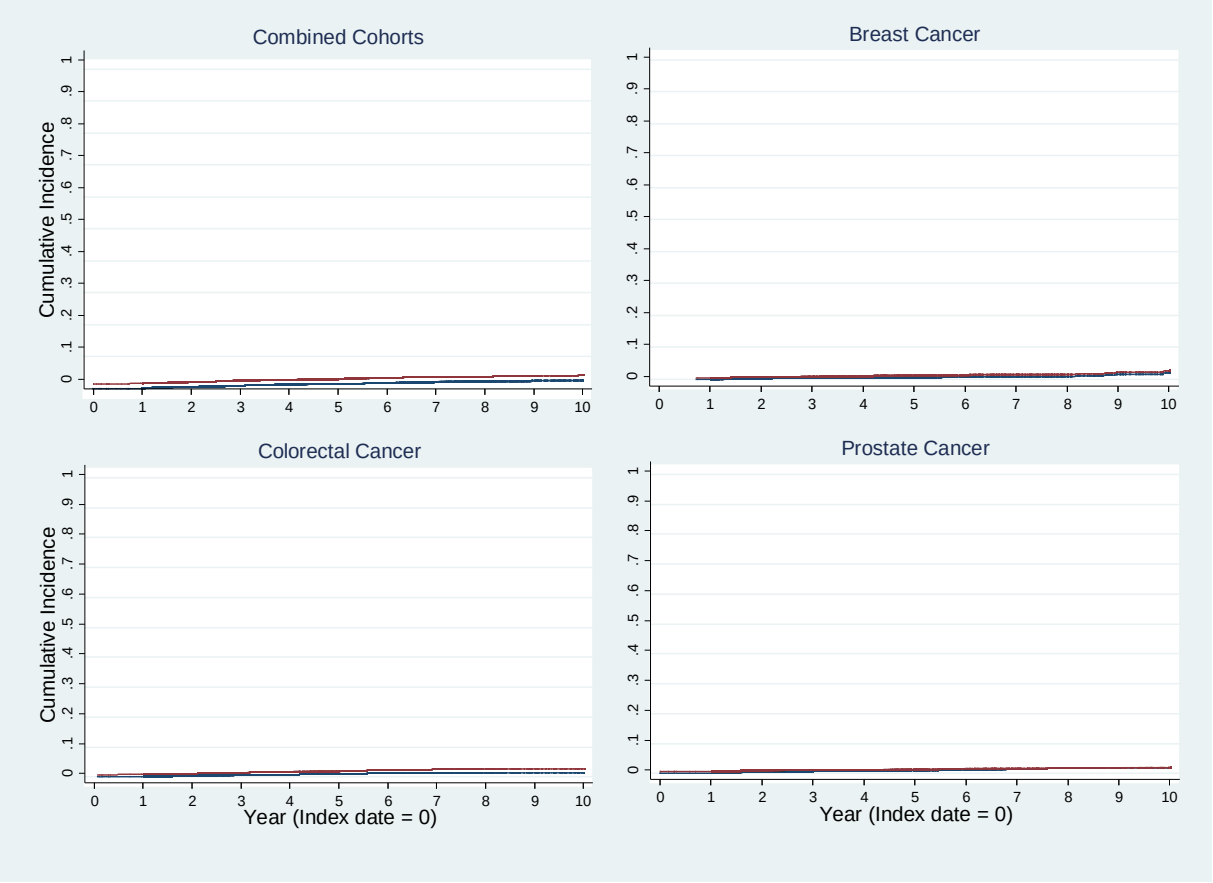
Figure 6.2: Unadjusted Cumulative Incidence of Chronic Kidney Disease



6.3.1.3 Nephropathy

The unadjusted cumulative incidence of nephropathy (Figure 6.3) was less than 5%, and virtually identical in cancer patients (red) and controls (blue) (HR=1.12; 95% CI, 0.66-1.88). Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

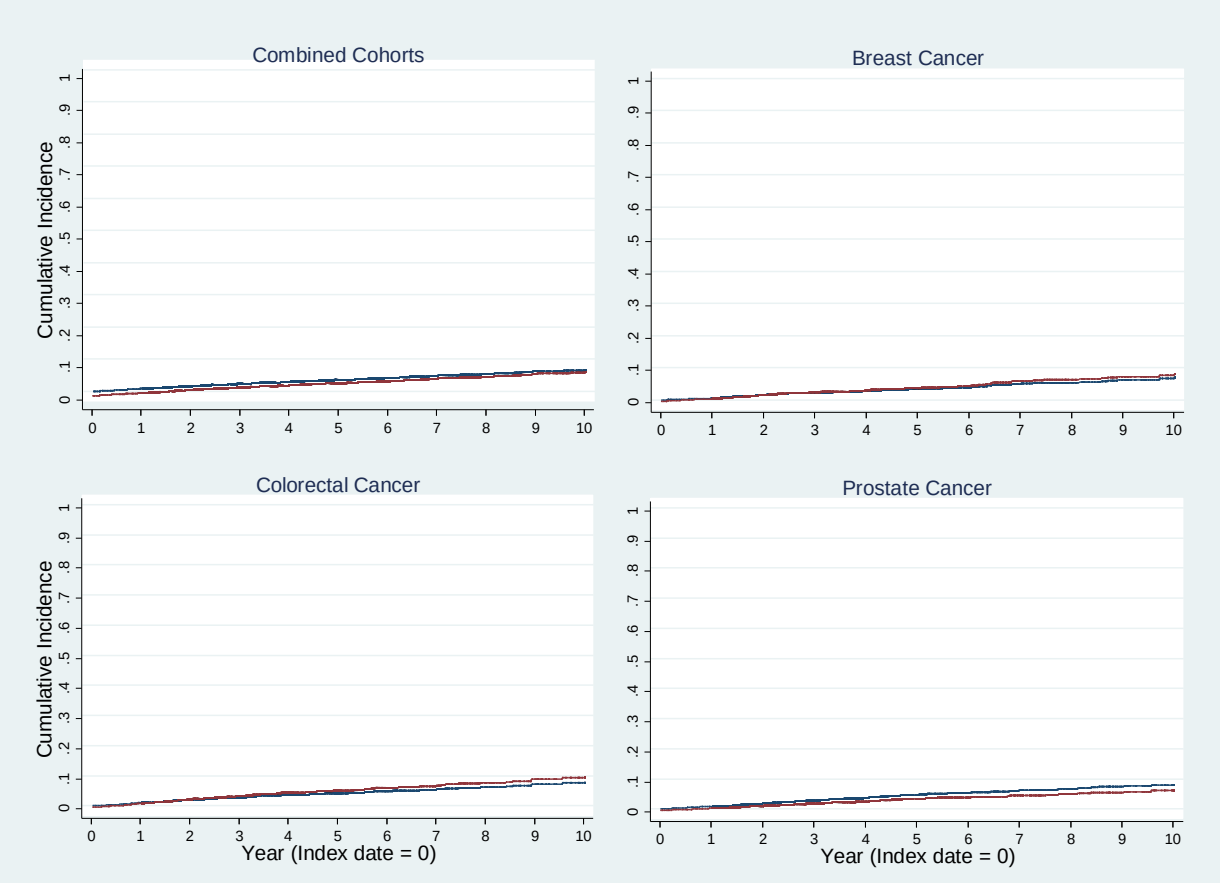
Figure 6.3: Unadjusted Cumulative Incidence of Nephropathy



6.3.1.4 Neuropathy

The unadjusted cumulative incidence of neuropathy (Figure 6.4) was approximately 10%, and virtually identical in cancer patients (red) and controls (blue) (HR=1.07; 95% CI, 0.88-1.31). Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

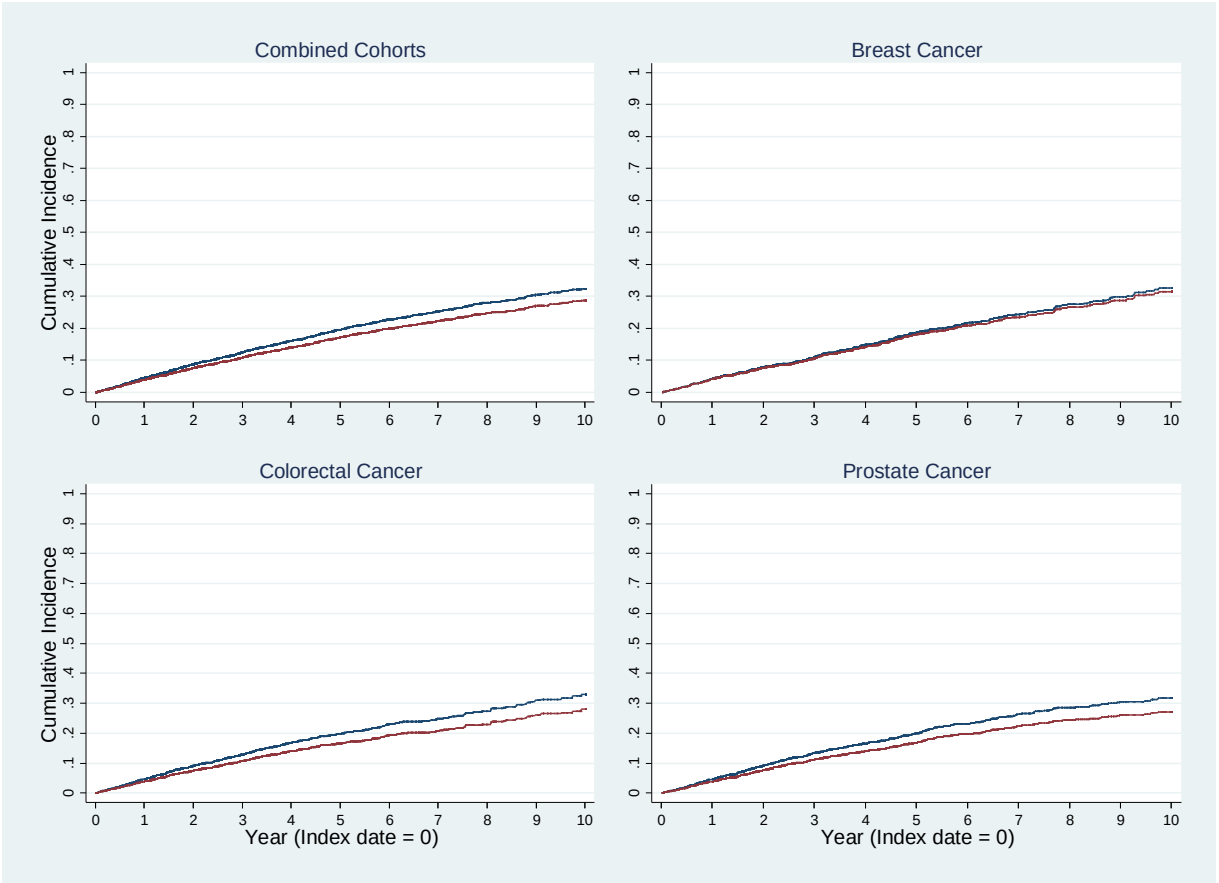
Figure 6.4: Unadjusted Cumulative Incidence of Neuropathy



6.3.1.5 Retinopathy

The unadjusted cumulative incidence of retinopathy (Figure 6.5) during 10 years of follow-up was statistically significantly lower (0.29) in cancer patients (red) than (0.32) in controls (blue) (HR=0.86; 95% CI, 0.77-0.96). However, the difference did not remain statistically significant after adjustment for multiple comparisons. Similar patterns and relative hazards (as indicated by the HRs) were observed in colorectal and prostate cancer.

Figure 6.5: Unadjusted Cumulative Incidence of Retinopathy



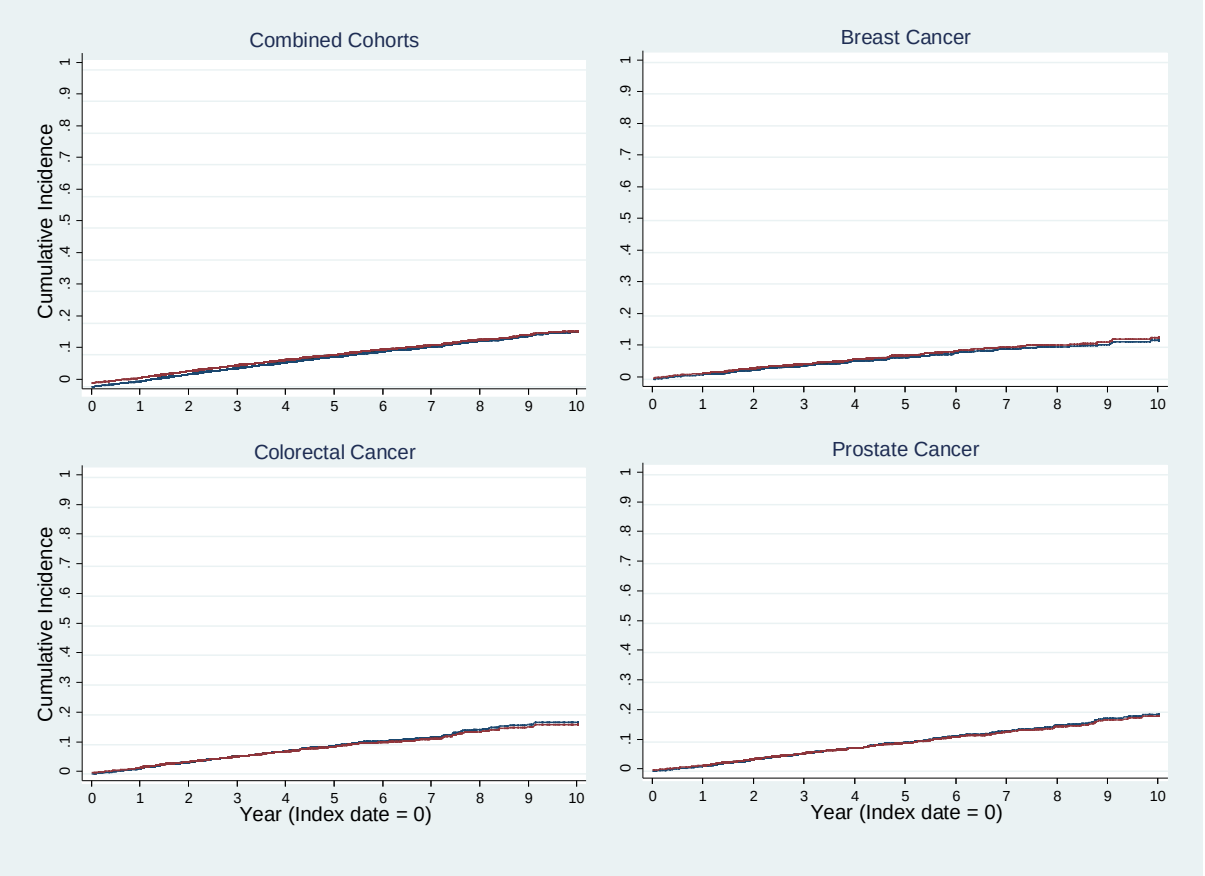
6.3.2 Plots of Diabetes Macrovascular Complications

Plots of the cumulative incidences of macrovascular complications in cancer patients (red) and controls (blue), which were generated from the unadjusted competing risks regression analyses, are presented in Figures 6.6-6.10. The text in this section describes the plots for the combined cohorts, with additional information on the individual cancer cohorts also provided if those plots differed substantially from the combined cohort.

6.3.2.1 Any Macrovascular Complication

The unadjusted cumulative incidence of any macrovascular complication (Figure 6.6) during 10 years of follow-up was 0.15 in cancer patients (red) and 0.16 in controls (blue) (HR=0.94; 95% CI, 0.80-1.11). Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

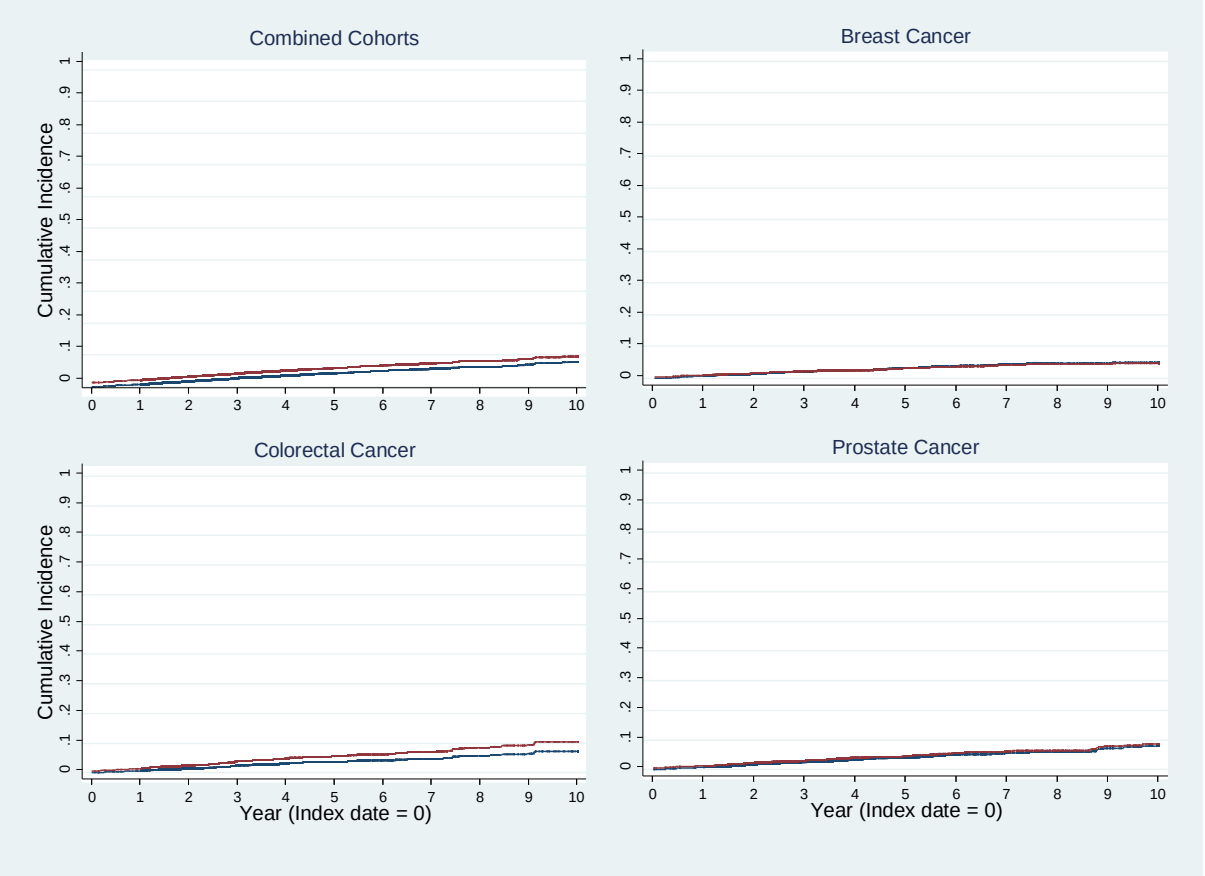
Figure 6.6: Unadjusted Cumulative Incidence of Any Macrovascular Complication



6.3.2.2 Acute Myocardial Infarction

The unadjusted cumulative incidence of acute myocardial infarction (Figure 6.7) was less than 10%, and virtually identical in cancer patients (red) and controls (blue) (HR=1.09; 95% CI, 0.87-1.37). Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

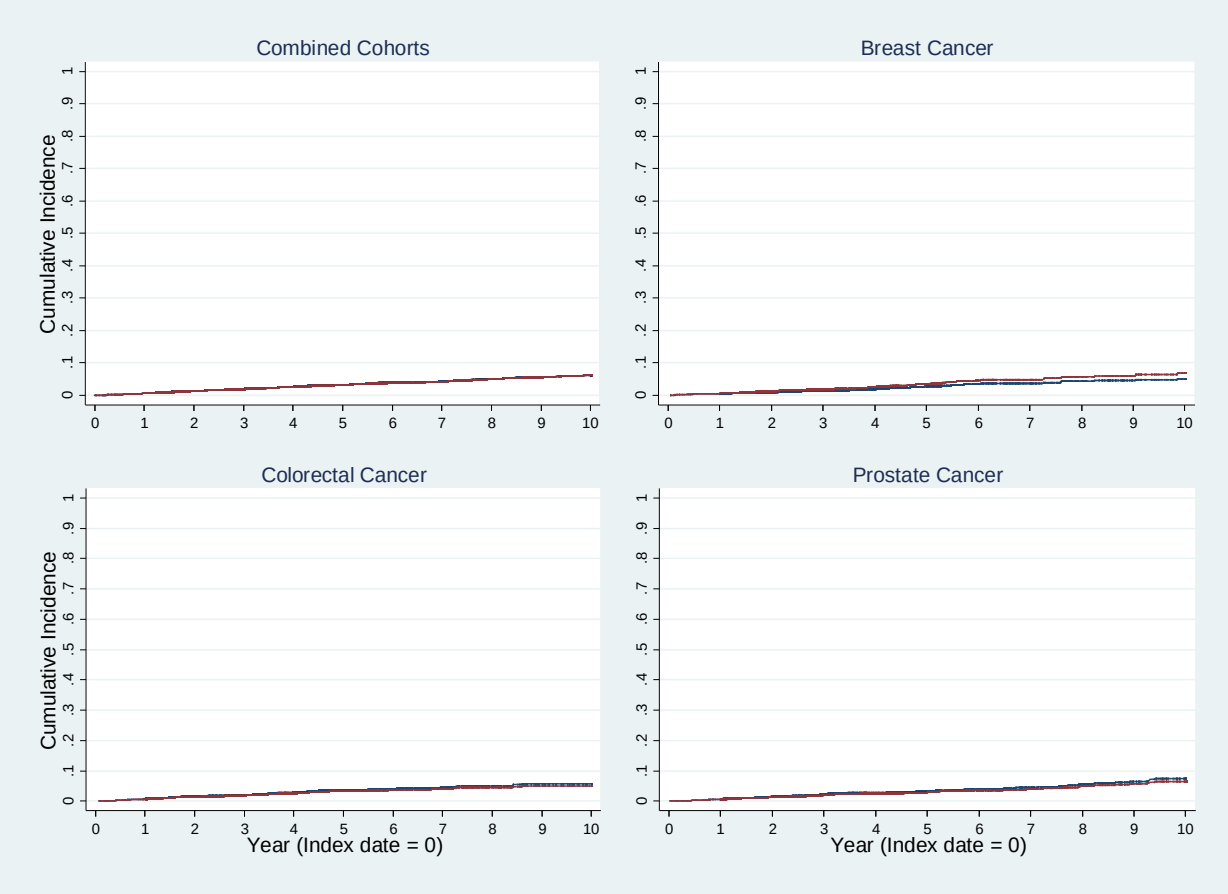
Figure 6.7: Unadjusted Cumulative Incidence of Acute Myocardial Infarction



6.3.2.3 Cerebrovascular Accident

The unadjusted cumulative incidence of cerebrovascular accident (Figure 6.8) was less than 10%, and virtually identical in cancer patients (red) and controls (blue) (HR=0.99; 95% CI, 0.78-1.25). Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

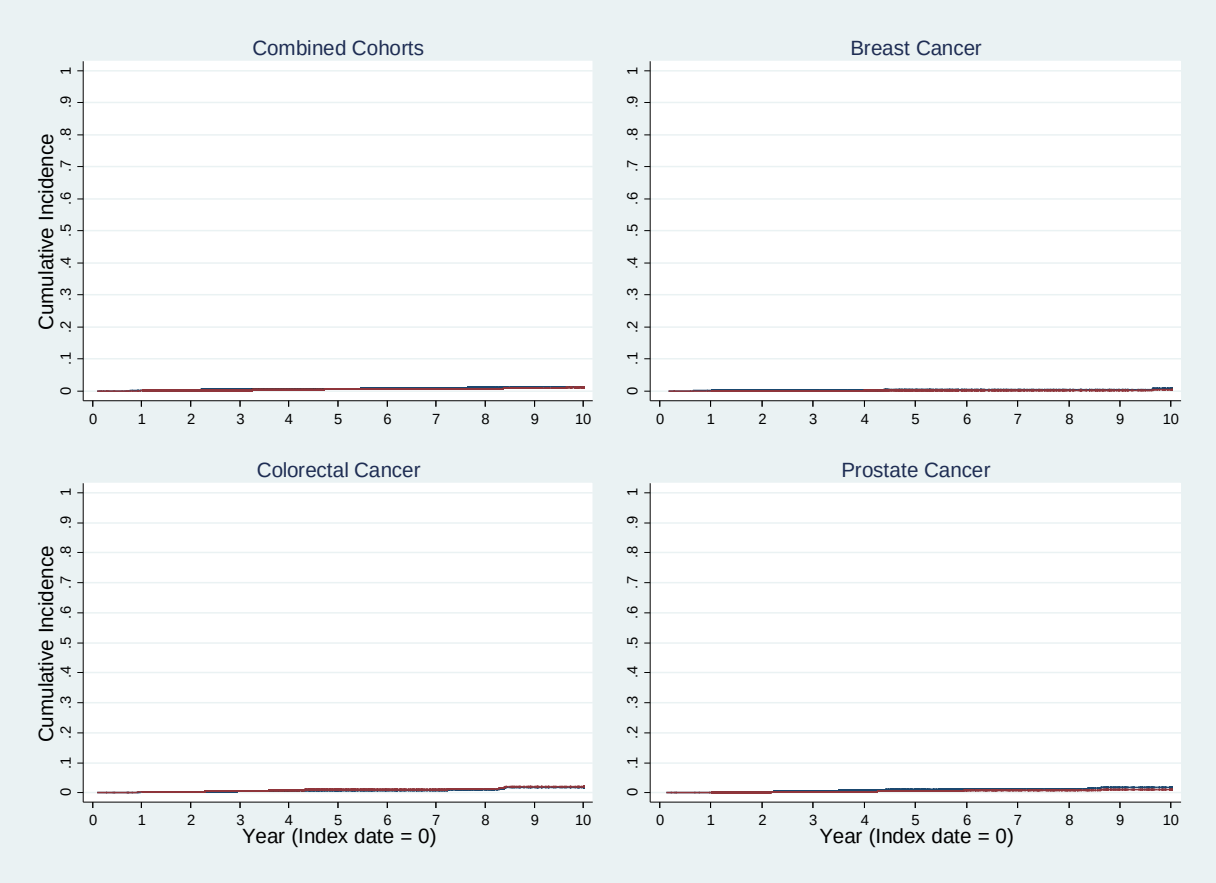
Figure 6.8: Unadjusted Cumulative Incidence of Cerebrovascular Accident



6.3.2.4 Lower Limb Amputation

The unadjusted cumulative incidence of lower limb amputation (Figure 6.9) was less than 3%, and virtually identical in cancer patients (red) and controls (blue) (HR=0.76; 95% CI, 0.45-1.29). Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

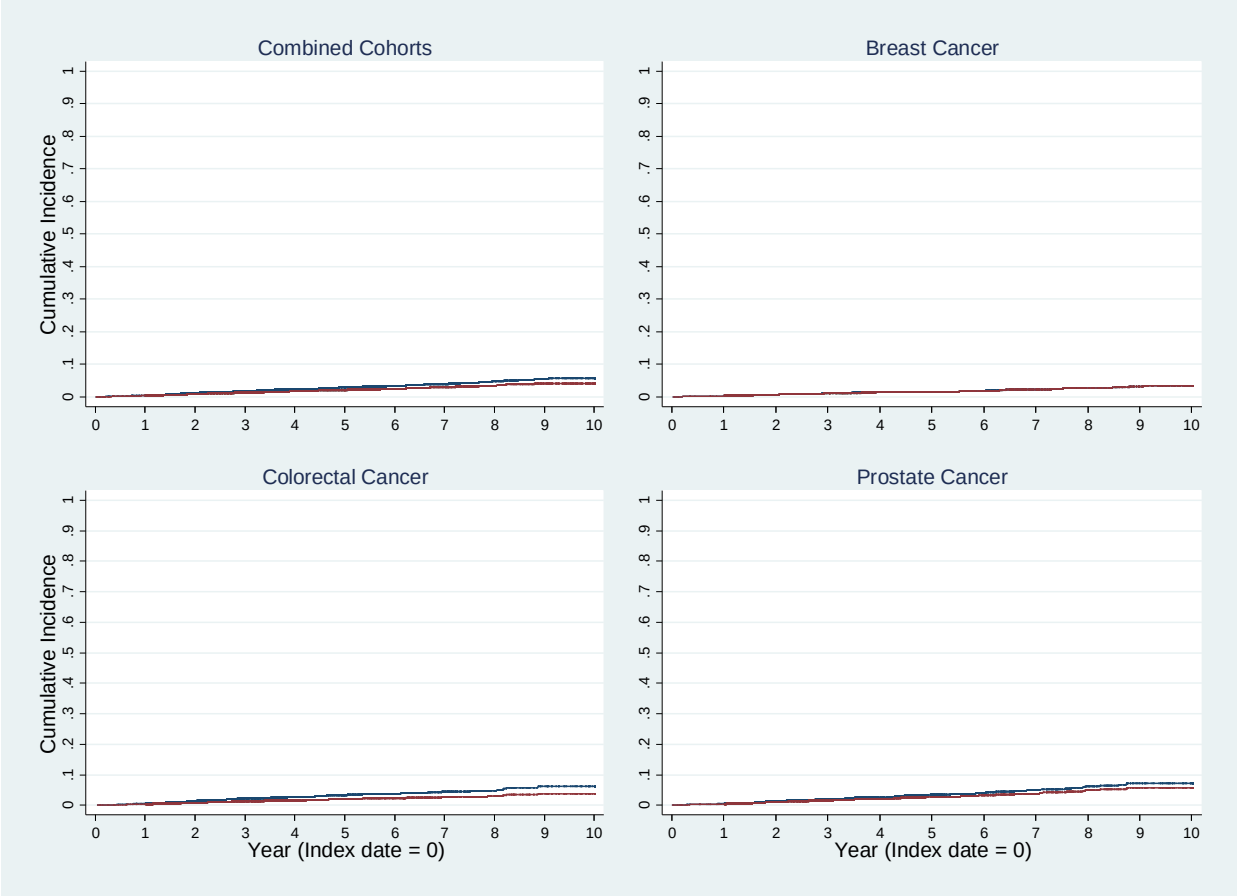
Figure 6.9: Unadjusted Cumulative Incidence of Lower Limb Amputation



6.3.2.5 Peripheral Arterial Disease

The unadjusted cumulative incidence of peripheral arterial disease (Figure 6.10) was less than 10%, but statistically significantly lower in cancer patients (red) than controls (blue) (HR=0.74; 95% CI, 0.56-0.97), before, but not after, adjustment for multiple comparisons. Similar patterns and relative hazards (as indicated by the HRs) were observed in all four cohorts.

Figure 6.10: Unadjusted Cumulative Incidence of Peripheral Arterial Disease



6.3.3 Primary Analyses of Diabetes Complications

There were no statistically significant ($p \leq 0.05$) differences between cancer patients and non-cancer controls in the rates of any microvascular or macrovascular complications (Tables 6.1 and 6.2) after adjusting for baseline patient characteristics and for multiple comparisons.

Table 6.1: Primary Analyses of Microvascular Complications

	Cohort							
	Combined		Breast		Colorectal		Prostate	
Type of Complication	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**
Any Microvascular	0.96 (0.87-1.06)	0.99 (0.89-1.09)	1.03 (0.86-1.23)	1.04 (0.86-1.25)	1.01 (0.85-1.20)	1.02 (0.85-1.22)	0.89 (0.76-1.05)	0.94 (0.80-1.11)
Chronic Kidney Disease	1.08 (0.85-1.36)	1.13 (0.89-1.43)	1.23 (0.83-1.82)	1.22 (0.81-1.82)	0.94 (0.62-1.44)	1.05 (0.68-1.64)	1.01 (0.68-1.51)	1.11 (0.74-1.68)
Nephropathy	1.12 (0.66-1.88)	1.19 (0.70-2.02)	1.16 (0.41-3.28)	1.19 (0.41-3.45)	1.71 (0.78-3.73)	1.82 (0.83-3.98)	0.65 (0.25-1.70)	MV did not converge
Neuropathy	1.07 (0.88-1.31)	1.10 (0.90-1.35)	1.22 (0.85-1.76)	1.23 (0.85-1.78)	1.31 (0.96-1.81)	1.30 (0.94-1.80)	0.83 (0.59-1.17)	0.84 (0.59-1.18)
Retinopathy	0.86** (0.77-0.96)	0.88* (0.79-0.98)	0.96 (0.79-1.17)	0.97 (0.79-1.18)	0.82 (0.67-1.00)	0.81* (0.66-0.99)	0.83* (0.69-0.99)	0.89 (0.74-1.06)

Notes to Table 6.1

* p <0.05, ** p <0.01, *** p <0.001 (none of these differences remained statistically significant after adjustment for multiple comparisons)

Adjusted analyses included the following baseline demographic and clinical covariates: age, sex (combined cohorts, colorectal cancer), year of index date, smoking status, drinking status, body mass index, type of cancer (in the analyses in which the three cancer types were combined), Charlson Comorbidity Index, Index of Multiple Deprivation score, baseline blood pressure, baseline total cholesterol, baseline HbA1c, and history of diabetes medications. MV multivariate.

Table 6.2: Primary Analyses of Macrovascular Complications

	Cohort							
	Combined		Breast		Colorectal		Prostate	
Type of Complication	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**	**Unadjusted Hazard Ratio (95% CI)**	**Adjusted Hazard Ratio (95% CI)**
Any Macrovascular	0.94 (0.80-1.11)	0.96 (0.82-1.13)	1.04 (0.77-1.40)	1.00 (0.74-1.37)	0.92 (0.69-1.21)	0.94 (0.71-1.24)	0.93 (0.72-1.21)	0.98 (0.75-1.26)
Acute Myocardial Infarction	1.09 (0.87-1.37)	1.11 (0.88-1.39)	0.82 (0.50-1.32)	0.79 (0.48-1.29)	1.42 (0.99-2.04)	1.37 (0.94-1.99)	1.03 (0.72-1.49)	1.12 (0.77-1.62)
Cerebrovascular Accident	0.99 (0.78-1.25)	0.99 (0.78-1.26)	1.33 (0.87-2.03)	1.42 (0.92-2.17)	0.90 (0.59-1.37)	0.97 (0.64-1.47)	0.87 (0.59-1.28)	MV did not converge
Lower Limb Amputation	0.76 (0.45-1.29)	0.83 (0.49-1.42)	0.51 (0.11-2.28)	0.45 (0.10-2.09)	1.18 (0.56-2.49)	1.21 (0.53-2.74)	0.55 (0.23-1.31)	0.62 (0.25-1.52)
Peripheral Arterial Disease	0.74* (0.56-0.97)	0.78 (0.59-1.03)	0.99 (0.56-1.74)	0.94 (0.52-1.72)	0.60* (0.36-1.00)	0.66 (0.39-1.10)	0.79 (0.52-1.18)	0.86 (0.57-1.30)

Notes to Table 6.2

* p <0.05, ** p <0.01, *** p <0.001 (none of these differences remained statistically significant after adjustment for multiple comparisons)

Adjusted analyses included the following baseline demographic and clinical covariates: age, sex (combined cohorts, colorectal cancer), year of index date, smoking status, drinking status, body mass index, type of cancer (in the analyses in which the three cancer types were combined), Charlson Comorbidity Index, Index of Multiple Deprivation score, baseline blood pressure, baseline total cholesterol, baseline glycosylated haemoglobin, and history of diabetes medications. MV multivariate.

6.3.4 Secondary Analyses of Diabetes Complications

The results of the secondary analyses of diabetes complications based on the propensity-matched cohorts (Table 6.3) were consistent with those of the primary analyses. There were no statistically significant differences in any of the complications between cancer patients and non-cancer controls after adjustment for multiple comparisons.

Table 6.3: Secondary Analyses of Complications – Propensity-Matched Cohorts

	Cohort			
	Combined	**Breast**	**Colorectal**	**Prostate**
Type of Complication	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
Any Microvascular	0.93 (0.76-1.14)	1.03 (0.86-1.23)	1.01 (0.85-1.20)	0.89 (0.76-1.05)
Chronic Kidney Disease	1.08 (0.64-1.81)	1.23 (0.83-1.82)	0.94 (0.62-1.44)	1.01 (0.68-1.51)
Nephropathy	0.69 (0.22-2.19)	1.16 (0.41-3.28)	1.71 (0.78-3.73)	0.65 (0.25-1.70)
Neuropathy	0.90 (0.59-1.38)	1.22 (0.85-1.76)	1.31 (0.96-1.81)	0.83 (0.59-1.17)
Retinopathy	0.91 (0.73-1.14)	0.96 (0.79-1.17)	0.82 (0.67-1.00)	0.83* (0.69-0.99)
Any Macrovascular	1.00 (0.72-1.39)	1.04 (0.77-1.40)	0.92 (0.69-1.21)	0.93 (0.72-1.21)
Acute Myocardial Infarction	1.26 (0.77-2.07)	0.82 (0.50-1.32)	1.42 (0.99-2.04)	1.03 (0.72-1.49)
Cerebrovascular Accident	0.73 (0.45-1.18)	1.33 (0.87-2.03)	0.90 (0.59-1.37)	0.87 (0.59-1.28)
Lower Limb Amputation	1.15 (0.35-3.79)	0.51 (0.11-2.28)	1.18 (0.56-2.49)	0.55 (0.23-1.31)
Peripheral Arterial Disease	0.85 (0.52-1.40)	0.99 (0.56-1.74)	0.60* (0.36-1.00)	0.79 (0.52-1.18)

* p <0.05, ** p <0.01, *** p <0.001 (no difference significant after adjustment for multiple comparisons)

6.3.5 Primary Analyses of Mortality

6.3.5.1 All-Cause Mortality

The cumulative incidence of *death from any cause* at 10 years after the index date (Figure 6.11, upper left panel) was 0.58 (red) in the cancer patients and 0.44 in the non-cancer controls (blue) (unadjusted HR=1.47; 95% CI, 1.33-1.63: Table 6.4). The largest difference in overall mortality was between colorectal cancer patients and their controls (Figure 6.11, lower left panel), where the cumulative incidence at 10 years was 0.66 for cancer and 0.48 for controls (unadjusted HR=1.64; 95% CI, 1.38-1.95: Table 6.4). All unadjusted differences remained statistically significant after adjusting for baseline characteristics. (Table 6.4)

Figure 6.11: Unadjusted Cumulative Incidence of Death due to All Causes

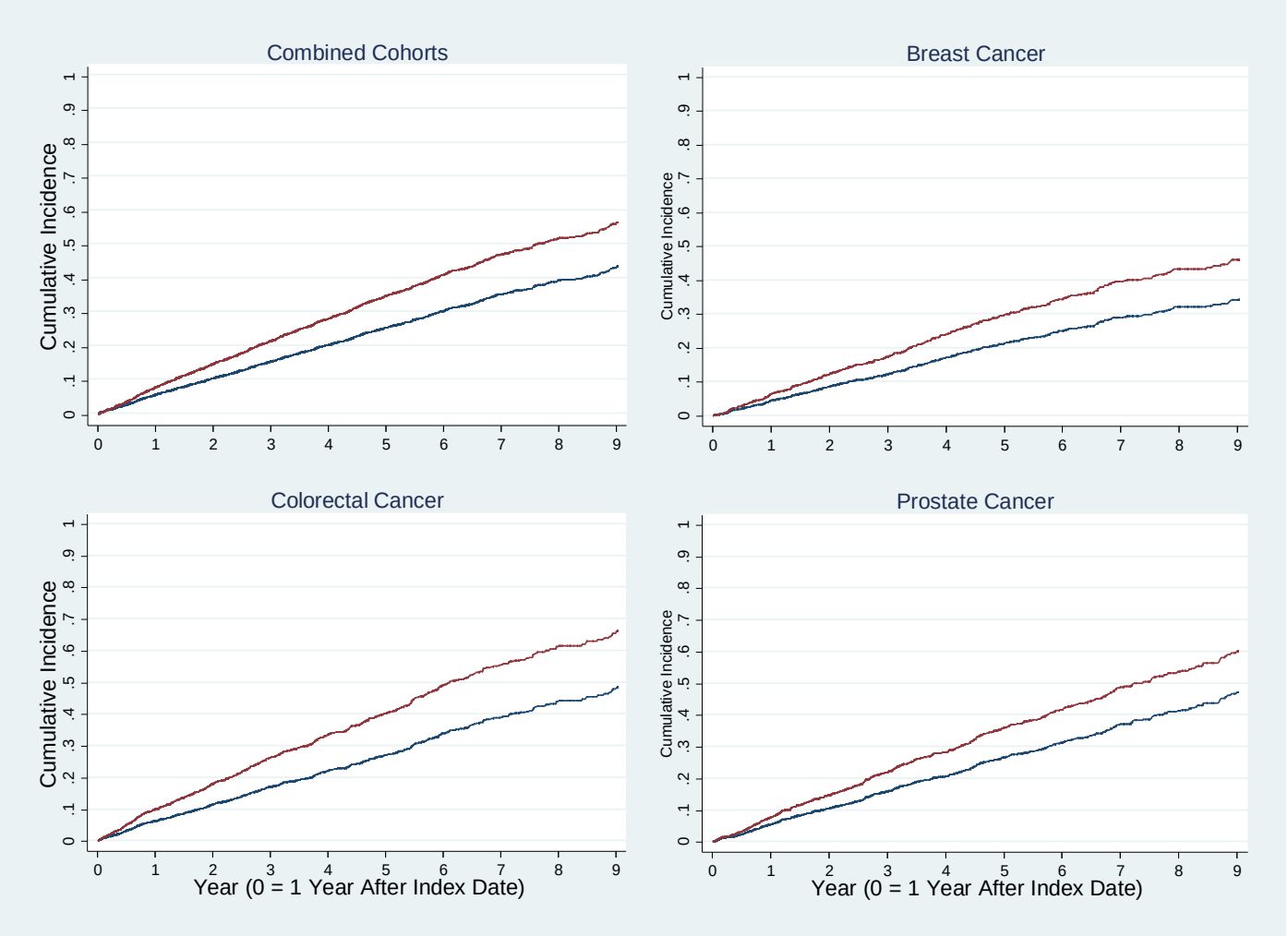


Table 6.4: Primary Analyses of Mortality

	Cohort							
	Combined		Breast		Colorectal		Prostate	
	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Mortality								
Overall	1.47***	1.57***	1.47**	1.52***	1.64***	1.71***	1.44***	1.60***
	(1.33-1.63)	(1.41-1.74)	(1.21-1.80)	(1.24-1.85)	(1.38-1.95)	(1.43-2.04)	(1.22-1.72)	(1.35-1.91)
Diabetes	0.73**	0.76***	0.87	0.91	0.88	0.87	0.57**	0.61***
	(0.59-0.90)	(0.61-0.94)	(0.58-1.31)	(0.59-1.40)	(0.63-1.23)	(0.62-1.23)	(0.40-0.82)	(0.43-0.88)

Notes to Table 6.4

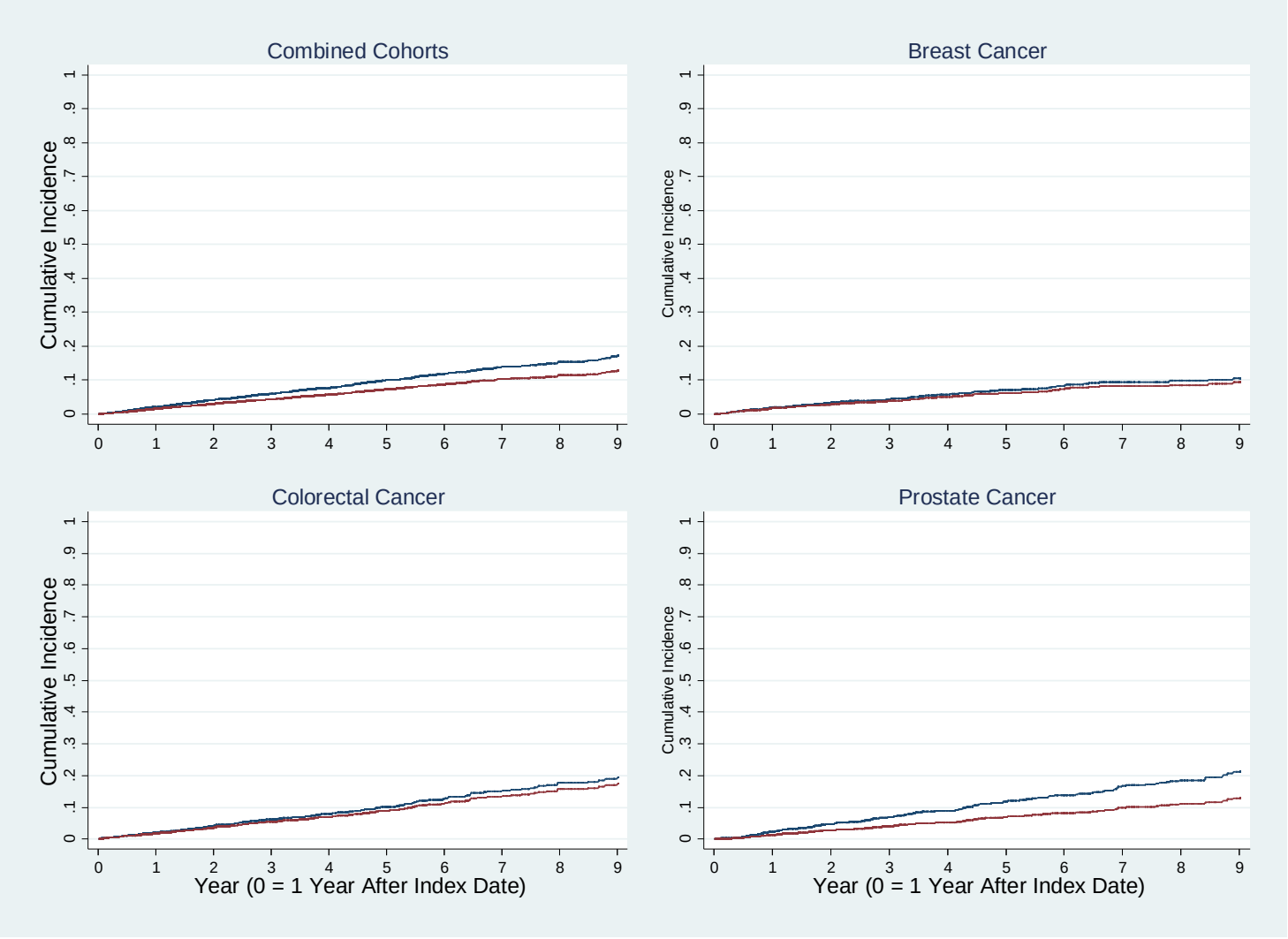
* p <0.05, ** p <0.01, *** p <0.001

Adjusted analyses included the following baseline demographic and clinical covariates: age, sex (combined cohorts, colorectal cancer), year of index date, smoking status, drinking status, body mass index, type of cancer (in the analyses in which the three cancer types were combined), Charlson Comorbidity Index, Index of Multiple Deprivation score, baseline blood pressure, baseline total cholesterol, baseline glycosylated haemoglobin, history of diabetes microvascular complications, history of diabetes macrovascular complications, and history of diabetes medications.

6.3.5.2 Diabetes-Related Mortality

The cumulative incidence of *death from diabetes-related causes* at 10 years after the index date (Figure 6.12, upper left panel) was 0.13 in the cancer patients (red) and 0.17 in the controls (blue) (unadjusted HR=0.73; 95% CI, 0.59-0.90: Table 6.4). The largest difference was between prostate cancer patients and their controls (Figure 6.12, lower right panel) where the cumulative incidence at 10 years was 0.13 for cancer patients (red) and 0.21 for controls (blue) (unadjusted HR=0.57; 95% CI, 0.40-0.82: Table 6.4). Unadjusted differences in diabetes-related mortality also remained statistically significant after adjusting for baseline characteristics. (Table 6.4)

Figure 6.12: Unadjusted Cumulative Incidence of Death due to Diabetes-Related Causes



6.3.6 Secondary Analyses of Mortality

Findings from the mortality analyses based on the propensity-matched cohorts (Table 6.5) were consistent with those from the primary analyses, except breast cancer also was associated with statistically significantly lower diabetes mortality (HR=0.63; 95% CI, 0.40-0.99).

Table 6.5: Secondary Analyses of Mortality – Propensity-Matched Cohorts

	Cohort			
	Combined	**Breast**	**Colorectal**	**Prostate**
Mortality	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
Overall	1.50**	1.42**	2.02***	1.46**
	(1.32-1.72)	(1.10-1.82)	(1.57-2.59)	(1.16-1.82)
Diabetes	0.70**	0.63*	0.98	0.56**
	(0.54-0.89)	(0.40-0.99)	(0.64-1.52)	(0.37-.86)

* p <0.05, ** p <0.01, *** p <0.001

6.4 DISCUSSION AND CONCLUSIONS

6.4.1 Summary of Findings

This chapter has presented the methods and findings of the primary research in which rates of microvascular and macrovascular complications of diabetes, as well as all-cause and diabetes-related mortality, were compared between cancer patients and controls. Among 80 unadjusted and adjusted comparisons, after adjustment for multiple comparisons[13-15] there was no instance in which cancer was associated with higher incidence of a complication. These findings are consistent with those presented in the preceding chapter, which indicated that the observed changes in biological parameters

associated with cancer would be neither of sufficient size nor of sufficient duration to substantially increase the risk of diabetes complications relative to non-cancer controls.

Cancer was associated with lower adjusted incidence of retinopathy in the colorectal cancer and the combined cohorts, but the reason for this is not immediately clear, and chance finding due to multiple testing cannot be ruled out. As might be expected, cancer was associated with higher all-cause mortality even though, as described in section 3.2.3 of Chapter 3, patients who survived less than one year were excluded from the study. However, there was no evidence of an adverse impact on diabetes-related mortality. In fact, the findings suggest prostate cancer was associated with lower diabetes mortality in competing risks regression that accounted for death due to other causes. Unadjusted analyses did suggest prostate cancer patients had a lower incidence of retinopathy, and the possibility that they were healthier in ways not accounted for in either the matching process during patient selection, or in the process of adjusting for residual differences in observed characteristics, cannot be ruled out, and has been identified as the cause of other improbable results in observational studies.[16]

6.4.2 Strengths and Limitations

6.4.2.1 Comparability of the Cohorts

The primary analyses reported in this chapter were based on the full cohorts. Therefore, multivariate competing risks regression analyses were used to adjust for differences in baseline characteristics between cancer patients and controls that were not accounted for in the matching process. Otherwise, these may have confounded associations between cancer and the risk of developing microvascular or macrovascular

complications of diabetes, and of overall and diabetes-related mortality. This was especially important in the mortality analysis, which was performed in the subset of patients who were eligible for linkage to the ONS data.[8] Also, since there was a reasonable chance overall mortality would be higher in cancer patients than controls, competing risks regression was used to estimate the cumulative incidence function and unadjusted and adjusted HRs for each microvascular and macrovascular complication, comparing cancer patients to non-cancer controls.

6.4.2.2 Assessment of Outcome

Complications of diabetes were identified based on the presence of specific Read codes in the primary care data. It is possible that had the HES[17] inpatient data from the CPRD linkage also been used additional complications would have been identified. However, only approximately two-thirds of the patients in the primary care data were eligible for linkage to HES.

6.4.2.3 Follow-Up

The length of follow-up for the primary research in this chapter was extended from five to 10 years after the index date to capture any impact variation in quality of diabetes primary care may have had on the development of long-term clinical complications of diabetes. However, most patients who had an index date in 2004 or later would have been censored before the end of the full 10 years, if they did not die or have the diabetes complication of interest in the analysis beforehand.

6.4.3 Conclusions and Implications

Overall, incident cancer appears to have had no adverse impact on the long-term outcomes of pre-existing diabetes during 10 years after a diagnosis of breast, colorectal, or prostate cancer.

6.5 CHAPTER REFERENCES

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CHAPTER SEVEN

Discussion and Conclusions

VII DISCUSSION AND CONCLUSIONS

7.1 SUMMARY OF CHAPTER FINDINGS

7.1.1 Chapter 1

Chapter 1 presented the background and rationale for selecting the thesis topic. Since early detection and advances in therapy and supportive care have substantially improved the relative survival of many of the most common types of cancer,[1] overall morbidity and mortality in cancer depend increasingly on the quality and outcomes of primary care for underlying conditions.[2] Therefore, overlooking other medical conditions during cancer treatment and follow-up could result in excess morbidity and mortality, thereby undermining gains associated with early detection and improved treatment of cancer, which is a concern that has been raised by leading cancer organizations in the UK.[3,4] Although cancer could have adverse impacts on many conditions, and vice-versa, the quality and outcomes of diabetes primary care in cancer deserve particular attention because cancer and diabetes co-occur at rates that are higher than what would be expected by chance alone,[5] some types of cancer treatment may cause or worsen diabetes,[6] and diabetes is associated with excess morbidity and mortality in cancer.[7]

The concept of quality of care was then introduced, including its principal components,[8-11] and the overarching theme in position statements,[8] clinical guidelines,[9,10] and incentive programmes[11] that high quality diabetes care depends on a partnership between the patient and a team of healthcare professionals, which is best served through regular delivery of recommended diabetes services by healthcare professionals, plus ongoing participation in diabetes self-management activities by the patient. Therefore, mechanisms by which cancer could adversely impact the quality and outcomes of diabetes care include (A) disrupting the regular delivery of diabetes services and (B) disrupting patient self-management activities.

VII DISCUSSION AND CONCLUSIONS

At the time that this thesis topic was developed there had been several published studies on the delivery of diabetes care in cancer patients,[12-19] but predominantly from the US. Evidence from the UK was limited to one study of long-term survivors, in which patient follow-up did not begin until at least five years after cancer diagnosis.[19] Therefore, that study did not address the impact cancer might have had on the quality and outcomes of diabetes care during the early stages of cancer treatment and follow-up when the greatest disruption in usual diabetes care might be expected to occur.

Chapter 1 then described biological mechanisms whereby cancer could adversely affect the quality and outcomes of diabetes care, and it presented the hypothesis that the overall impact of cancer on diabetes outcomes is likely to depend, in part, on whether changes in biological parameters, e.g., HbA1c, blood pressure, and lipids, resulting from the mechanisms described above, are of sufficient size and duration to increase the risk of diabetes complications. In addition, it presented evidence from UKPDS indicating that the risks of diabetic microvascular and macrovascular complications are strongly associated with long-term elevations in both HbA1c and systolic blood pressure,[20-23] and argued that, as such, the UKPDS provides an important benchmark to assess whether observed changes in biological parameters associated with cancer would likely be of sufficient size and duration to increase the risks of diabetes complications in cancer patients.

Chapter 1 also introduced the aim, objectives, research methods, and overall structure of the thesis. The structure of the thesis was designed around the methods of research, which consisted of (A) a systematic review and qualitative synthesis of the literature on the quality of diabetes care in cancer (Chapter 2), and (B) primary research on the quality and outcomes of diabetes care in older patients diagnosed with breast, colorectal, or prostate cancer using the UK

CPRD. The primary research was quite extensive. Therefore, four chapters (Chapters 3-6) have been devoted to presenting the methods and findings of the primary research.

7.1.2 Chapter 2

Chapter 2 presented the methods and results of the systematic review and qualitative synthesis of evidence on the quality of diabetes care in patients diagnosed with cancer. The methods of research were conducted and reported according to the checklist included in the 2009 PRISMA guidelines,[24,25] and the results also were reported according to these guidelines.

Within the 15 studies retained for the systematic review,[12-19,26-32] there were 88 comparisons of the quality of diabetes care (either between cancer patients and controls, or before versus after cancer), which were classified as A) no different between cancer patients and controls (or after versus before cancer), B) better in cancer patients than controls (or after versus before cancer), or C) worse in cancer patients than controls (or after versus before cancer). Of these 88, which comprised health care visits, monitoring/testing, glycaemic/other control, and adherence to diabetes and other medications, 47 (53%; 95% CI, 52%-55%) were no different, 12 (14%; 95% CI, 13%-14%) were better in cancer patients, and 29 (33%; 95% CI, 32%-34%) were worse in cancer patients than controls (or worse after than before cancer diagnosis).

Findings differed both within and between studies, with many reporting outcomes that fell into each of the three categories: no different; cancer better; cancer worse. No clear patterns emerged according to study design, patient population, or methods of adjustment, and even statistically significant differences reported in the articles tended to be small and of questionable clinical relevance, as indicated by the narrow ranges of RRs (generally between 0.9 and 1.1) that were calculated. Perhaps the strongest evidence of an adverse impact of cancer was obtained from studies on diabetes

medication adherence/persistence. These tended to be recent studies with a before and after design. However, there was also evidence of an adverse impact on monitoring/testing from a study of long-term survivors of breast, colorectal, or prostate cancer, which was conducted in the UK.[19]

Overall, there was no consistent evidence that cancer is associated with lower, or worsening in the case of before and after studies, quality of diabetes care except that in the UK cancer was associated with significantly lower rates of blood pressure, cholesterol, and HbA1c control in long-term survivors of three of the most common types of cancers.[19] Given findings from the UK study of long-term survivors, and the fact that recent studies of incident cancer in patients with pre-existing diabetes had detected differences in outcomes, it seemed reasonable to conclude that primary research would be useful for examining the impact of incident cancer on a broader range of diabetes quality of care outcomes in the UK.

Chapter 2 concluded with a series of statements on the implications of the findings from the systematic review for the design of future primary research. These were subsequently incorporated into the methods of primary research for the thesis.

7.1.3 Chapter 3

Chapter 3 presented the methods of primary research on the quality and outcomes of diabetes care in patients diagnosed with breast, colorectal, or prostate cancer compared to matched, non-cancer controls, which was conducted using data from the CPRD and data held under the CPRD Linkage Scheme.[33] Chapter 3 included sections on the study aim and objectives, study design and data source, patient selection, construction of

baseline demographic and clinical variables for the research, and a summary of the analytic plan for the following three chapters. This chapter also reported the baseline demographic and clinical characteristics of the patients who were included in the final cohorts for the primary research.

The objectives of the primary research focused primarily on (A) whether cancer disrupted the delivery of recommended diabetes services in primary care, (B) whether the aggregate effect of disruptions in primary care diabetes services, lapses in patient self-management, and cancer treatment was to increase levels of biological parameters that also are risk factors for diabetes complications, and (C) whether the aggregate effect of the mechanisms above, including their direct and/or indirect impact on levels of important biological parameters, was to increase the risk of diabetes complications and mortality.

The overall design of the primary research was an historical cohort study using the CPRD. Cancer patients were included if they were diagnosed with breast, colorectal, or prostate cancer on or after 1 January 2000, and were diagnosed with type 1 or type 2 diabetes at least two years before their date of cancer diagnosis (index date). Each cancer patient (case) was matched to up to four non-cancer patients (controls) on GP practice number, sex (colorectal cancer only), and age (±1 year) at cancer diagnosis. Matched controls were assigned an index date within one year of their cancer case. All patients had to have survived at least one year after their index date to be included in the final cohort. Patients were followed from two years before, to up to five years after their index date for the quality of diabetes care outcomes, and to up to 10 years after

their index date for the microvascular and macrovascular complications of diabetes and mortality (diabetes and all-cause) outcomes.

There were 14,517 patients in the cohort that combined all three types of cancer patients and their controls: 3,382 (23.3%) were cancer patients and 11,135 (76.7%) were controls (ratio of 3.3:1 control to cancer). Breast cancer patients accounted for 30.6%, colorectal cancer patients accounted for 31.6%, and prostate cancer patients accounted for 37.8% of cancer patients in the combined cancer cohort. The average age at cancer diagnosis (matched date for controls) was 72.3 years, and 19.9% of patients were age 80 years or older. Males accounted for 58.7% of patients, and 40.8% were diagnosed—had their index date—in 2010 or later. The majority of cancer patients also were included in the propensity-matched cohorts.

Based on comparisons with other studies in the systematic review, the conclusion reached was that the cohort constructed for the primary research would be sufficiently large to detect clinically meaningful differences between cancer patients and controls, and to detect "before and after" changes in cancer patients. Moreover, key variables that should be used to adjust for potential confounding, such as smoking, BMI, baseline cholesterol, and baseline HbA1c, were well-populated. Some imbalances in the baseline characteristics of cancer cases and controls indicated that statistical analyses should consist of both unadjusted and multivariate (for baseline characteristics) comparisons of quality and outcomes between cancer patients and controls to adjust for potential confounding due to these imbalances. Further, they indicated that secondary analyses

should be conducted in the propensity-matched cohort, where the balance in the baseline characteristics was improved considerably.

7.1.4 Chapter 4

Chapter 4 presented the methods and results of the primary research in which changes in the quality of diabetes care over time were compared between cancer patients and controls. Quality measures were constructed based on the Department of Health, Data and Business Rules, Diabetes Mellitus Indicator Set, Version No. 25.0, version date 28/03/13,[11] which includes indicators for blood pressure, cholesterol, and HbA1c control; diabetes services, e.g., foot examination; and other general primary care services, e.g., influenza immunisation. Unadjusted and adjusted multilevel logistic regression analysis[34-36] was used to investigate changes in whether or not patients met each of the quality measures over time, and whether those patterns of change over time differed between cancer patients and controls. Primary analyses were performed using the full cohorts with up to five years of follow-up after cancer diagnosis or matched date in non-cancer controls. Secondary analyses were performed using the full cohorts with up to seven years of observation (two years before, up to five years after, cancer or matched date), and also using the propensity matched cohorts.

The findings from the analyses reported in this chapter showed that cancer patients were less likely than non-cancer controls to meet quality measures for cholesterol and HbA1c control, and for albumin creatinine ratio testing. Cancer patients were no less likely than their matched controls to meet quality measures for diabetes services, including retinal screening, foot examination, and dietary review. They were more likely

to receive influenza immunisation, and male patients in the combined cohort (prostate and colorectal cancer) were more likely to receive advice about erectile dysfunction.

In some instances, the impact of cancer on the quality of diabetes care differed across the three individual cancer cohorts. For instance, breast cancer patients were as likely as their controls to achieve cholesterol control. However, prostate cancer patients were less likely than theirs to achieve cholesterol control. Prostate cancer patients were more likely than their controls to receive influenza immunisation. In other instances, findings were consistent across the cohorts. For example, cancer patients in all three individual cohorts, and in the combined cohort, were less likely than the non-cancer controls to achieve adequate HbA1c control.

Overall, cancer appeared to have had little adverse impact on the delivery of high quality diabetes care services during the first five years after cancer diagnosis. However, diabetic patients with cancer were less likely to achieve target thresholds for cholesterol and HbA1c.

7.1.5 Chapter 5

Chapter 5 presented the methods and results of the primary research in which changes in actual blood pressure, cholesterol, and HbA1c levels over time were compared between cancer patients and controls. Unadjusted and adjusted multilevel regression analyses[34,37,38] were used to investigate changes in clinical and laboratory values over time, and whether those patterns of change over time differed between cancer patients and controls.

VII DISCUSSION AND CONCLUSIONS

Overall, the findings showed that in most instances cancer was associated with, at most, very modest changes in levels of blood pressure, cholesterol, and HbA1c over time. The largest changes occurred in colorectal cancer, where blood pressure and HbA1c levels were slightly (albeit statistically significantly) lower during the quarter of cancer diagnosis, but then rebounded to levels similar to control patients soon thereafter. Patterns of change for blood pressure and HbA1c in colorectal cancer were similar to the pattern of weight loss and then gain to previous levels observed in these patients. There was no evidence that cancer had a long-term impact on blood pressure, cholesterol, or HbA1c in any of the four cohorts.

In Chapter 1 (Section 1.1), the overall impact of cancer on diabetes outcomes was hypothesized to depend in part on the extent to which observed changes in biological parameters due to cancer were of sufficient size and duration to increase the risk of diabetes complications, with the UKPDS serving as an important benchmark. In UKPDS 35,[20] a prospective observational study to determine the relation between exposure to glycaemia over time and the risk of microvascular and macrovascular complications in patients newly diagnosed with type II diabetes, each 1% reduction in updated mean HbA1c[x] was associated with large reductions in risk for any endpoint related to diabetes, for deaths related to diabetes, for myocardial infarction, and for microvascular complications. In UKPDS 36,[21] each 10mm Hg decrease in updated mean systolic blood pressure was associated with reductions in risk for any complication related to diabetes,

[x] Calculated for each individual from baseline to each year of follow-up (mean duration of 10 years)

for deaths related to diabetes, for myocardial infarction, and for microvascular complications.

The findings from the primary research presented in this chapter suggest that, relative to UKPDS, the observed changes in biological parameters associated with cancer were neither of sufficient size nor of sufficient duration to substantially increase the risk of diabetes complications relative to non-cancer controls.

7.1.6 Chapter 6

Chapter 6 presented the methods and results of the primary research in which diabetes complications and mortality were compared between cancer patients and controls. Microvascular complications consisted of chronic kidney disease (stage 4 or 5), nephropathy, neuropathy, and retinopathy. Macrovascular complications consisted of acute myocardial infarction or acute coronary syndrome, cerebrovascular accident, lower limb amputation, and peripheral arterial disease. Unadjusted and adjusted competing risks regression analyses[39,40] were performed to estimate the cumulative incidence of each diabetes complication in cancer patients and controls, as well as to estimate the HRs (cancer compared to control) for each complication, using up to 10 years of follow-up after the index date. Competing risks regression also was used to estimate the cumulative incidence, as well as the unadjusted and adjusted HRs, for overall and diabetes-related mortality.

Among 80 unadjusted and adjusted comparisons, after adjustment for multiple comparisons[41-43] there was no instance in which cancer was associated with higher incidence of a complication. Cancer was associated with lower adjusted incidence of

retinopathy in the colorectal cancer and the combined cohorts, but the reason for this is not immediately clear, and chance finding due to multiple testing cannot be ruled out. Overall, these findings are consistent with those presented in Chapter 5, which indicated that, relative to UKPDS,[20-23] the observed changes in biological parameters associated with cancer would be neither of sufficient size nor of sufficient duration to substantially increase the risk of diabetes complications relative to non-cancer controls.

As might be expected, cancer was associated with higher all-cause mortality even though patients who survived less than one year were excluded from the study. However, there was no evidence of an adverse impact on diabetes-related mortality. In fact, the findings suggest prostate cancer was associated with lower diabetes mortality in competing risks regression that accounted for death due to other causes. Unadjusted analyses did suggest prostate cancer patients had a lower incidence of retinopathy, and the possibility that they were healthier in ways not accounted for in either the matching process during patient selection, or in the process of adjusting for residual differences in observed characteristics, cannot be ruled out. This has been identified as the cause of other improbable results in observational studies.[44]

7.2 STRENGTHS AND LIMITATIONS OF THE RESEARCH

7.2.1 Systematic Review

The systematic review has important strengths and limitations. Overall, the quality of the 15 studies was high. However, there were insufficient data for performing a formal synthesis of outcomes across individual studies. Had a formal synthesis been feasible, it

is possible more statistically significant differences in the quality of diabetes care measures between the cancer cases and non-cancer controls would have been detected.

The search strategy had several limitations. First, additional articles/information may have been discovered had other databases in addition to Medline and Embase had been included, and also if grey literature resources, dissertations and theses, and conference proceedings, or if non-English language articles had been included. Second, the approach of beginning the search by tabulating MeSH terms from articles previously reviewed as part of developing the topic for this thesis could have resulted in failing to find relevant articles, which otherwise might have been identified if lists of keywords and index/subject terms had been constructed independently of those included in the original eight articles, or if lists had been obtained/constructed from other sources. Third, as the preliminary search produced in excess of 20,000 articles, it was then narrowed to those articles with specific key words the title. An alternative approach would have been to review the titles, and possibly also the abstracts, of all 20,000+ articles in the preliminary search, which could have resulted in retaining articles that were inadvertently excluded when the search was narrowed based on the presence of key terms in the title.

7.2.2 Primary Research

The strengths and limitations of the study design for the primary research were assessed with the same instrument used to assess the quality of studies in the systematic review (Chapter 2), the Newcastle-Ottawa Quality Assessment Scale Cohort Studies (Box 3.1).[45]

7.2.2.1 Representativeness of the Exposed Cohort

One strength of the study design for the primary research is that it was based on CPRD, which includes patients who are broadly representative of the UK general population in terms of age, sex, and ethnicity.[46] However, since only patients age ≥50 years at the time they were diagnosed with breast, colorectal, or prostate cancer were selected, a limitation of the design for the primary research is that younger patients with diabetes, or those with diabetes who were diagnosed with other types of cancer, were not included. Another limitation is that baseline patient characteristics were established at cancer diagnosis (or the assigned date in matched, non-cancer controls), rather than at the time of diabetes diagnosis, as is usually the case in studies of newly diagnosed patients. Information on patients at the time they were diagnosed could have revealed important, and potentially confounding, differences between cases and controls subsequently managed through multivariate analyses and/or propensity score matching.

7.2.2.2 Selection of the Non-Exposed Cohort

Another strength of the study design is that patients in the non-diabetic control group were matched to individual cancer patients based on age, sex, and GP practice number. Matched controls were assigned an index date within one year of their cancer case, and, like the cancer cases, had to have been diagnosed with diabetes at least two years before their index date. Therefore, selection of the control patients was designed to minimize potential confounding caused by imbalances in some of the baseline characteristics of the cancer patients and non-cancer controls that may also have affected the outcomes. One limitation of this approach is that in order to maximize the

number of cancer patients with at least one matched control, only a subset of potential confounders was included in the matching. However, cohorts based on propensity matching that included a much larger set of demographic and clinical variable also were constructed.

7.2.2.3 Ascertainment of the Exposure

Since the primary research compared cancer patients to controls, cancer was the exposure in this instance. One limitation of the study design is that it was not possible to link the CPRD data to information from the NCIN,[47] which would have allowed use of the registry data to identify cancer patients. Instead, Read codes in the primary care data, which do have a high sensitivity and specificity for identifying cancer, were used.[48]

Cancer registry data also may have allowed exclusion from among the cancer patients those who were diagnosed with metastatic disease. Read codes in the primary care data files and ICD-10 codes in the HES[49] inpatient data were considered as alternatives. However, there are no studies in the UK that validate the use of ICD-10 codes for this purpose; and because only two-thirds of the patients in the research were linked to HES data, doing so would have limited the sample sizes. Instead, patients who died within the first year after their index date were excluded from the study. Failing to take this step could have resulted in including cancer patients with a relatively poor prognosis, for whom cancer care would be made a priority over diabetes care; inclusion of such patients could create a bias toward finding less receipt of recommended diabetes care among cancer patients.

7.2.2.4 Comparability of the Cohorts

Several steps were taken to maximize the comparability of the cancer patients and non-cancer controls. Non-cancer controls were matched to cancer patients on age, sex, and GP practice, assigned an index date within one year of their cancer case, and also required to have been diagnosed with diabetes at least two years before their index date. Also, cohorts were constructed based on propensity matching that included a broad array of patient variables. Virtually all differences in baseline demographic and clinical characteristics between propensity matched cancer patients and controls were eliminated at this stage. However, since the primary analyses for comparing the quality and outcomes of diabetes care between cancer patients and controls were based on the full cohorts, multivariate statistical methods were used to adjust for differences in baseline characteristics. Also, patients in this study were followed from two years before, up to five years after, their index date. Therefore, the quality of diabetes care also was compared "before and after" cancer, and in those analyses cancer patients served as their own controls.

Another strength is that the study population was similar in size to, or larger than, those of other studies that have examined the impact of incident cancer on adherence to glucose-lowering treatment in diabetes,[28,29] on general practitioner consultation rates in diabetes,[30] on testing, and on control of diabetes.[19,31] Those studies were sufficiently large to detect clinically meaningful and statistically significant changes in the diabetes outcomes of interest associated with incident cancer diagnosis. Therefore, it seems reasonable to infer that the cohort constructed to conduct the primary care research of

this thesis was sufficiently large to detect differences in the outcomes of interest in this study, especially since many of the analyses entailed repeated measures on individual patients.

7.2.2.5 Assessment of Outcomes

All of the outcomes included in the primary research on the quality of diabetes care were based on the QOF Diabetes Indicator Set,[11] and there are considerable incentives for primary care practices to record the delivery of all services and test results pertaining to these indicators. In this research, the same Read codes used for the QOF indicators, in some instances supplemented with other types of codes, were used to identify the quality of diabetes care outcomes. Therefore, it is likely this approach was highly sensitive and specific. Also, during follow-up patients were required to have survived for the full year to be "at risk" for meeting the outcomes during that year. This was designed to minimize the chance that any observed differences in the probabilities of meeting the quality measures might have been due to differences in person-time at risk between cancer patients and controls, the most likely source of which would have been excess mortality in the cancer cohort.

High quality diabetes care depends on a coordinated approach between the patient and providers in both primary and secondary care, which entails both regular delivery of recommended diabetes services by the healthcare team, plus ongoing participation in diabetes self-management activities by the patient. If any part of the mechanism is disrupted, this may compromise the quality and outcomes of diabetes care, directly and/or through its impact on biological parameters that also are risk factors for diabetes

outcomes. While the CPRD is an excellent source of data with which to examine these mechanisms, it does not contain sufficient data to directly assess disruptions in patient self-management activities such as adherence to diet and exercise regimens, or changes in patient attitudes toward diabetes care during cancer treatment.

Differences between cancer patients and controls in quality measures based on testing and control of cholesterol and HbA1c were observed. One limitation is that some services, including testing, that were provided by a specialist during cancer treatment and follow-up, may not have been recorded in the primary care data. Moreover, HES[49] inpatient data do not contain the level of detail required to reliably identify the quality measures based on testing and control, and are available for only approximately two-thirds of the CPRD population. Therefore, HES data were not used to supplement the primary care data.

In the primary research on the microvascular and macrovascular complications of diabetes, complications were identified based on the presence of specific Read codes in the primary care data. It is possible that had HES[49] inpatient data also been used additional complications would have been identified. However, this was not done because only approximately two-thirds of the patients in the primary care data were eligible for linkage to HES.

7.2.2.6 Length of Follow-Up

The length of follow-up was established to capture differences in outcomes throughout the continuum of cancer care, from cancer diagnosis and initial treatment through to long-term survivorship. However, the study was not designed to assess the quality of

diabetes care in long-term survivors of cancer, as others have previously done.[19] Therefore, it did not capture the impact of long-term cancer recurrence (occurring >5 years after initial diagnosis) on the quality of diabetes care, for instance. The length of follow-up for the primary research on diabetes complications and mortality was extended from five to 10 years after the index date to capture any impact that variation in quality of diabetes care might have had on the development of long-term clinical complications of diabetes.

7.2.2.7 Adequacy of Follow-Up of the Cohorts

The median length of follow-up in the quality of care research was 3.5 years after the index date, with a minimum of one year and a maximum of five. Reasons for attrition before the maximum were death or administrative (right) censoring. In order to maximize the size of the cohort, all patients with at least one year of follow-up before the end of their data were eligible for inclusion, which meant patients with an index date later in the calendar window, e.g. 2013, had shorter follow-up. Nevertheless, the combined cohort for these analyses accounted for 44,507 patient-years for follow-up, and unadjusted plots of the proportions of patients meeting, for instance, the quality of care indicators show that the CIs remained quite narrow throughout the observation period.

7.3 CONCLUSIONS AND IMPLICATIONS OF THESIS

Leading cancer organizations in the UK have raised concerns that overlooking other medical conditions during cancer treatment and follow-up could undermine gains associated with early detection and improved treatment of cancer. Overall, the findings

presented in this thesis indicate that diabetes is not overlooked in older patients diagnosed with breast, colorectal, or prostate cancer; and that the quality of diabetes care in cancer patients is, for the most part, comparable to that in diabetic, non-cancer patients throughout the continuum of cancer treatment and long-term follow-up, with the exception, perhaps, of short-term HbA1c and cholesterol control in cancer.

Options to improve short-term achievement of target thresholds for HbA1c and cholesterol control in cancer patients could include the development of specific indicators and incentives to promote greater coordination of care between oncologists and GPs, especially to identify and address instances in which cancer treatment may cause blood sugar and/or cholesterol concentrations to rise, and the development of diabetes programs that are tailored specifically to cancer patients. However, the findings from the research conducted in this thesis also indicate that cancer had no adverse impact on the development of diabetes complications or on diabetes-related mortality. Therefore, the costs of developing and implementing diabetes programs that are tailored specifically to cancer patients, and the additional burden on patients and caregivers, should be weighed against their potential benefits.

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APPENDICES

CHAPTER 2 APPENDIX

Candidate MeSH Terms for Systematic Review

	Article							
MeSH term	Snyder 2013	Irizarry 2013	Bayliss 2010	Chiao 2010	Khan 2010	Hanchate 2009	Keating 2007	Earle 2004
Adult							✓	
Age Factors						✓		
Aged	✓	✓	✓	✓	✓	✓	✓	✓
Aged, 80 and over						✓		
Angiotensin-Converting Enzyme Inhibitors/therapeutic use							✓	
Blood Pressure							✓	
Breast Neoplasms/diagnosis						✓		
Breast Neoplasms/mortality	✓					✓		
Breast Neoplasms/prevention & control					✓			
Breast Neoplasms/therapy	✓					✓		
Carcinoma/epidemiology				✓				
Carcinoma/mortality				✓				
Case-Control Studies								✓
Cholesterol, LDL/blood							✓	
Chronic Disease/prevention & control					✓			
Chronic Disease/therapy					✓			
Cohort Studies			✓	✓		✓	✓	✓
Colorectal neoplasms/drug therapy								✓
Colorectal neoplasms/epidemiology				✓				✓
Colorectal Neoplasms/mortality	✓			✓				✓
Colorectal Neoplasms/prevention & control					✓			
Colorectal Neoplasms/therapy	✓							
Comorbidity	✓		✓	✓		✓	✓	
Comorbidity/trends		✓						

	Article							
MeSH term	Snyder 2013	Irizarry 2013	Bayliss 2010	Chiao 2010	Khan 2010	Hanchate 2009	Keating 2007	Earle 2004
Cross-Sectional Studies	✓							
Delivery of Health Care					✓			
Delivery of Health Care/trends						✓		
Delivery of Health Care/utilization						✓		
Diabetes Complications/epidemiology				✓				
Diabetes Complications/mortality				✓				
Diabetes Mellitus, Type 2/complications			✓					
Diabetes Mellitus, Type 2/drug therapy							✓	
Diabetes Mellitus, Type 2/epidemiology			✓				✓	
Diabetes Mellitus, Type 2/therapy			✓				✓	
Diabetes Mellitus/epidemiology		✓		✓				
Diabetes Mellitus/pathology				✓				
Diabetes Mellitus/therapy		✓		✓				
Disease Management		✓						
Disease Progression			✓	✓				
Female	✓	✓		✓	✓	✓	✓	✓
Follow-Up Studies						✓		
Great Britain					✓			
Health Status								✓
Haemoglobin A, Glycosylated/analysis							✓	
Humans	✓	✓	✓	✓	✓	✓	✓	✓
Hypoglycaemic Agents/therapeutic use							✓	
Incidence			✓					
Logistic Models	✓							
Longitudinal Studies			✓			✓		
Male	✓	✓	✓	✓	✓		✓	✓
Middle Aged		✓	✓	✓			✓	
Neoplasms/complications	✓		✓					

	Article							
MeSH term	Snyder 2013	Irizarry 2013	Bayliss 2010	Chiao 2010	Khan 2010	Hanchate 2009	Keating 2007	Earle 2004
Neoplasms/drug therapy							✓	
Neoplasms/epidemiology		✓	✓				✓	
Neoplasms/mortality	✓							
Neoplasms/prevention & control					✓			
Neoplasms/therapy	✓	✓	✓				✓	
Outcome and Process Assessment (Health Care)							✓	
Outcome Assessment (Health Care)				✓				
Patient Acceptance of Health Care						✓		
Patient Education as Topic/organization & administration		✓						
Prevalence				✓				
Preventive Health Services/utilization								✓
Primary Health Care					✓			
Program Development/methods		✓						
Prospective Studies						✓		
Prostatic Neoplasms/prevention & control					✓			
Quality Indicators, Health Care							✓	
Quality of Health Care	✓				✓			✓
Quality of Health Care/trends						✓		
Quality of Life				✓				
Registries							✓	
Research Design				✓				
Retrospective Studies	✓							
SEER-Program	✓							✓
Sickness Impact Profile				✓				
Survival Analysis				✓				
Survival Rate	✓							

	Article							
MeSH term	Snyder 2013	Irizarry 2013	Bayliss 2010	Chiao 2010	Khan 2010	Hanchate 2009	Keating 2007	Earle 2004
Survival Rate/trends						✓		
Survivors					✓		✓	
Survivors/statistics & numerical data								✓
United States/epidemiology		✓					✓	

Candidate Title Keywords for Systematic Review

	Article							
Title Word or String	**Snyder 2013**	**Irizarry 2013**	**Bayliss 2010**	**Chiao 2010**	**Khan 2010**	**Hanchate 2009**	**Keating 2007**	**Earle 2004**
Cancer	✓	✓	✓	✓	✓	✓	✓	✓
Chronic					✓			
Comorbid…	✓	✓		✓		✓		
Diabetes		✓	✓	✓			✓	
Quality	✓			✓	✓	✓	✓	
Surviv…	✓			✓		✓	✓	

CHAPTER 3 APPENDIX

Read Codes Used to Identify Diabetes

			Diabetes
5 Digit Read	**Included**	**Excluded**	**Text Description**
C10..	1	0	Diabetes mellitus
C100.	1	0	Diabetes mellitus with no mention of complication
C1000	1	0	Diabetes mellitus, juvenile type, no mention of complication
C1001	1	0	Maturity onset diabetes
C100z	1	0	Diabetes mellitus NOS with no mention of complication
C101.	1	0	Diabetes mellitus with ketoacidosis
C1010	1	0	Diabetes mellitus, juvenile type, with ketoacidosis
C1011	1	0	Diabetes mellitus, adult onset, with ketoacidosis
C101y	1	0	Other specified diabetes mellitus with ketoacidosis
C101z	1	0	Diabetes mellitus NOS with ketoacidosis
C102.	1	0	Diabetes mellitus with hyperosmolar coma
C1020	1	0	Diabetes mellitus, juvenile type, with hyperosmolar coma
C1021	1	0	Diabetes mellitus, adult onset, with hyperosmolar coma
C102z	1	0	Diabetes mellitus NOS with hyperosmolar coma
C103.	1	0	Diabetes mellitus with ketoacidotic coma
C1030	1	0	Diabetes mellitus, juvenile type, with ketoacidotic coma
C1031	1	0	Diabetes mellitus, adult onset, with ketoacidotic coma
C103y	1	0	Other specified diabetes mellitus with coma
C103z	1	0	Diabetes mellitus NOS with ketoacidotic coma
C104.	1	0	Diabetes mellitus with renal manifestation
C1040	1	0	Diabetes mellitus, juvenile type, with renal manifestation
C1041	1	0	Diabetes mellitus, adult onset, with renal manifestation
C104y	1	0	Other specified diabetes mellitus with renal complications
C104z	1	0	Diabetes mellitis with nephropathy NOS
C105.	1	0	Diabetes mellitus with ophthalmic manifestation
C1050	1	0	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C1051	1	0	Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y	1	0	Other specified diabetes mellitus with ophthalmic complicatn
C105z	1	0	Diabetes mellitus NOS with ophthalmic manifestation
C106.	1	0	Diabetes mellitus with neurological manifestation
C1060	1	0	Diabetes mellitus, juvenile, + neurological manifestation
C1061	1	0	Diabetes mellitus, adult onset, + neurological manifestation
C106y	1	0	Other specified diabetes mellitus with neurological comps
C106z	1	0	Diabetes mellitus NOS with neurological manifestation
C107.	1	0	Diabetes mellitus with gangrene
C1070	1	0	Diabetes mellitus, juvenile +peripheral circulatory disorder
C1071	1	0	Diabetes mellitus, adult, + peripheral circulatory disorder
C1072	1	0	Diabetes mellitus, adult with gangrene
C1073	1	0	IDDM with peripheral circulatory disorder

Diabetes

5 Digit Read	Included	Excluded	Text Description
C1074	1	0	NIDDM with peripheral circulatory disorder
C107y	1	0	Other specified diabetes mellitus with periph circ comps
C107z	1	0	Diabetes mellitus NOS with peripheral circulatory disorder
C108.	1	0	Type 1 diabetes mellitus
C1080	1	0	Type 1 diabetes mellitus with renal complications
C1081	1	0	Insulin-dependent diabetes mellitus with ophthalmic comps
C1082	1	0	Type 1 diabetes mellitus with neurological complications
C1083	1	0	Insulin dependent diabetes mellitus with multiple complicatn
C1084	1	0	Unstable insulin dependent diabetes mellitus
C1085	1	0	Type 1 diabetes mellitus with ulcer
C1086	1	0	Insulin dependent diabetes mellitus with gangrene
C1087	1	0	Insulin dependent diabetes mellitus with retinopathy
C1088	1	0	Type 1 diabetes mellitus - poor control
C1089	1	0	Type I diabetes mellitus maturity onset
C108A	1	0	Insulin-dependent diabetes without complication
C108B	1	0	Type I diabetes mellitus with mononeuropathy
C108C	1	0	Insulin dependent diabetes mellitus with polyneuropathy
C108D	1	0	Insulin dependent diabetes mellitus with nephropathy
C108E	1	0	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108F	1	0	Type I diabetes mellitus with diabetic cataract
C108G	1	0	Insulin dependent diab mell with peripheral angiopathy
C108H	1	0	Type I diabetes mellitus with arthropathy
C108J	1	0	Type I diabetes mellitus with neuropathic arthropathy
C108y	1	0	Other specified diabetes mellitus with multiple comps
C108z	1	0	Unspecified diabetes mellitus with multiple complications
C109.	1	0	NIDDM - Non-insulin dependent diabetes mellitus
C1090	1	0	Non-insulin-dependent diabetes mellitus with renal comps
C1091	1	0	Type 2 diabetes mellitus with ophthalmic complications
C1092	1	0	Non-insulin-dependent diabetes mellitus with neuro comps
C1093	1	0	Non-insulin-dependent diabetes mellitus with multiple comps
C1094	1	0	Non-insulin dependent diabetes mellitus with ulcer
C1095	1	0	Type 2 diabetes mellitus with gangrene
C1096	1	0	Type 2 diabetes mellitus with retinopathy
C1097	1	0	Non-insulin dependent diabetes mellitus - poor control
C1098	1	0	Reaven's syndrome
C1099	1	0	Type II diabetes mellitus without complication
C109A	1	0	Non-insulin dependent diabetes mellitus with mononeuropathy
C109B	1	0	Type II diabetes mellitus with polyneuropathy
C109C	1	0	Type II diabetes mellitus with nephropathy

Diabetes

5 Digit Read	Included	Excluded	Text Description
C109D	1	0	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109E	1	0	Non-insulin depend diabetes mellitus with diabetic cataract
C109F	1	0	Type II diabetes mellitus with peripheral angiopathy
C109G	1	0	Type 2 diabetes mellitus with arthropathy
C109H	1	0	Non-insulin dependent d m with neuropathic arthropathy
C109J	1	0	Insulin treated Type II diabetes mellitus
C109K	1	0	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10C.	1	0	Maturity onset diabetes in youth
C10D.	1	0	Diabetes mellitus autosomal dominant type 2
C10E.	1	0	Type 1 diabetes mellitus
C10E0	1	0	Insulin-dependent diabetes mellitus with renal complications
C10E1	1	0	Type I diabetes mellitus with ophthalmic complications
C10E2	1	0	Type 1 diabetes mellitus with neurological complications
C10E3	1	0	Type 1 diabetes mellitus with multiple complications
C10E4	1	0	Unstable type I diabetes mellitus
C10E5	1	0	Type 1 diabetes mellitus with ulcer
C10E6	1	0	Type I diabetes mellitus with gangrene
C10E7	1	0	Type I diabetes mellitus with retinopathy
C10E8	1	0	Insulin dependent diabetes mellitus - poor control
C10E9	1	0	Type I diabetes mellitus maturity onset
C10EA	1	0	Insulin-dependent diabetes without complication
C10EB	1	0	Type 1 diabetes mellitus with mononeuropathy
C10EC	1	0	Type 1 diabetes mellitus with polyneuropathy
C10ED	1	0	Insulin dependent diabetes mellitus with nephropathy
C10EE	1	0	Type 1 diabetes mellitus with hypoglycaemic coma
C10EF	1	0	Type 1 diabetes mellitus with diabetic cataract
C10EG	1	0	Type 1 diabetes mellitus with peripheral angiopathy
C10EH	1	0	Type 1 diabetes mellitus with arthropathy
C10EJ	1	0	Type 1 diabetes mellitus with neuropathic arthropathy
C10EK	1	0	Type 1 diabetes mellitus with persistent proteinuria
C10EL	1	0	Type 1 diabetes mellitus with persistent microalbuminuria
C10EM	1	0	Type I diabetes mellitus with ketoacidosis
C10EN	1	0	Type 1 diabetes mellitus with ketoacidotic coma
C10EP	1	0	Type 1 diabetes mellitus with exudative maculopathy
C10EQ	1	0	Type 1 diabetes mellitus with gastroparesis
C10ER	1	0	Latent autoimmune diabetes mellitus in adult
C10F.	1	0	Type 2 diabetes mellitus
C10F0	1	0	Type 2 diabetes mellitus with renal complications
C10F1	1	0	Type 2 diabetes mellitus with ophthalmic complications
C10F2	1	0	Type 2 diabetes mellitus with neurological complications
C10F3	1	0	Type 2 diabetes mellitus with multiple complications

Diabetes

5 Digit Read	Included	Excluded	Text Description
C10F4	1	0	Type II diabetes mellitus with ulcer
C10F5	1	0	Type 2 diabetes mellitus with gangrene
C10F6	1	0	Type II diabetes mellitus with retinopathy
C10F7	1	0	Type II diabetes mellitus - poor control
C10F9	1	0	Type 2 diabetes mellitus without complication
C10FA	1	0	Type 2 diabetes mellitus with mononeuropathy
C10FB	1	0	Type 2 diabetes mellitus with polyneuropathy
C10FC	1	0	Type II diabetes mellitus with nephropathy
C10FD	1	0	Type 2 diabetes mellitus with hypoglycaemic coma
C10FE	1	0	Type 2 diabetes mellitus with diabetic cataract
C10FF	1	0	Type 2 diabetes mellitus with peripheral angiopathy
C10FG	1	0	Type 2 diabetes mellitus with arthropathy
C10FH	1	0	Type 2 diabetes mellitus with neuropathic arthropathy
C10FJ	1	0	Insulin treated Type II diabetes mellitus
C10FK	1	0	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FL	1	0	Type 2 diabetes mellitus with persistent proteinuria
C10FM	1	0	Type 2 diabetes mellitus with persistent microalbuminuria
C10FN	1	0	Type 2 diabetes mellitus with ketoacidosis
C10FP	1	0	Type II diabetes mellitus with ketoacidotic coma
C10FQ	1	0	Type 2 diabetes mellitus with exudative maculopathy
C10FR	1	0	Type 2 diabetes mellitus with gastroparesis
C10FS	1	0	Maternally inherited diabetes mellitus
C10G.	1	0	Secondary pancreatic diabetes mellitus
C10G0	1	0	Secondary pancreatic diabetes mellitus without complication
C10H.	1	0	Diabetes mellitus induced by non-steroid drugs
C10H0	1	0	DM induced by non-steroid drugs without complication
C10M.	1	0	Lipoatrophic diabetes mellitus
C10M0	1	0	Lipoatrophic diabetes mellitus without complication
C10N.	1	0	Secondary diabetes mellitus
C10N0	1	0	Secondary diabetes mellitus without complication
C10N1	1	0	Cystic fibrosis related diabetes mellitus
C10y.	1	0	Diabetes mellitus with other specified manifestation
C10y0	1	0	Diabetes mellitus, juvenile, + other specified manifestation
C10y1	1	0	Diabetes mellitus, adult, + other specified manifestation
C10yy	1	0	Other specified diabetes mellitus with other spec comps
C10yz	1	0	Diabetes mellitus NOS with other specified manifestation
C10z.	1	0	Diabetes mellitus with unspecified complication
C10z0	1	0	Diabetes mellitus, juvenile type, + unspecified complication
C10z1	1	0	Diabetes mellitus, adult onset, + unspecified complication
C10zy	1	0	Other specified diabetes mellitus with unspecified comps
C10zz	1	0	Diabetes mellitus NOS with unspecified complication
Cyu2.	1	0	[X]Diabetes mellitus

Diabetes			
5 Digit Read	**Included**	**Excluded**	**Text Description**
Cyu20	1	0	[X]Other specified diabetes mellitus
Cyu23	1	0	[X]Unspecified diabetes mellitus with renal complications
L1805	1	0	Pre-existing diabetes mellitus, insulin-dependent
L1806	1	0	Pre-existing diabetes mellitus, non-insulin-dependent
L180X	1	0	Pre-existing diabetes mellitus, unspecified
Lyu29	1	0	[X]Pre-existing diabetes mellitus, unspecified
PKyP.	1	0	Diabetes insipidus, diabetes mellitus, optic atrophy and deafness
250 A	1	0	NIDDM (NON-INSULIN DEPENDENT DIABETES)
250 N	1	0	UNSTABLE DIABETIC
66A3.	1	0	Diabetic on diet only
66A4.	1	0	Diabetic on oral treatment
66A5.	1	0	Diabetic on insulin
66AI.	1	0	Diabetic - good control
66AJ.	1	0	Unstable diabetes
66AJ1	1	0	Brittle diabetes
66AJz	1	0	Diabetic - poor control NOS
66AK.	1	0	Diabetic - cooperative patient
66AL.	1	0	Diabetic-uncooperative patient
66AV.	1	0	Diabetic on insulin and oral treatment
21263	0	1	Diabetes Resolved
212H.	0	1	Diabetes Resolved

Read Codes Used to Identify Cancer

Breast Cancer			
5 Digit Read	**Included**	**Excluded**	**Text Description**
B34..	1	0	Malignant neoplasm of female breast
B340.	1	0	Malignant neoplasm of nipple and areola of female breast
B3400	1	0	Malignant neoplasm of nipple of female breast
B3401	1	0	Malignant neoplasm of areola of female breast
B340z	1	0	Malignant neoplasm of nipple or areola of female breast NOS
B341.	1	0	Malignant neoplasm of central part of female breast
B342.	1	0	Malignant neoplasm of upper-inner quadrant of female breast
B343.	1	0	Malignant neoplasm of lower-inner quadrant of female breast
B344.	1	0	Malignant neoplasm of upper-outer quadrant of female breast
B345.	1	0	Malignant neoplasm of lower-outer quadrant of female breast
B346.	1	0	Malignant neoplasm of axillary tail of female breast
B347.	1	0	Malignant neoplasm, overlapping lesion of breast
B34y.	1	0	Malignant neoplasm of other site of female breast
B34y0	1	0	Malignant neoplasm of ectopic site of female breast
B34yz	1	0	Malignant neoplasm of other site of female breast NOS

B34z.	1	0	Malignant neoplasm of female breast NOS

Colorectal Cancer

5 Digit Read	Included	Excluded	Text Description
B13..	1	0	Malignant neoplasm of colon
B130.	1	0	Malignant neoplasm of hepatic flexure of colon
B131.	1	0	Malignant neoplasm of transverse colon
B132.	1	0	Malignant neoplasm of descending colon
B133.	1	0	Malignant neoplasm of sigmoid colon
B134.	1	0	Malignant neoplasm of caecum
B135.	1	0	Malignant neoplasm of appendix
B136.	1	0	Malignant neoplasm of ascending colon
B137.	1	0	Malignant neoplasm of splenic flexure of colon
B138.	1	0	Malignant neoplasm, overlapping lesion of colon
B139.	1	0	Hereditary nonpolyposis colon cancer
B13y.	1	0	Malignant neoplasm of other specified sites of colon
B13z.	1	0	Malignant neoplasm of colon NOS
B141.	1	0	Malignant neoplasm of rectum

Prostate Cancer

5 Digit Read	Included	Excluded	Text Description
B46..	1	0	Malignant neoplasm of prostate

Read Codes Used to Identify Other Cardiovascular Conditions

Atrial Fibrillation

5 Digit Read	Included	Excluded	Text Description
G573.	1	0	Atrial fibrillation and flutter
G5730	1	0	Atrial fibrillation
G5732	1	0	Paroxysmal atrial fibrillation
G5733	1	0	Non-rheumatic atrial fibrillation
G5734	1	0	Permanent atrial fibrillation
G5735	1	0	Persistent atrial fibrillation
G573z	1	0	Atrial fibrillation and flutter NOS
212R.	0	1	Atrial fibrillation resolved

Coronary Heart Disease

5 Digit Read	Included	Excluded	Text Description
G3...	1	0	Ischaemic heart disease
G30..	1	0	Acute myocardial infarction
G300.	1	0	Acute anterolateral infarction
G301.	1	0	Other specified anterior myocardial infarction
G3010	1	0	Acute anteroapical infarction

Coronary Heart Disease

5 Digit Read	Included	Excluded	Text Description
G3011	1	0	Acute anteroseptal infarction
G301z	1	0	Anterior myocardial infarction NOS
G302.	1	0	Acute inferolateral infarction
G303.	1	0	Acute inferoposterior infarction
G304.	1	0	Posterior myocardial infarction NOS
G305.	1	0	Lateral myocardial infarction NOS
G306.	1	0	True posterior myocardial infarction
G307.	1	0	Acute subendocardial infarction
G3070	1	0	Acute non-Q wave infarction
G3071	1	0	Acute non-ST segment elevation myocardial infarction
G308.	1	0	Inferior myocardial infarction NOS
G309.	1	0	Acute Q-wave infarct
G30A.	1	0	Mural thrombosis
G30B.	1	0	Acute posterolateral myocardial infarction
G30X.	1	0	Acute transmural myocardial infarction of unspecified site
G30X0	1	0	Acute ST segment elevation myocardial infarction
G30y.	1	0	Other acute myocardial infarction
G30y0	1	0	Acute atrial infarction
G30y1	1	0	Acute papillary muscle infarction
G30y2	1	0	Acute septal infarction
G30yz	1	0	Other acute myocardial infarction NOS
G30z.	1	0	Acute myocardial infarction NOS
G31..	1	0	Other acute and subacute ischaemic heart disease
G310.	1	0	Postmyocardial infarction syndrome
G311.	1	0	Preinfarction syndrome
G3110	1	0	Myocardial infarction aborted
G3111	1	0	Unstable angina
G3112	1	0	Angina at rest
G3113	1	0	Refractory angina
G3114	1	0	Worsening angina
G3115	1	0	Acute coronary syndrome
G311z	1	0	Preinfarction syndrome NOS
G312.	1	0	Coronary thrombosis not resulting in myocardial infarction
G31y.	1	0	Other acute and subacute ischaemic heart disease
G31y0	1	0	Acute coronary insufficiency
G31y1	1	0	Microinfarction of heart
G31y2	1	0	Subendocardial ischaemia
G31y3	1	0	Transient myocardial ischaemia
G31yz	1	0	Other acute and subacute ischaemic heart disease NOS
G32..	1	0	Old myocardial infarction
G33..	1	0	Angina pectoris

Coronary Heart Disease

5 Digit Read	Included	Excluded	Text Description
G330.	1	0	Angina decubitus
G3300	1	0	Nocturnal angina
G330z	1	0	Angina decubitus NOS
G33z.	1	0	Angina pectoris NOS
G33z0	1	0	Status anginosus
G33z1	1	0	Stenocardia
G33z2	1	0	Syncope anginosa
G33z3	1	0	Angina on effort
G33z4	1	0	Ischaemic chest pain
G33z5	1	0	Post infarct angina
G33z6	1	0	New onset angina
G33z7	1	0	Stable angina
G33zz	1	0	Angina pectoris NOS
G34..	1	0	Other chronic ischaemic heart disease
G340.	1	0	Coronary atherosclerosis
G3400	1	0	Single coronary vessel disease
G3401	1	0	Double coronary vessel disease
G342.	1	0	Atherosclerotic cardiovascular disease
G343.	1	0	Ischaemic cardiomyopathy
G344.	1	0	Silent myocardial ischaemia
G34y.	1	0	Other specified chronic ischaemic heart disease
G34y0	1	0	Chronic coronary insufficiency
G34y1	1	0	Chronic myocardial ischaemia
G34yz	1	0	Other specified chronic ischaemic heart disease NOS
G34z.	1	0	Other chronic ischaemic heart disease NOS
G34z0	1	0	Asymptomatic coronary heart disease
G35..	1	0	Subsequent myocardial infarction
G350.	1	0	Subsequent myocardial infarction of anterior wall
G351.	1	0	Subsequent myocardial infarction of inferior wall
G353.	1	0	Subsequent myocardial infarction of other sites
G35X.	1	0	Subsequent myocardial infarction of unspecified site
G36..	1	0	Certain current complications following acute myocardial infarction
G360.	1	0	Haemopericardium as current complication following acute myocardial infarction
G361.	1	0	Atrial septal defect as current complication following acute myocardial infarction
G362.	1	0	Ventricular septal defect as current complication following acute myocardial infarction
G363.	1	0	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
G364.	1	0	Rupture of chordae tendinae as current complication following acute myocardial infarction

Coronary Heart Disease

5 Digit Read	Included	Excluded	Text Description
G365.	1	0	Rupture of papillary muscle as current complication following acute myocardial infarction
G366.	1	0	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
G38..	1	0	Postoperative myocardial infarction
G380.	1	0	Postoperative transmural myocardial infarction of anterior wall
G381.	1	0	Postoperative transmural myocardial infarction of inferior wall
G382.	1	0	Postoperative transmural myocardial infarction of other sites
G383.	1	0	Postoperative transmural myocardial infarction of unspecified site
G384.	1	0	Postoperative subendocardial myocardial infarction
G38z.	1	0	Postoperative myocardial infarction, unspecified
G3y..	1	0	Other specified ischaemic heart disease
G3z..	1	0	Ischaemic heart disease NOS
Gyu3.	1	0	Text Description Not Included in Pegasus Medical Look-Up Table
Gyu30	1	0	Text Description Not Included in Pegasus Medical Look-Up Table
Gyu31	1	0	Text Description Not Included in Pegasus Medical Look-Up Table
Gyu32	1	0	Text Description Not Included in Pegasus Medical Look-Up Table
Gyu33	1	0	Text Description Not Included in Pegasus Medical Look-Up Table
Gyu34	1	0	Text Description Not Included in Pegasus Medical Look-Up Table
Gyu35	1	0	Text Description Not Included in Pegasus Medical Look-Up Table
Gyu36	1	0	Text Description Not Included in Pegasus Medical Look-Up Table

Heart Failure

5 Digit Read	Included	Excluded	Text Description
G58..	1	0	Heart failure
G580.	1	0	Congestive heart failure
G5800	1	0	Acute congestive heart failure
G5801	1	0	Chronic congestive heart failure
G5802	1	0	Decompensated cardiac failure
G5803	1	0	Compensated cardiac failure
G5804	1	0	Congestive heart failure due to valvular disease
G581.	1	0	Left ventricular failure
G5810	1	0	Acute left ventricular failure
G582.	1	0	Acute heart failure

Heart Failure

5 Digit Read	Included	Excluded	Text Description
G583.	1	0	Heart failure with normal ejection fraction
G584	1	0	Right ventricular failure
G58z.	1	0	Heart failure NOS
G1yz1	1	0	Rheumatic left ventricular failure
662f.	1	0	New York Heart Association classification - class I
662g.	1	0	New York Heart Association classification - class II
662h.	1	0	New York Heart Association classification - class IV
662i.	1	0	New York Heart Association classification - class III
585f.	1	0	Echocardiogram shows left ventricular systolic dysfunction
G5yy9	1	0	Left ventricular systolic dysfunction

Hypertension

5 Digit Read	Included	Excluded	Text Description
G2...	1	0	Hypertensive disease
G20..	1	0	Essential hypertension
G200.	1	0	Malignant essential hypertension
G201.	1	0	Benign essential hypertension
G202.	1	0	Systolic hypertension
G203.	1	0	Diastolic hypertension
G20z.	1	0	Essential hypertension NOS
G24..	1	0	Secondary hypertension
G240.	1	0	Secondary malignant hypertension
G240z	1	0	Secondary malignant hypertension NOS
G241.	1	0	Secondary benign hypertension
G241z	1	0	Secondary benign hypertension NOS
G244.	1	0	Hypertension secondary to endocrine disorders
G24z.	1	0	Secondary hypertension NOS
G24z0	1	0	Secondary renovascular hypertension NOS
G24zz	1	0	Secondary hypertension NOS
G2y..	1	0	Other specified hypertensive disease
G2z..	1	0	Hypertensive disease NOS
21261	0	1	Hypertension resolved
212K.	0	1	Hypertension resolved
G27..	1	0	Hypertension resistant to drug therapy

Stroke/Transient Ischaemic Attack

5 Digit Read	Included	Excluded	Text Description
Fyu55	1	0	[X]Other transnt cerebral ischaemic attacks+related syndroms
G61..	1	0	Intracerebral haemorrhage
G610.	1	0	Cortical haemorrhage
G611.	1	0	Internal capsule haemorrhage
G612.	1	0	Basal nucleus haemorrhage
G613.	1	0	Cerebellar haemorrhage
G614.	1	0	Pontine haemorrhage

Stroke/Transient Ischaemic Attack

5 Digit Read	Included	Excluded	Text Description
G615.	1	0	Bulbar haemorrhage
G616.	1	0	External capsule haemorrhage
G618.	1	0	Intracerebral haemorrhage, multiple localized
G61X.	1	0	Intracerebral haemorrhage in hemisphere, unspecified
G61X0	1	0	Left sided intracerebral haemorrhage, unspecified
G61X1	1	0	Right sided intracerebral haemorrhage, unspecified
G61z.	1	0	Intracerebral haemorrhage NOS
G63y.	1	0	Other precerebral artery occlusion
G63y0	1	0	Cerebral infarct due to thrombosis of precerebral arteries
G63y1	1	0	Cerebral infarction due to embolism of precerebral arteries
G64..	1	0	Cerebral arterial occlusion
G640.	1	0	Cerebral thrombosis
G6400	1	0	Cerebral infarction due to thrombosis of cerebral arteries
G641.	1	0	Cerebral embolus
G6410	1	0	Cerebral infarction due to embolism of cerebral arteries
G64z.	1	0	Cerebellar infarction
G64z0	1	0	Brainstem infarction
G64z1	1	0	Wallenberg syndrome
G64z2	1	0	Left sided cerebral infarction
G64z3	1	0	Right sided cerebral infarction
G64z4	1	0	Infarction of basal ganglia
G65..	1	0	Transient ischaemic attack
G650.	1	0	Basilar artery syndrome
G651.	1	0	Vertebral artery syndrome
G6510	1	0	Vertebro-basilar artery syndrome
G652.	1	0	Subclavian steal syndrome
G653.	1	0	Carotid artery syndrome hemispheric
G654.	1	0	Multiple and bilateral precerebral artery syndromes
G656.	1	0	Vertebrobasilar insufficiency
G657.	1	0	Carotid territory transient ischaemic attack
G65y.	1	0	Other transient cerebral ischaemia
G65z.	1	0	Transient cerebral ischaemia NOS
G65z0	1	0	Impending cerebral ischaemia
G65z1	1	0	Intermittent cerebral ischaemia
G65zz	1	0	Transient cerebral ischaemia NOS
G66..	1	0	CVA unspecified
G660.	1	0	Middle cerebral artery syndrome
G661.	1	0	Anterior cerebral artery syndrome
G662.	1	0	Posterior cerebral artery syndrome
G663.	1	0	Brain stem stroke syndrome
G664.	1	0	Cerebellar stroke syndrome
G665.	1	0	Pure motor lacunar syndrome
G666.	1	0	Pure sensory lacunar syndrome
G667.	1	0	Left sided CVA

Stroke/Transient Ischaemic Attack

5 Digit Read	Included	Excluded	Text Description
G668.	1	0	Right sided CVA
G676.	1	0	Nonpyogenic venous sinus thrombosis
G6760	1	0	Cereb infarct due cerebral venous thrombosis, nonpyogenic
G6W..	1	0	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..	1	0	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu63	1	0	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu64	1	0	[X]Other cerebral infarction
Gyu65	1	0	[X]Occlusion and stenosis of other precerebral arteries
Gyu66	1	0	[X]Occlusion and stenosis of other cerebral arteries
Gyu6F	1	0	[X]intracerebral haemorrhage in hemisphere, unspecified
Gyu6G	1	0	[X]Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
ZV12D	1	0	[V]Personal history of transient ischaemic attack
Zv12D	1	0	[V]Personal history of transient ischaemic attack

Read Codes Used to Identify Microvascular Complications

Microvascular Complications

5 Digit Read	Type	Text Description
2BBP.	1	O/E - right eye background diabetic retinopathy
2BBQ.	1	O/E - left eye background diabetic retinopathy
2BBR.	1	O/E - right eye preproliferative diabetic retinopathy
2BBS.	1	O/E - left eye preproliferative diabetic retinopathy
2BBT.	1	O/E - right eye proliferative diabetic retinopathy
2BBV.	1	O/E - left eye proliferative diabetic retinopathy
2BBY.	1	O/E - referable retinopathy
2BBa.	1	O/E- non-referable retinopathy
2BBk.	1	O/E - right eye stable treated prolif diabetic retinopathy
2BBl.	1	O/E - left eye stable treated prolif diabetic retinopathy
2BBo.	1	O/E - sight threatening diabetic retinopathy
2BBr.	1	Impaired vision due to diabetic retinopathy
C1096	1	Type 2 diabetes mellitus with retinopathy
C1096	1	Type 2 diabetes mellitus with retinopathy
C1096	1	Type 2 diabetes mellitus with retinopathy
C10F6	1	Type II diabetes mellitus with retinopathy
C10F6	1	Type II diabetes mellitus with retinopathy
F420.	1	Diabetic retinopathy
F4200	1	Background diabetic retinopathy
F4201	1	Proliferative diabetic retinopathy
F4202	1	Preproliferative diabetic retinopathy
F4206	1	Non proliferative diabetic retinopathy
F4207	1	High risk proliferative diabetic retinopathy
F4208	1	High risk non proliferative diabetic retinopathy
F420z	1	Diabetic retinopathy NOS
F422z	1	Proliferative retinopathy NOS
C106.	2	Diabetes mellitus with polyneuropathy
C106.	2	Diabetes mellitus with polyneuropathy
C106.	2	Diabetes mellitus with polyneuropathy
C106.	2	Diabetes mellitus with polyneuropathy
C109A	2	Type II diabetes mellitus with mononeuropathy
C109A	2	Type II diabetes mellitus with mononeuropathy
C109B	2	Type II diabetes mellitus with polyneuropathy
C109B	2	Type II diabetes mellitus with polyneuropathy
C109H	2	Type II diabetes mellitus with neuropathic arthropathy
C109H	2	Type II diabetes mellitus with neuropathic arthropathy
C109H	2	Type II diabetes mellitus with neuropathic arthropathy
C10FA	2	Type 2 diabetes mellitus with mononeuropathy
C10FA	2	Type 2 diabetes mellitus with mononeuropathy
C10FB	2	Type II diabetes mellitus with polyneuropathy
C10FB	2	Type II diabetes mellitus with polyneuropathy

Microvascular Complications

5 Digit Read	Type	Text Description
C10FH	2	Type 2 diabetes mellitus with neuropathic arthropathy
F1711	2	Autonomic neuropathy due to diabetes
F171z	2	Peripheral autonomic neuropathy due to disease NOS
F366.	2	Polyneuropathy
F367.	2	Peripheral neuropathy
F372.	2	Polyneuropathy in diabetes
F372.	2	Polyneuropathy in diabetes
F372.	2	Polyneuropathy in diabetes
F3720	2	Acute painful diabetic neuropathy
F3721	2	Chronic painful diabetic neuropathy
F3722	2	Asymptomatic diabetic neuropathy
F374z	2	Polyneuropathy in disease NOS
F37y1	2	Axonal sensorimotor neuropathy
F37z.	2	Polyneuropathy unspecified
F37z.	2	Polyneuropathy unspecified
F3y0.	2	Diabetic mononeuropathy
Fyu6B	2	[X]Other mononeuropathies of lower limb
Fyu7C	2	[X] Polyneuropathy; unspecified
FyuAC	2	[X]Autonomic neuropathy/endocrine+metabolic diseases CE
N035.	2	Neuropathic arthropathy
N035.	2	Neuropathic arthropathy
N035.	2	Neuropathic arthropathy
N2423	2	Neuropathic pain
C104.	3	Diabetic nephropathy
C104.	3	Diabetic nephropathy
C104z	3	Diabetes mellitus with nephropathy NOS
C108D	3	Insulin dependent diabetes mellitus with nephropathy
C108D	3	Insulin dependent diabetes mellitus with nephropathy
C109C	3	Type 2 diabetes mellitus with nephropathy
C109C	3	Type 2 diabetes mellitus with nephropathy
C109C	3	Type 2 diabetes mellitus with nephropathy
C10FC	3	Type 2 diabetes mellitus with nephropathy
C10FC	3	Type 2 diabetes mellitus with nephropathy
K02..	3	Nephropathy - chronic
K02..	3	Nephropathy - chronic
K02..	3	Nephropathy - chronic
K03..	3	Nephropathy; unspecified
K03..	3	Nephropathy; unspecified
K03..	3	Nephropathy; unspecified
K08yA	3	Proteinuric diabetic nephropathy
1Z13.	4	Chronic kidney disease stage 4
1Z14.	4	Chronic kidney disease stage 5
1Z1H.	4	CKD stage 4 with proteinuria
1Z1H.	4	CKD stage 4 with proteinuria

Microvascular Complications

5 Digit Read	Type	Text Description
1Z1J.	4	Chronic kidney disease stage 4 without proteinuria
1Z1J.	4	Chronic kidney disease stage 4 without proteinuria
1Z1K.	4	Chronic kidney disease stage 5 with proteinuria
1Z1K.	4	Chronic kidney disease stage 5 with proteinuria
1Z1L.	4	Chronic kidney disease stage 5 without proteinuria
1Z1L.	4	Chronic kidney disease stage 5 without proteinuria
K054.	4	Chronic kidney disease stage 4
K055.	4	Chronic kidney disease stage 5

Read Codes Used to Identify Macrovascular Complications

Macrovascular Complications

5 Digit Read	Type	Text Description
readcode5	type	description
G70..	1	Atherosclerosis
G70..	1	Atherosclerosis
G700.	1	Aortic atherosclerosis
G700.	1	Aortic atherosclerosis
G73..	1	Ischaemia of legs
G73..	1	Ischaemia of legs
G73..	1	Ischaemia of legs
G73..	1	Ischaemia of legs
G73y.	1	Other specified peripheral vascular disease
G73yz	1	Other specified peripheral vascular disease NOS
G73z.	1	Peripheral vascular disease NOS
G73z0	1	Intermittent claudication
G73z0	1	Intermittent claudication
G73z0	1	Intermittent claudication
G73zz	1	Peripheral vascular disease NOS
G742z	1	Peripheral arterial embolism and thrombosis NOS
G74y3	1	Embolism and thrombosis of the iliac artery unspecified
G76z0	1	Iliac artery occlusion
Gyu74	1	[X]Other specified peripheral vascular diseases
G30..	2	Cardiac rupture following myocardial infarction (MI)
G30..	2	Cardiac rupture following myocardial infarction (MI)
G30..	2	Cardiac rupture following myocardial infarction (MI)
G30..	2	Cardiac rupture following myocardial infarction (MI)
G30..	2	Cardiac rupture following myocardial infarction (MI)
G30..	2	Cardiac rupture following myocardial infarction (MI)
G30..	2	Cardiac rupture following myocardial infarction (MI)
G30..	2	Cardiac rupture following myocardial infarction (MI)
G300.	2	Acute anterolateral infarction
G301.	2	Other specified anterior myocardial infarction

Macrovascular Complications

5 Digit Read	Type	Text Description
G3010	2	Acute anteroapical infarction
G3011	2	Acute anteroseptal infarction
G301z	2	Anterior myocardial infarction NOS
G302.	2	Acute inferolateral infarction
G303.	2	Acute inferoposterior infarction
G304.	2	Posterior myocardial infarction NOS
G305.	2	Lateral myocardial infarction NOS
G306.	2	True posterior myocardial infarction
G307.	2	Acute subendocardial infarction
G3070	2	Acute non-Q wave infarction
G3071	2	Acute non-ST segment elevation myocardial infarction
G308.	2	Inferior myocardial infarction NOS
G309.	2	Acute Q-wave infarct
G30B.	2	Acute posterolateral myocardial infarction
G30X.	2	Acute transmural myocardial infarction of unspecif site
G30X0	2	Acute ST segment elevation myocardial infarction
G30y.	2	Other acute myocardial infarction
G30y1	2	Acute papillary muscle infarction
G30y2	2	Acute septal infarction
G30yz	2	Other acute myocardial infarction NOS
G30z.	2	Acute myocardial infarction NOS
G3110	2	Myocardial infarction aborted
G3110	2	Myocardial infarction aborted
G3115	2	Acute coronary syndrome
G35..	2	Subsequent myocardial infarction
G350.	2	Subsequent myocardial infarction of anterior wall
G351.	2	Subsequent myocardial infarction of inferior wall
G353.	2	Subsequent myocardial infarction of other sites
G35X.	2	Subsequent myocardial infarction of unspecified site
G360.	2	Haemopericardium/current comp folow acut myocard infarct
G362.	2	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.	2	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.	2	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.	2	Rupture papillary muscle/curr comp fol acute myocard infarct
G38..	2	Postoperative myocardial infarction
G380.	2	Postoperative transmural myocardial infarction anterior wall
G381.	2	Postoperative transmural myocardial infarction inferior wall
G384.	2	Postoperative subendocardial myocardial infarction
G38z.	2	Postoperative myocardial infarction; unspecified
G5740	2	Cardiac arrest-ventricular fibrillation
G5740	2	Cardiac arrest-ventricular fibrillation
G575.	2	Cardiac arrest
G575.	2	Cardiac arrest
G575.	2	Cardiac arrest

Macrovascular Complications

5 Digit Read	Type	Text Description
G5750	2	Cardiac arrest with successful resuscitation
G5751	2	Sudden cardiac death; so described
G575z	2	Cardiac arrest; unspecified
Gyu34	2	[X]Acute transmural myocardial infarction of unspecif site
Gyu36	2	[X]Subsequent myocardial infarction of unspecified site
G61..	3	Intracerebral haemorrhage
G61..	3	Intracerebral haemorrhage
G61..	3	Intracerebral haemorrhage
G610.	3	Cortical haemorrhage
G611.	3	Internal capsule haemorrhage
G612.	3	Basal nucleus haemorrhage
G613.	3	Cerebellar haemorrhage
G614.	3	Pontine haemorrhage
G615.	3	Bulbar haemorrhage
G616.	3	External capsule haemorrhage
G617.	3	Intracerebral haemorrhage; intraventricular
G618.	3	Intracerebral haemorrhage; multiple localized
G61X.	3	Intracerebral haemorrhage in hemisphere; unspecified
G61X0	3	Left sided intracerebral haemorrhage; unspecified
G61X1	3	Right sided intracerebral haemorrhage; unspecified
G61z.	3	Intracerebral haemorrhage NOS
G63..	3	Infarction - precerebral
G63..	3	Infarction - precerebral
G63..	3	Infarction - precerebral
G632.	3	Vertebral artery occlusion
G63y0	3	Cerebral infarct due to thrombosis of precerebral arteries
G63y1	3	Cerebral infarction due to embolism of precerebral arteries
G64..	3	Stroke due to cerebral arterial occlusion
G64..	3	Stroke due to cerebral arterial occlusion
G64..	3	Stroke due to cerebral arterial occlusion
G64..	3	Stroke due to cerebral arterial occlusion
G640.	3	Cerebral thrombosis
G6400	3	Cerebral infarction due to thrombosis of cerebral arteries
G641.	3	Cerebral embolism
G641.	3	Cerebral embolism
G6410	3	Cerebral infarction due to embolism of cerebral arteries
G64z.	3	Cerebellar infarction
G64z.	3	Cerebellar infarction
G64z.	3	Cerebellar infarction
G64z0	3	Brainstem infarction
G64z1	3	Lateral medullary syndrome
G64z1	3	Lateral medullary syndrome
G64z2	3	Left sided cerebral infarction
G64z3	3	Right sided cerebral infarction

Macrovascular Complications

5 Digit Read	Type	Text Description
G64z4	3	Infarction of basal ganglia
G66..	3	Stroke and cerebrovascular accident unspecified
G66..	3	Stroke and cerebrovascular accident unspecified
G66..	3	Stroke and cerebrovascular accident unspecified
G66..	3	Stroke and cerebrovascular accident unspecified
G661.	3	Anterior cerebral artery syndrome
G662.	3	Posterior cerebral artery syndrome
G663.	3	Brain stem stroke syndrome
G664.	3	Cerebellar stroke syndrome
G665.	3	Pure motor lacunar syndrome
G666.	3	Pure sensory lacunar syndrome
G667.	3	Left sided CVA
G668.	3	Right sided CVA
G671.	3	Generalised ischaemic cerebrovascular disease NOS
G6710	3	Acute cerebrovascular insufficiency NOS
G671z	3	Generalised ischaemic cerebrovascular disease NOS
G6760	3	Cereb infarct due cerebral venous thrombosis; nonpyogenic
G6W..	3	Cereb infarct due unsp occlus/stenos precerebr arteries
G6X..	3	Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu62	3	[X]Other intracerebral haemorrhage
Gyu63	3	[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs
Gyu64	3	[X]Other cerebral infarction
Gyu6F	3	[X]Intracerebral haemorrhage in hemisphere; unspecified
Gyu6G	3	[X]Cereb infarct due unsp occlus/stenos precerebr arteries
7L06.	4	Amputation of leg
7L064	4	Amputation below knee
7L064	4	Amputation below knee
7L064	4	Amputation below knee
7L07.	4	Amputation of foot
7L070	4	Syme amputation of foot through ankle
7L070	4	Syme amputation of foot through ankle
7L073	4	Amputation through metatarsal bones
7L073	4	Amputation through metatarsal bones
7L073	4	Amputation through metatarsal bones
7L07y	4	Other specified amputation of foot
7L07z	4	Amputation of foot NOS
7L07z	4	Amputation of foot NOS
7L08.	4	Amputation of toe
7L08.	4	Amputation of toe
7L080	4	Amputation great toe
7L080	4	Amputation great toe
7L081	4	Amputation of phalanx of toe
7L083	4	Amputation lesser toe
7L08y	4	Other specified amputation of toe

Macrovascular Complications

5 Digit Read	Type	Text Description
7L08z	4	Amputation of toe NOS
7L08z	4	Amputation of toe NOS
7L0L2	4	Amputation of supernumerary toe
M2710	4	Ischaemic ulcer diabetic foot
R0543	4	[D]Widespread diabetic foot gangrene

ISAC Protocol – Amended Version (Approved)

ISAC APPLICATION FORM
PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

ISAC use only: Protocol Number Date submitted		**IMPORTANT** **If you have any queries, please contact ISAC Secretariat:** ISAC@cprd.com

1. Study Title Quality and Outcomes of Care for Chronic Conditions in Older Patients Diagnosed with Breast, Colorectal, or Prostate Cancer Compared to Non-Cancer Controls: An Observational Study Using the Clinical Practice Research Datalink.

2. Principal Investigator (full name, job title, organisation & e-mail address for correspondence regarding this protocol) Dr Robert I. Griffiths, MS, ScD, Senior Research Fellow, Nuffield Department of Primary Care Health Sciences, New Radcliffe House, 2nd Floor, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG 01865 289 300 *Email:* robert.griffiths@conted.ox.ac.uk

3. Affiliation (full address): Nuffield Department of Primary Care Health Sciences, New Radcliffe House, 2nd Floor, Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG

4. Protocol's Author (if different from the principal investigator)

5. List of all investigators/collaborators (*please list the names, affiliations and e-mail addresses* of all collaborators*, other than the principal investigator)

Clare R. Bankhead, DPhil, MSc. University Research Lecturer. University of Oxford.

Email: clare.bankhead@phc.ox.ac.uk
Nancy L. Keating, MD, MPH. Associate Professor of Medicine and Health Policy. Harvard University.
Email: keating@hcp.med.harvard.edu
Nada F. Khan, DPhil. Kings College London. *Email:* nada.khan@kcl.ac.uk
Bernadette Lavery, MD. Medical Director. Thames Valley Cancer Network. *Email:* bernadette.lavery@nhs.net
Richard J. Stevens, MSc PhD. University Research Lecturer, Deputy Director, Statistics Group. University of Oxford
Email: Richard.stevens@phc.ox.ac.uk
Jose M. Valderas, MD, MPH, PhD. University of Exeter Medical School. *Email:* J.M.Valderas@exeter.ac.uk

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

6. Type of Institution (please tick one box below)

Academia	☒	Research Service Provider	☐	Pharmaceutical Industry	☐
NHS	☐	Government Departments	☐	Others	☐

7. Financial Sponsor of study

Pharmaceutical Industry *(please specify)* ☐ Academia *(please specify)* ☐

Government / NHS *(please specify)* ☐ None ☐

Other *(please specify)* ☒ Cancer Research UK (Funding Awarded)

8. Data source *(please tick one box below)*

Sponsor has on-line access ☐ Purchase of ad hoc dataset ☒

Commissioned study ☐

Other ☐ *(please specify)*

9. Has this protocol been peer reviewed by another Committee?

Yes* ☒ No ☐

A version of this protocol has been reviewed by the Population Research Committee at Cancer Research UK. The protocol was submitted there November 2012. It underwent peer-review in January 2013, and we received reviewer comments at that time. We addressed the reviewers' comments. In late April/early May 2013, Cancer Research UK's Advisory Board met to review the application, the reviews, and our responses. The outcome of this review was that Cancer Research UK awarded a grant in full to conduct the study. We note that we had originally exemplified the list of cancer comorbidities with cardiovascular conditions. In order to more accurately reflect the breadth of scope primary care, this application includes also respiratory, and musculoskeletal conditions, mental health and other relevant conditions.

** Please state in your protocol the name of the reviewing Committee(s) and provide an outline of the review process and outcome.*

10. Type of Study *(please tick all the relevant boxes which apply)*

Adverse Drug Reaction/Drug Safety ☐ Drug Use ☐ Disease Epidemiology ☐

Drug Effectiveness ☐ Pharmacoeconomic ☐ Other ☒

Quality and outcomes of care for chronic conditions in patients diagnosed with cancer

11. This study is intended for:

Publication in peer reviewed journals ☒ Presentation at scientific conference ☒

Presentation at company/institutional meetings ☐ Other

12. Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?

Yes ☒ No ☐

13. If you are seeking access to data held under the CPRD Data Linkage Scheme*, please select the source(s) of linked data being requested.

☒ Hospital Episode Statistics ☐ Cancer Registry Data**

☐ MINAP ☒ ONS Mortality Data

☒ Index of Multiple Deprivation/ Townsend Score

☐ Mother Baby Link ☐ Other: (please specify)

We hereby consent to have our study title and study institution published on the UK Cancer Registry website.

** As part of the ISAC review of linkages, the protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.*

***Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss this requirement further.*

14. If you are seeking access to data held under the CPRD Data Linkage Scheme, have you already discussed your request with a member of the Research team?

Yes ☒ No* ☐

**Please contact the CPRD Research Team on +44 (20) 3080 6383 or email kc@cprd.com to discuss your requirements before submitting your application.*

Please list below the name of the person/s at the CPRD with whom you have discussed your request.

Helen Strongman, Arlene Gallagher

15. If you are seeking access to data held under the CPRD Data Linkage Scheme, please provide the following information:

The number of linked datasets requested: 4

A synopsis of the purpose(s) for which the linkages are required:

Since our analyses encompass quality of care, hospitalization, and mortality outcomes we request access to the HES and ONS mortality. We propose accounting for Townsend score in our multivariate analyses. Therefore, we request also IMD/Townsend.

Is linkage to a local dataset with <1 million patients being requested?

Yes* ☐ No ☒

** If yes, please provide further details:*

16. If you have requested linked data sets, please indicate whether the Principal Investigator or any of the collaborators listed in response to question 5 above, have access to any of the linked datasets in a patient identifiable form, or associated with a patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

17. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** Please indicate what will be required:*

Completion of questionnaires by the GP[ψ] Yes ☐ No ☐

Provision of anonymised records (e.g. hospital discharge summaries) Yes ☐ No ☐

Other (please describe)

ψ Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.

18. Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*

*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

19. Does this study involve linking to patient *identifiable* data from other sources?

Yes ☐ No ☒

20. Does this study require contact with patients in order for them to complete a questionnaire?

Yes ☐ No ☒

N.B. Any questionnaire for completion by patients must be approved by ISAC before circulation for completion.

21. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected*

22. Experience/expertise available

Please complete the following questions to indicate the experience/expertise available within the team of researchers actively involved in the proposed research, including analysis of data and interpretation of results

	Previous GPRD/CPRD Studies	Publications using GPRD/CPRD data
None	☐	☐
1-3	☐	☐
>3	☒	☒

	Yes	No
Is statistical expertise available within the research team?	☒	☐

If yes, please outline level of experience

Richard Stevens, Deputy Director Statistics Group, Department of Primary Care Health Sciences

Is experience of handling large data sets (>1 million records) available within the research team?	☒	☐

If yes, please outline level of experience

Jose Valderas approximately 19 years clinical experience; 10 years with UK and US databases

Robert Griffiths approximately 25 years experience with US databases

Nada Khan approximately 5 years experience with UK databases, including linking cancer registry data to GPRD prior to the formation of CPRD

Is UK primary care experience available within the research team?	☒	☐

If yes, please outline level of experience

Jose Valderas – Practising primary care physician: 19 years.

23. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study.

Khan NF, Mant D, Carpenter L, Forman D, Rose PW. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. *Br J Cancer*. 2011;105 Suppl 1:S29-37.

Khan NF, Mant D, Rose PW. Quality of care for chronic diseases in a British cohort of long-term cancer survivors. *Ann Fam Med*. 2010;8(5):418-24.

Griffiths RI, Danese MD, Gleeson ML, Valderas JM. Epidemiology and Outcomes of Previously Undiagnosed Diabetes in Older Women Diagnosed With Breast Cancer: An Observational Cohort Study Based on SEER-Medicare. *BMC Cancer*, 2012;12:613.

PROTOCOL CONTENT CHECKLIST

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced instructions on the content of protocols for research using CPRD data. These instructions are available on the CPRD website (www.cprd.com/ISAC). All protocols using CPRD data which are submitted for review by ISAC must contain information on the areas detailed in the instructions. IF you do not feel that a specific area required by ISAC is relevant for your protocol, you will need to justify this decision to ISAC.

Applicants must complete the checklist below to confirm that the protocol being submitted includes all the areas required by ISAC, or to provide justification where a required area is not considered to be relevant for a specific protocol. Protocols will not be circulated to ISAC for review until the checklist has been completed by the applicant.

Please note, your protocol will be returned to you if you do not complete this checklist, or if you answer 'no' and fail to include justification for the omission of any required area.

	Included in protocol?		
Required area	Yes	No	If no, reason for omission
Lay Summary (max.200 words)	☒	☐	
Background	☒	☐	
Objective, specific aims and rationale	☒	☐	
Study Type *Descriptive* *Hypothesis Generating* *Hypothesis Testing*	 ☐ ☐ ☒	 ☐ ☐ ☐	
Study Design	☒	☐	
Sample size/power calculation *(Please provide justification of sample size in the protocol)*	☒	☐	
Study population *(including estimate of expected number of relevant patients in the CPRD)*	☒	☐	
Selection of comparison group(s) or controls	☒	☐	
Exposures, outcomes and covariates *Exposures are clearly described* *Outcomes are clearly described*	☒ ☒ ☒	☐ ☐ ☐	

Use of linked data *(if applicable)*	☒	☐	
Data/ Statistical Analysis Plan *There is plan for addressing confounding* *There is a plan for addressing missing data*	☒ ☒ ☒	☐ ☐ ☐	
Patient/ user group involvement †	☒	☐	
Limitations of the study design, data sources and analytic methods	☒	☐	
Plans for disseminating and communicating study results	☒	☐	

† It is expected that many studies will benefit from the involvement of patient or user groups in their planning and refinement, and/or in the interpretation of the results and plans for further work. This is particularly, but not exclusively true of studies with interests in the impact on quality of life. Please indicate whether or not you intend to engage patients in any of the ways mentioned above.

Voluntary registration of ISAC approved studies:
Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted using MHRA databases. This will not replace information on ISAC approved protocols that may be published in its summary minutes or annual report. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

[PLEASE INSERT THE STUDY PROTOCOL DOCUMENT HERE]

Quality and Outcomes of Care for Chronic Conditions in Older Patients Diagnosed with Breast, Colorectal, or Prostate Cancer Compared to Non-Cancer Controls: An Observational Study Using the Clinical Practice Research Datalink.

Funded by a Cancer Research UK Population Research Committee Project Award

Lay Summary (200 words)

As cancer care continues to improve, overall morbidity and mortality in cancer patients depends increasingly on the quality of care for other medical conditions during cancer treatment and follow-up, especially in older patients who have other chronic medical conditions before cancer diagnosis. Cancer Research UK (CRUK) and other national bodies, such as the National Cancer Survivorship Initiative (NCSI), have expressed concern that these conditions may be overlooked during cancer treatment and follow-up, resulting in preventable morbidity and mortality in cancer patients. The aims of this research are to assess the quality and outcomes of care for chronic medical conditions in older patients diagnosed with breast, colorectal, or prostate cancer, and to compare quality and outcomes in cancer patients to non-cancer patients. The findings will serve as the benchmark for informing changes to practice management to improve quality of care and outcomes of chronic conditions in cancer. If our study shows quality and outcomes of care for other medical conditions are worse in cancer patients, it will provide the evidence that can lead to policy and practice changes promoting greater coordination of care between specialists and generalists, and ensuring management of other conditions is not overlooked during cancer treatment and follow-up.

Objectives

The objective of this research is to compare the quality and outcomes of care for chronic medical conditions in cancer patients to matched controls. The null hypothesis is that there is no difference in quality and outcomes of care for chronic conditions between cancer patients and controls.

Specific Aims

The specific aims are (A) to estimate rates of compliance with indicators of quality and safety of care, rates of inpatient and outpatient visits, and mortality rates, in breast, colorectal, and prostate cancer patients who were diagnosed with one or more chronic medical conditions prior to cancer, (B) to estimate these rates in non-cancer controls, and (C) to compare quality and safety of care, episodes of care, and mortality in cancer patients to non-cancer controls.

Rationale

CRUK and other major organisations, such as the NCSI and Macmillan Cancer Support, have expressed concern that management of chronic conditions may be overlooked during cancer treatment and follow-up, leading to preventable morbidity and mortality among cancer survivors due to other conditions. This study will compare the quality and outcomes of care for chronic medical conditions in cancer patients to matched controls. Showing that quality and outcomes of care for other medical conditions are worse in cancer patients than non-cancer

patients could lead to policy and practice changes that encourage greater coordination of care between specialists and generalists to ensure management of other conditions is not overlooked during cancer treatment and follow-up.

Background

Incidence rates of the most common cancers, including breast, colorectal, and prostate cancer, increase considerably with age, and in the UK more than three out of five (63%) cancers are diagnosed in people ≥65 years old. (1) Older age also is associated with higher rates of other significant medical conditions. For instance, the prevalence of diabetes increases from 8.5% of males and 6.0% of females aged 55-64, to 15.7% and 10.4%, respectively, in those aged 65-74. (2) In turn, diabetes is associated with increased risk and worse outcomes of cancer, and explanations include that the diagnosis of cancer may distract both the patient and the healthcare team from appropriate management of glycaemia, blood pressure, and lipids. (3,4)

As cancer survival rates continue to improve, more of those diagnosed with cancer will die of other diseases (5) – up to half, according to a recent study out of the United States. (6,7) The lead investigator of this study, Professor Yi Ning from Virginia Commonwealth University, was quoted by CRUK (5) as saying,

> "After the detection of cancer, clinicians and cancer survivors pay less attention to the prevention and treatment of other diseases and complications. We shouldn't neglect other aspects of health because we are focused on cancer and overlook other chronic conditions."

Increasingly, therefore, overall survival in cancer is likely to depend on prevention and high-quality management of other conditions throughout the continuum of cancer care, from diagnosis, through initial treatment, to long-term follow-up. This is especially true among older cancer patients, who tend to have higher rates of other serious medical conditions.

The General Practice Research Database (GPRD) has been used to examine the long-term health outcomes (8), quality of care for chronic diseases (9), primary care consultation behaviours (10), and patterns of cancer screening and preventative care (11) among breast, colorectal, and prostate cancer patients *who survived 5 years or more*. That research was led by Dr. Nada Khan, a member of our research team, and others at the University of Oxford. In the process, they laid the foundation for the research proposed in this protocol, including developing coding algorithms for identifying chronic medical conditions and measuring quality standards for these conditions (8-12). However, since linkage to Hospital Episode Statistics (HES) data was not feasible or evaluated at the time, Khan and colleagues did not assess the quality and outcomes of care for chronic conditions during the first five years after cancer diagnosis. The new CPRD Data Linkage Scheme provides an opportunity to fill this important gap.

Study Type

This study is *hypothesis testing,* since the primary objective is to compare the quality and outcomes of care for chronic medical conditions in cancer patients to matched controls. The null hypothesis is that there is no difference in quality and outcomes of care for chronic conditions between cancer patients and controls.

Study Design

This is an historical cohort study using the CPRD, and data held under the CPRD Data Linkage Scheme, including HES, ONS mortality data, and Index of Multiple Deprivation/Townsend Score. Study subjects will consist of patients diagnosed with breast, colorectal, or prostate cancer plus a cohort of non-cancer patients matched 4:1 on age, sex, practice, and chronic condition(s). The index date for the controls will be the index date of the corresponding matched case. Due to concerns regarding access to CPRD data linked to NCIN cancer registry data in the correct format, and with the approval of the Population Research Committee at CRUK, the funding agency for this research, this study will not entail linkage to the NCIN data (Approval letter received May 7, 2014).

Patients will be followed from two years before cancer diagnosis up to five years after diagnosis (matched index date for controls). The observation period will be divided by the research team into one-year intervals. During each interval, we will calculate annual rates of compliance with Quality Outcomes Framework (QOF) quality of care indicators, rates of inpatient and outpatient visits, and mortality rates in cancer patients and controls.

Study Population

Based on CPRD Gold and data held under the CPRD Data Linkage Scheme, we will identify cohorts of patients diagnosed with breast, colorectal, or prostate cancer from 01/01/2000 through the last day of HES/ONS/IMD merged data in the current linkage, who were aged 50 or older at the time of cancer diagnosis, and who had been diagnosed with at least one of the following six chronic conditions prior to cancer: hypertension, diabetes, coronary heart disease, heart failure, stroke or transient ischaemic attack, atrial fibrillation.

These conditions will be identified based on READ codes within the primary care practice data (13,14, Appendix 1 [NHS Herefordshire code lists provided for illustrative purposes; national QOF Business Rules will be used in the project]) in the CPRD and/or International Classification of Diseases, 10th Revision (ICD-10) codes within the HES. We will not search free-text fields to identify conditions. All cancer and control patients will be required to have had at least two years of information prior to their index date in which to identify the conditions.

Selection of Comparison Group

We also will identify a cohort of non-cancer patients matched 4:1 on age, sex, practice, and chronic condition(s). The index date for the controls will be the index date of the corresponding matched case. Hence we seek to create 18 matched cohorts, one for each combination of cancer type and comorbidity.

Expected Number of Patients

We submitted a preliminary data request to CPRD, which identified approximately 45,441 research quality patients diagnosed with breast, colorectal, or prostate cancer on or after 01/01/2000, who had at least 24 months of information prior to cancer.[y] Therefore, we

[y] Personal communication by email, Helen Strongman, Research Scientist, MHRA/Clinical Practice Research Datalink, 16 October 2012

anticipate that our entire study cohort (including controls) will include in excess of 200,000 patients.

Sample Size

We intend to obtain information on all research quality patients diagnosed with breast, colorectal, or prostate cancer on or after 01/01/2000. Khan and colleagues' study on the quality of care for chronic diseases in long-term breast, colorectal, and prostate cancer survivors with hypertension, coronary artery disease, diabetes, or cerebrovascular disease included 21,366 patients. (9) Their study produced reliable estimates of rates of quality of care indicators, including blood pressure, cholesterol, and HbA1c monitoring. Our final cohort of cancer patients is likely to be considerably larger.

Exposures, Outcomes, and Covariates

The main exposure of interest is whether or not a patient is diagnosed with cancer. Read codes from the primary care data will be used to identify breast, colorectal, and prostate cancer. Boggon et al. (15) have shown Read codes within primary care data to have a high sensitivity and specificity for the identification of cancer patients compared to registry data.

The primary outcome measures will be QOF indicators of "ongoing management" for chronic conditions. The following specific indicators will be included: blood pressure, cholesterol and smoking status (all), HbA1c (diabetes), physical activity evaluation and advice (hypertension), risk of stroke (atrial fibrillation). These indicators will be constructed using READ codes within the primary care practice data, and will be based on algorithms in the HSCIC QOF Business Rules http://www.hscic.gov.uk/qof– See Appendix 2 for an example.

Secondary outcome measures will consist of inpatient admissions and hospital outpatient encounters for chronic conditions, which will be identified from HES based on ICD codes, and mortality, which will be identified from ONS.

Covariates will consist of demographic, socioeconomic, and clinical variables to describe cancer patients at the time of cancer diagnosis, and non-cancer patients at the time of their matched date, including the following:

- Age
- Gender (colorectal cancer only)
- Ethnicity (which will be available through the HES linkage)
- Year of cancer diagnosis or matched date
- Type (breast, colorectal, prostate) of cancer
- Types of chronic conditions
- Body mass index
- Smoking status
- Townsend Score
- Comorbidity index (Charlson [16] but excluding cancer)
- General Practitioner practice or post code

Data/Statistical Analyses

Each QOF quality of care indictor will be specified as a binary variable in each 12-month interval (or smaller, depending on exploratory analyses) from 24 months (minimum) before up to 60 months after cancer diagnosis (matched date). In each interval, we will calculate unadjusted and

adjusted rates of attainment of the QOF indicator, e.g. per 1,000 patient-years at risk, for cancer and control patients. Patients (and rates) in both groups will be stratified by demographic characteristics (above) and type(s) of chronic conditions. In the cancer group, patients also will be stratified by type of cancer. The adjusted odds of each QOF indicator will be estimated in each time interval based on multivariate logistic regression. Multivariate repeated measures analyses with fixed and random effects will be used to examine adjusted associations between cancer diagnosis and each of the QOF indicators, with cancer diagnosis introduced as a time-dependent covariate in the models to assess its impact on quality of care for the conditions within and between patients. In patients with cancer, the association between quality of care for comorbidities and the quality of care for cancer in primary care will be also established.

Rates of episodes of care for chronic conditions will be calculated in each of the time intervals, as described above. Poisson regression will be used to estimate the adjusted odds of having episodes in each of the time intervals. Cox regression will be used to estimate factors associated with all-cause, cancer, and condition-specific mortality. Multivariate models with episodes of care or mortality as the outcome variable will include prior compliance with QOF indicators as independent variables, so that the impact of variability in quality of care on outcomes can be assessed.

MISSING DATA.

Of the variables in our list under the heading 'Exposures, Outcomes and Covariates' some will be missing very rarely (e.g. age, gender) and some are considered absent when no data is present (e.g. READ code for diabetes). Some, such as BMI and smoking for example, may be subject to missing data. In our previous analyses in a CPRD study of cancer survivors and contols (Khan, PhD thesis University of Oxford 2012) BMI was 84% complete and smoking status was 96% complete, and, further, incidence rate ratios for diabetes were near identical whether we used complete case analysis, multiple imputation or missing indicator method (IRR=1.25, 1.27 and 1.25 respectively). In this project therefore we propose to use complete case analysis but conduct sensitivity analyses using multiple imputation.

The variables in our condition-specific clusters are process outcomes (e.g. % with blood pressure measurement) for which missingness is part of the outcome rather than a data problem, and health/intermediate outcomes for which we will assume that missingness counts as out of range (e.g. the % with blood pressure within range will be calculated as 'total with a measurement below target' divided by 'total eligible').

Patient or User Group Involvement

Throughout the study we will provide our funding agency, CRUK, with updates on our progress, including a complete study protocol, preliminary tables of outputs, research abstracts, and manuscripts.

Limitations of the Study Design, Data Sources, and Analytic Methods

We are likely to encounter several types of issues with the linkages. Not all patients in the CPRD with evidence of specialist consultations will be linked to HES data. These should be identified, compared with linked patients, and then probably dropped from the study. The algorithms used to link data may result in duplicate records for some patients, which we will need to identify and remove to avoid overestimating the number of encounters. We will need to resolve

discrepancies between different sources reporting the same patient information, such as date of death from CPRD and the Office of National Statistics.

There are two important sources of potential confounding in our study. The first, which is a form of "confounding by indication," could occur because risk factors for cancer, such as obesity and smoking, also may adversely affect QOF performance in cancer patients. Failure to adjust for these factors could result in biased estimates of differences in QOF performance between cancer cases and controls. The unadjusted comparisons of QOF performance between cancer patients and controls will be stratified by these potential confounders, and they also will be included in all multivariate analyses.

The second type of potential confounding is the existence of a contemporaneous "exposure" -- in this instance, the use of cancer therapy -- in the cancer patient group, which could affect the group's QOF performance and/or other outcomes. While this may affect our ability to *know why* there are differences between cancer patients and controls, we submit that since *both* the transfer of primary responsibility for care from general practitioner to specialist *and* the "exposure" to chemotherapy are potentially important factors affecting QOF in cancer patients, this type of confounding will not bias observed differences between cancer patients and controls. Prior to beginning the study, as part of our protocol, we will develop a list of chemotherapy and other therapeutic agents that could adversely impact QOF or exacerbate underlying comorbidities. This will be accomplished through a search of the literature and with our consulting oncologist. If necessary, we will seek additional clinical input. OPCS codes, where present in either NCIN or HES data, will provide insight into the types of agents received. However, specific OPCS codes may cover more than one regimen, so it will not be possible to identify with certainty each agent a patient received. Analysis of QOF performance in cancer patients will be stratified by these indicators of chemotherapy and other types of cancer therapy.

Plans for Disseminating and Communicating Study Results

Our study results will be disseminated and communicated through presentations at professional society meetings, such as the National Cancer Research Institute annual meeting, and publication in medical journals.

Collaborators (in alphabetical order)

Clare R. Bankhead, DPhil, MSc. University Research Lecturer. University of Oxford.
Robert I. Griffiths, MS, ScD. Senior Research Fellow. University of Oxford.
Nancy L. Keating, MD, MPH. Associate Professor of Medicine and Health Policy. Harvard University.
Nada F. Khan, DPhil, MSc. Kings College London/University College London.
Bernadette Lavery, MD. Medical Director. Thames Valley Cancer Network.
Richard J. Stevens, MSc PhD. University Research Lecturer, Deputy Director, Statistics Group. University of Oxford
Jose M. Valderas, MD, PhD, MPH. Senior Clinical Research Fellow. University of Oxford. *Lead Investigator

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Characteristics of Patients in the Individual Cancer Cohorts

Demographic Characteristics

	Breast Cancer						Colorectal Cancer						Prostate Cancer					
	Cancer		Control		Total		Cancer		Control		Total		Cancer		Control		Total	
Age	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
<60	130	12.5	392	12.0	522	12.1	73	6.8	275	6.4	348	6.5	45	3.5	139	3.5	184	3.5
60-<70	311	30.0	965	29.6	1,276	29.7	275	25.7	1,068	25.0	1,343	25.2	360	28.2	1,149	28.6	1,509	28.5
70-<80	367	35.4	1,206	37.0	1,573	36.6	486	45.5	2,006	47.0	2,492	46.7	645	50.5	2,053	51.1	2,698	50.9
>=80	228	22.0	699	21.4	927	21.6	235	22.0	916	21.5	1,151	21.6	227	17.8	679	16.9	906	17.1
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
mean (SD)	1,036	71.4(9.68)	3,262	71.4(9.28)	4,298	71.4(9.38)	1,069	72.7(8.33)	4,265	72.9(8.02)	5,334	72.9(8.08)	1,277	72.8(7.35)	4,020	72.7(7.10)	5,297	72.7(7.16)
Sex																		
Male	Not Applicable						697	65.2	2,799	65.6	3,496	65.5	1,277	100.0	4,020	100.0	5,297	100.0
Female	1,036	100.0	3,262	100.0	4,298	100.0	372	34.8	1,466	34.4	1,838	34.5	Not Applicable					
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Year of Diagnosis																		
2000-2004	186	18.0	544	16.7	730	17.0	146	13.7	555	13.0	701	13.1	214	16.8	613	15.2	827	15.6
2005-2009	450	43.4	1,426	43.7	1,876	43.6	500	46.8	1,937	45.4	2,437	45.7	550	43.1	1,724	42.9	2,274	42.9
>=2010	400	38.6	1,292	39.6	1,692	39.4	423	39.6	1,773	41.6	2,196	41.2	513	40.2	1,683	41.9	2,196	41.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Smoking Status																		
Non Smoker	421	40.6	1,443	44.2	1,864	43.4	284	26.6	1,201	28.2	1,485	27.8	286	22.4	843	21.0	1,129	21.3
Ex Smoker	404	39.0	1,181	36.2	1,585	36.9	585	54.7	2,259	53.0	2,844	53.3	727	56.9	2,420	60.2	3,147	59.4
Current Smoker	111	10.7	372	11.4	483	11.2	89	8.3	474	11.1	563	10.6	124	9.7	423	10.5	547	10.3
Not Recorded	100	9.7	266	8.2	366	8.5	111	10.4	331	7.8	442	8.3	140	11.0	334	8.3	474	8.9
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
						P=0.093						**P=0.002**						**P=0.012**
Drinking Status																		
Drinker	393	37.9	1,174	36.0	1,567	36.5	491	45.9	1,844	43.2	2,335	43.8	597	46.8	1,962	48.8	2,559	48.3
Non-Drinker	206	19.9	722	22.1	928	21.6	119	11.1	621	14.6	740	13.9	123	9.6	372	9.3	495	9.3
Not Reported	437	42.2	1,366	41.9	1,803	41.9	459	42.9	1,800	42.2	2,259	42.4	557	43.6	1,686	41.9	2,243	42.3
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
												P=0.012						
Index of Multiple Deprivation																		
1	137	13.2	423	13.0	560	13.0	118	11.0	509	11.9	627	11.8	183	14.3	548	13.6	731	13.8
2	160	15.4	469	14.4	629	14.6	143	13.4	591	13.9	734	13.8	191	15.0	609	15.1	800	15.1
3	139	13.4	472	14.5	611	14.2	142	13.3	575	13.5	717	13.4	198	15.5	606	15.1	804	15.2
4	145	14.0	425	13.0	570	13.3	126	11.8	557	13.1	683	12.8	154	12.1	506	12.6	660	12.5
5	85	8.2	300	9.2	385	9.0	105	9.8	424	9.9	529	9.9	91	7.1	329	8.2	420	7.9
Not Reported	370	35.7	1,173	36.0	1,543	35.9	435	40.7	1,609	37.7	2,044	38.3	460	36.0	1,422	35.4	1,882	35.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0

Clinical Characteristics

	Breast Cancer						Colorectal Cancer						Prostate Cancer					
	Cancer		Control		Total		Cancer		Control		Total		Cancer		Control		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Body Mass Index																		
<25	163	15.7	580	17.8	743	17.3	199	18.6	739	17.3	938	17.6	217	17.0	686	17.1	903	17.0
25-<30	310	29.9	1,008	30.9	1,318	30.7	403	37.7	1,628	38.2	2,031	38.1	559	43.8	1,710	42.5	2,269	42.8
>=30	515	49.7	1,553	47.6	2,068	48.1	406	38.0	1,754	41.1	2,160	40.5	423	33.1	1,513	37.6	1,936	36.5
Not Reported	48	4.6	121	3.7	169	3.9	61	5.7	144	3.4	205	3.8	78	6.1	111	2.8	189	3.6
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
												P=0.002						**P<0.001**
mean (SD)	988	31.0(6.41)	3,141	30.8(6.67)	4,129	30.8(6.61)	1,008	29.5(5.59)	4,121	29.7(5.41)	5,129	29.6(5.44)	1,199	28.7(4.30)	3,909	29.3(5.04)	5,108	29.1(4.88)
																		P=0.005
Charlson Comorbidity Index																		
1-2	575	55.5	1,741	53.4	2,316	53.9	563	52.7	2,195	51.5	2,758	51.7	740	57.9	2,154	53.6	2,894	54.6
3-4	313	30.2	1,073	32.9	1,386	32.2	349	32.6	1,379	32.3	1,728	32.4	382	29.9	1,272	31.6	1,654	31.2
>4	148	14.3	448	13.7	596	13.9	157	14.7	691	16.2	848	15.9	155	12.1	594	14.8	749	14.1
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.011
Atrial Fibrillation																		
No	951	91.8	3,034	93.0	3,985	92.7	960	89.8	3,878	90.9	4,838	90.7	1,179	92.3	3,626	90.2	4,805	90.7
Yes	85	8.2	228	7.0	313	7.3	109	10.2	387	9.1	496	9.3	98	7.7	394	9.8	492	9.3
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.023
Coronary Heart Disease																		
No	974	94.0	3,063	93.9	4,037	93.9	954	89.2	3,788	88.8	4,742	88.9	1,106	86.6	3,474	86.4	4,580	86.5
Yes	62	6.0	199	6.1	261	6.1	115	10.8	477	11.2	592	11.1	171	13.4	546	13.6	717	13.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Heart Failure																		
No	967	93.3	3,075	94.3	4,042	94.0	997	93.3	3,959	92.8	4,956	92.9	1,211	94.8	3,709	92.3	4,920	92.9
Yes	69	6.7	187	5.7	256	6.0	72	6.7	306	7.2	378	7.1	66	5.2	311	7.7	377	7.1
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.002
Hypertension																		
No	289	27.9	918	28.1	1,207	28.1	339	31.7	1,306	30.6	1,645	30.8	448	35.1	1,393	34.7	1,841	34.8
Yes	747	72.1	2,344	71.9	3,091	71.9	730	68.3	2,959	69.4	3,689	69.2	829	64.9	2,627	65.3	3,456	65.2
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Stroke or Transient Ischaemic Attack																		
No	940	90.7	2,976	91.2	3,916	91.1	972	90.9	3,744	87.8	4,716	88.4	1,142	89.4	3,581	89.1	4,723	89.2
Yes	96	9.3	286	8.8	382	8.9	97	9.1	521	12.2	618	11.6	135	10.6	439	10.9	574	10.8
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
												P=0.004						

Microvascular Complications

	Breast Cancer						Colorectal Cancer						Prostate Cancer					
	Cancer		Control		Total		Cancer		Control		Total		Cancer		Control		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Microvascular Complication of Diabetes																		
No	752	72.6	2,309	70.8	3,061	71.2	730	68.3	2,956	69.3	3,686	69.1	930	72.8	2,755	68.5	3,685	69.6
Yes	284	27.4	953	29.2	1,237	28.8	339	31.7	1,309	30.7	1,648	30.9	347	27.2	1,265	31.5	1,612	30.4
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.004
Retinopathy																		
No	813	78.5	2,506	76.8	3,319	77.2	794	74.3	3,241	76.0	4,035	75.6	1,008	78.9	3,025	75.2	4,033	76.1
Yes	223	21.5	756	23.2	979	22.8	275	25.7	1,024	24.0	1,299	24.4	269	21.1	995	24.8	1,264	23.9
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.007
Neuropathy																		
No	966	93.2	3,025	92.7	3,991	92.9	971	90.8	3,896	91.3	4,867	91.2	1,182	92.6	3,672	91.3	4,854	91.6
Yes	70	6.8	237	7.3	307	7.1	98	9.2	369	8.7	467	8.8	95	7.4	348	8.7	443	8.4
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Nephropathy																		
No	1,029	99.3	3,236	99.2	4,265	99.2	1,053	98.5	4,205	98.6	5,258	98.6	1,265	99.1	3,963	98.6	5,228	98.7
Yes	7	0.7	26	0.8	33	0.8	16	1.5	60	1.4	76	1.4	12	0.9	57	1.4	69	1.3
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
CKD																		
No	1,024	98.8	3,191	97.8	4,215	98.1	1,057	98.9	4,185	98.1	5,242	98.3	1,256	98.4	3,959	98.5	5,215	98.5
Yes	12	1.2	71	2.2	83	1.9	12	1.1	80	1.9	92	1.7	21	1.6	61	1.5	82	1.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
						P=0.038						**P=0.091**						

Macrovascular Complications

	Breast Cancer						Colorectal Cancer						Prostate Cancer					
	Cancer		Control		Total		Cancer		Control		Total		Cancer		Control		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Macrovascular Complication																		
No	890	85.9	2,753	84.4	3,643	84.8	842	78.8	3,245	76.1	4,087	76.6	949	74.3	2,998	74.6	3,947	74.5
Yes	146	14.1	509	15.6	655	15.2	227	21.2	1,020	23.9	1,247	23.4	328	25.7	1,022	25.4	1,350	25.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
												P=0.064						
Peripheral Vascular Disease																		
No	995	96.0	3,052	93.6	4,047	94.2	979	91.6	3,874	90.8	4,853	91.0	1,171	91.7	3,645	90.7	4,816	90.9
Yes	41	4.0	210	6.4	251	5.8	90	8.4	391	9.2	481	9.0	106	8.3	375	9.3	481	9.1
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
						P=0.003												
Acute Myocardial Infarction																		
No	974	94.0	3,063	93.9	4,037	93.9	954	89.2	3,788	88.8	4,742	88.9	1,106	86.6	3,474	86.4	4,580	86.5
Yes	62	6.0	199	6.1	261	6.1	115	10.8	477	11.2	592	11.1	171	13.4	546	13.6	717	13.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Cerebrovascular Accident																		
No	981	94.7	3,094	94.8	4,075	94.8	1,009	94.4	3,948	92.6	4,957	92.9	1,187	93.0	3,747	93.2	4,934	93.1
Yes	55	5.3	168	5.2	223	5.2	60	5.6	317	7.4	377	7.1	90	7.0	273	6.8	363	6.9
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
												P=0.038						
Lower Limb Amputation																		
No	1,029	99.3	3,244	99.4	4,273	99.4	1,062	99.3	4,222	99.0	5,284	99.1	1,266	99.1	3,969	98.7	5,235	98.8
Yes	7	0.7	18	0.6	25	0.6	7	0.7	43	1.0	50	0.9	11	0.9	51	1.3	62	1.2
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0

Clinical and Laboratory Values

	Breast Cancer						Colorectal Cancer						Prostate Cancer					
	Cancer		Control		Total		Cancer		Control		Total		Cancer		Control		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Blood Pressure <= 140/80 mm Hg																		
Yes	582	56.2	1,940	59.5	2,522	58.7	680	63.6	2,614	61.3	3,294	61.8	764	59.8	2,479	61.7	3,243	61.2
No	446	43.1	1,290	39.5	1,736	40.4	345	32.3	1,598	37.5	1,943	36.4	459	35.9	1,508	37.5	1,967	37.1
Not Reported	8	0.8	32	1.0	40	0.9	44	4.1	53	1.2	97	1.8	54	4.2	33	0.8	87	1.6
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
												P<0.001						**P<0.001**
systolic mean(SD)	1,028	138(16)	3,230	137(17)	4,258	137(17)	1,025	134(15)	4,212	137(16)	5,237	136(16)	1,223	136(15)	3,987	136(15)	5,210	136(15)
												P<0.001						
diastolic mean(SD)	1,028	75(10)	3,230	75(9)	4,258	75(10)	1,025	73.3(10)	4,212	74(9)	5,237	74(9)	1,223	74(9)	3,987	74(9)	5,210	74(9)
												P=0.001						
Total Cholesterol <= 5mmol/L																		
Yes	747	72.1	2,450	75.1	3,197	74.4	898	84.0	3,449	80.9	4,347	81.5	1,061	83.1	3,416	85.0	4,477	84.5
No	243	23.5	703	21.6	946	22.0	102	9.5	690	16.2	792	14.8	130	10.2	484	12.0	614	11.6
Not Reported	46	4.4	109	3.3	155	3.6	69	6.5	126	3.0	195	3.7	86	6.7	120	3.0	206	3.9
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
						P=0.087						**P<0.001**						**P<0.001**
mean(SD)	990	4.5(1.0)	3,153	4.5(1.0)	4,143	4.5(1.0)	1,000	4.0(0.89)	4,139	4.2(0.99)	5,139	4.2(0.97)	1,191	4.0(0.85)	3,900	4.1(2.23)	5,091	4.1(2.0)
												P<0.001						**P=0.081**
HbA1c(mmol/mol)																		
<=59	640	61.8	2,031	62.3	2,671	62.1	681	63.7	2,645	62.0	3,326	62.4	858	67.2	2,580	64.2	3,438	64.9
59-<=64	99	9.6	293	9.0	392	9.1	87	8.1	429	10.1	516	9.7	124	9.7	363	9.0	487	9.2
65-<=75	104	10.0	330	10.1	434	10.1	109	10.2	385	9.0	494	9.3	109	8.5	394	9.8	503	9.5
>75	55	5.3	200	6.1	255	5.9	67	6.3	298	7.0	365	6.8	63	4.9	230	5.7	293	5.5
Not Reported	138	13.3	408	12.5	546	12.7	125	11.7	508	11.9	633	11.9	123	9.6	453	11.3	576	10.9
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
mean(SD)	898	54.3(12.1)	2,854	54.5(12.9)	3,752	54.4(12.7)	944	54.5(12.9)	3,757	54.7(13.3)	4,701	54.7(13.2)	1,154	53.3(12.4)	3,567	54.1(13.1)	4,721	53.9(13.0)
																		P=0.037
Serum Creatinine (umol/L)																		
<=130	867	83.7	2,684	82.3	3,551	82.6	853	79.8	3,373	79.1	4,226	79.2	1,010	79.1	3,122	77.7	4,132	78.0
>130	45	4.3	165	5.1	210	4.9	111	10.4	400	9.4	511	9.6	166	13.0	453	11.3	619	11.7
Not Reported	124	12.0	413	12.7	537	12.5	105	9.8	492	11.5	597	11.2	101	7.9	445	11.1	546	10.3
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.002

Antidiabetic Medications

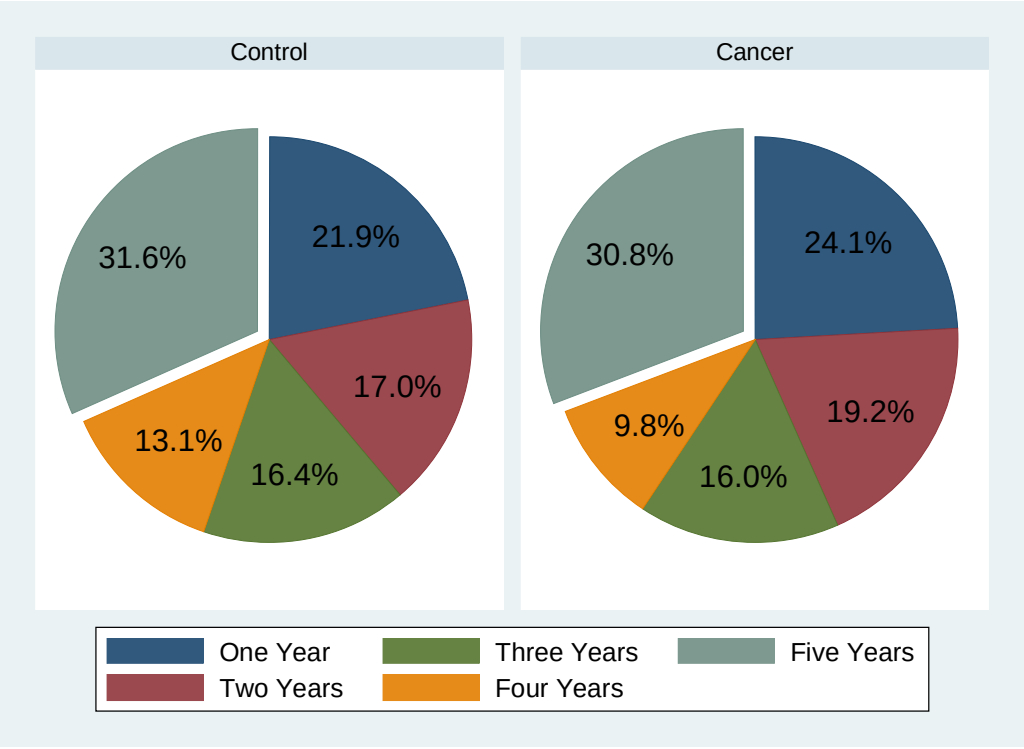
	Breast Cancer						Colorectal Cancer						Prostate Cancer					
	Cancer		Control		Total		Cancer		Control		Total		Cancer		Control		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Antidiabetic Agent																		
No	244	23.6	696	21.3	940	21.9	230	21.5	907	21.3	1,137	21.3	295	23.1	860	21.4	1,155	21.8
Yes	792	76.4	2,566	78.7	3,358	78.1	839	78.5	3,358	78.7	4,197	78.7	982	76.9	3,160	78.6	4,142	78.2
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Insulin																		
No	868	83.8	2,670	81.9	3,538	82.3	885	82.8	3,578	83.9	4,463	83.7	1,094	85.7	3,370	83.8	4,464	84.3
Yes	168	16.2	592	18.1	760	17.7	184	17.2	687	16.1	871	16.3	183	14.3	650	16.2	833	15.7
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Biguinide																		
No	452	43.6	1,325	40.6	1,777	41.3	441	41.3	1,770	41.5	2,211	41.5	525	41.1	1,685	41.9	2,210	41.7
Yes	584	56.4	1,937	59.4	2,521	58.7	628	58.7	2,495	58.5	3,123	58.5	752	58.9	2,335	58.1	3,087	58.3
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
						P=0.087												
Sulphonylurea																		
No	709	68.4	2,195	67.3	2,904	67.6	671	62.8	2,715	63.7	3,386	63.5	809	63.4	2,499	62.2	3,308	62.5
Yes	327	31.6	1,067	32.7	1,394	32.4	398	37.2	1,550	36.3	1,948	36.5	468	36.6	1,521	37.8	1,989	37.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Other Antidiabetic																		
No	932	90.0	2,930	89.8	3,862	89.9	951	89.0	3,788	88.8	4,739	88.8	1,138	89.1	3,529	87.8	4,667	88.1
Yes	104	10.0	332	10.2	436	10.1	118	11.0	477	11.2	595	11.2	139	10.9	491	12.2	630	11.9
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0

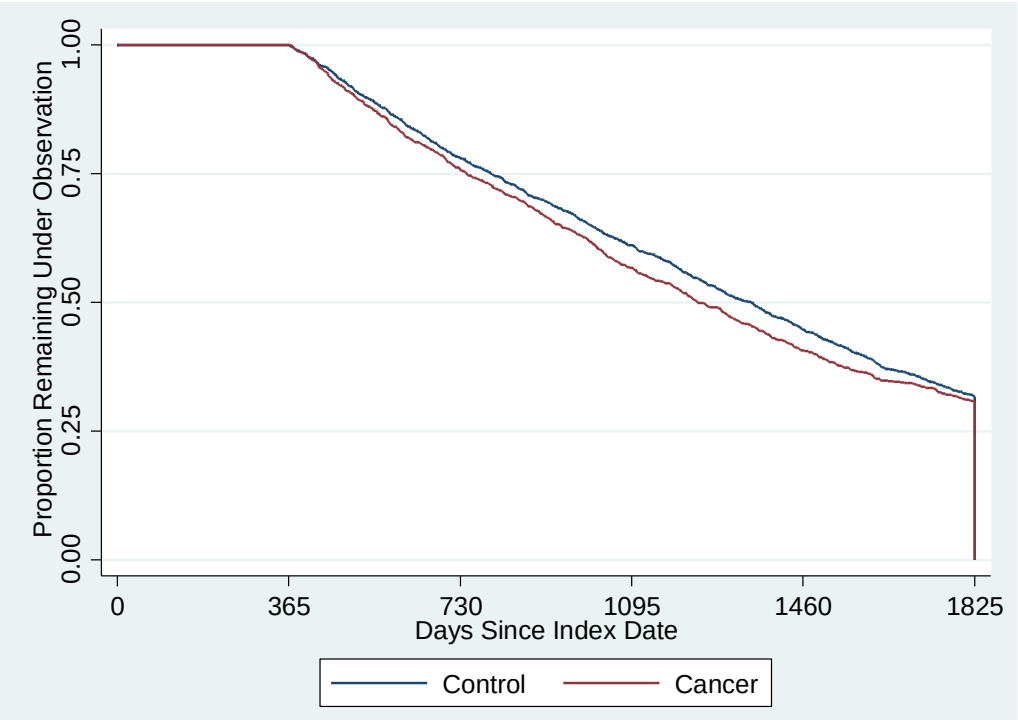
Other Medications

	Breast Cancer						Colorectal Cancer						Prostate Cancer					
	Cancer		Control		Total		Cancer		Control		Total		Cancer		Control		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Statin																		
No	258	24.9	812	24.9	1,070	24.9	242	22.6	974	22.8	1,216	22.8	342	26.8	947	23.6	1,289	24.3
Yes	778	75.1	2,450	75.1	3,228	75.1	827	77.4	3,291	77.2	4,118	77.2	935	73.2	3,073	76.4	4,008	75.7
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.019
ACE Inhibitor																		
No	540	52.1	1,667	51.1	2,207	51.3	502	47.0	1,932	45.3	2,434	45.6	562	44.0	1,723	42.9	2,285	43.1
Yes	496	47.9	1,595	48.9	2,091	48.7	567	53.0	2,333	54.7	2,900	54.4	715	56.0	2,297	57.1	3,012	56.9
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Angiotensin Receptor Blocker																		
No	811	78.3	2,552	78.2	3,363	78.2	873	81.7	3,431	80.4	4,304	80.7	1,055	82.6	3,262	81.1	4,317	81.5
Yes	225	21.7	710	21.8	935	21.8	196	18.3	834	19.6	1,030	19.3	222	17.4	758	18.9	980	18.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Beta Blocker																		
No	743	71.7	2,316	71.0	3,059	71.2	734	68.7	2,858	67.0	3,592	67.3	877	68.7	2,766	68.8	3,643	68.8
Yes	293	28.3	946	29.0	1,239	28.8	335	31.3	1,407	33.0	1,742	32.7	400	31.3	1,254	31.2	1,654	31.2
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Calcium Channel Blocker																		
No	645	62.3	2,029	62.2	2,674	62.2	658	61.6	2,641	61.9	3,299	61.8	776	60.8	2,467	61.4	3,243	61.2
Yes	391	37.7	1,233	37.8	1,624	37.8	411	38.4	1,624	38.1	2,035	38.2	501	39.2	1,553	38.6	2,054	38.8
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Thiazide Related Diuretic																		
No	741	71.5	2,269	69.6	3,010	70.0	789	73.8	3,167	74.3	3,956	74.2	969	75.9	3,090	76.9	4,059	76.6
Yes	295	28.5	993	30.4	1,288	30.0	280	26.2	1,098	25.7	1,378	25.8	308	24.1	930	23.1	1,238	23.4
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Other Diuretic																		
No	793	76.5	2,532	77.6	3,325	77.4	858	80.3	3,478	81.5	4,336	81.3	1,099	86.1	3,324	82.7	4,423	83.5
Yes	243	23.5	730	22.4	973	22.6	211	19.7	787	18.5	998	18.7	178	13.9	696	17.3	874	16.5
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.005
Antiplatelet																		
No	528	51.0	1,625	49.8	2,153	50.1	458	42.8	1,759	41.2	2,217	41.6	496	38.8	1,591	39.6	2,087	39.4
Yes	508	49.0	1,637	50.2	2,145	49.9	611	57.2	2,506	58.8	3,117	58.4	781	61.2	2,429	60.4	3,210	60.6
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Anticoagulant																		
No	968	93.4	3,088	94.7	4,056	94.4	974	91.1	3,947	92.5	4,921	92.3	1,189	93.1	3,683	91.6	4,872	92.0
Yes	68	6.6	174	5.3	242	5.6	95	8.9	318	7.5	413	7.7	88	6.9	337	8.4	425	8.0
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
																		P=0.087
Antiarrhythmic																		
No	1,010	97.5	3,158	96.8	4,168	97.0	1,033	96.6	4,141	97.1	5,174	97.0	1,229	96.2	3,864	96.1	5,093	96.1
Yes	26	2.5	104	3.2	130	3.0	36	3.4	124	2.9	160	3.0	48	3.8	156	3.9	204	3.9
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0
Aspirin																		
No	557	53.8	1,714	52.5	2,271	52.8	503	47.1	1,900	44.5	2,403	45.1	541	42.4	1,706	42.4	2,247	42.4
Yes	479	46.2	1,548	47.5	2,027	47.2	566	52.9	2,365	55.5	2,931	54.9	736	57.6	2,314	57.6	3,050	57.6
Total	1,036	100.0	3,262	100.0	4,298	100.0	1,069	100.0	4,265	100.0	5,334	100.0	1,277	100.0	4,020	100.0	5,297	100.0

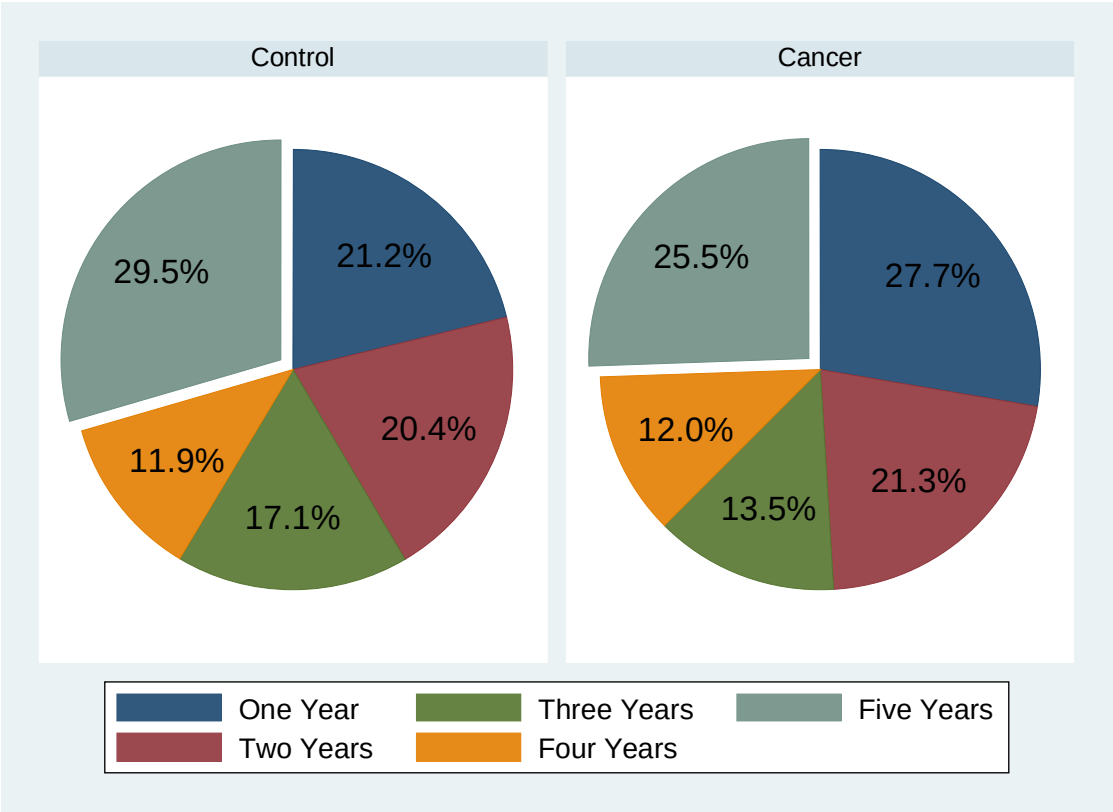
Follow-up in the Individual Cohorts

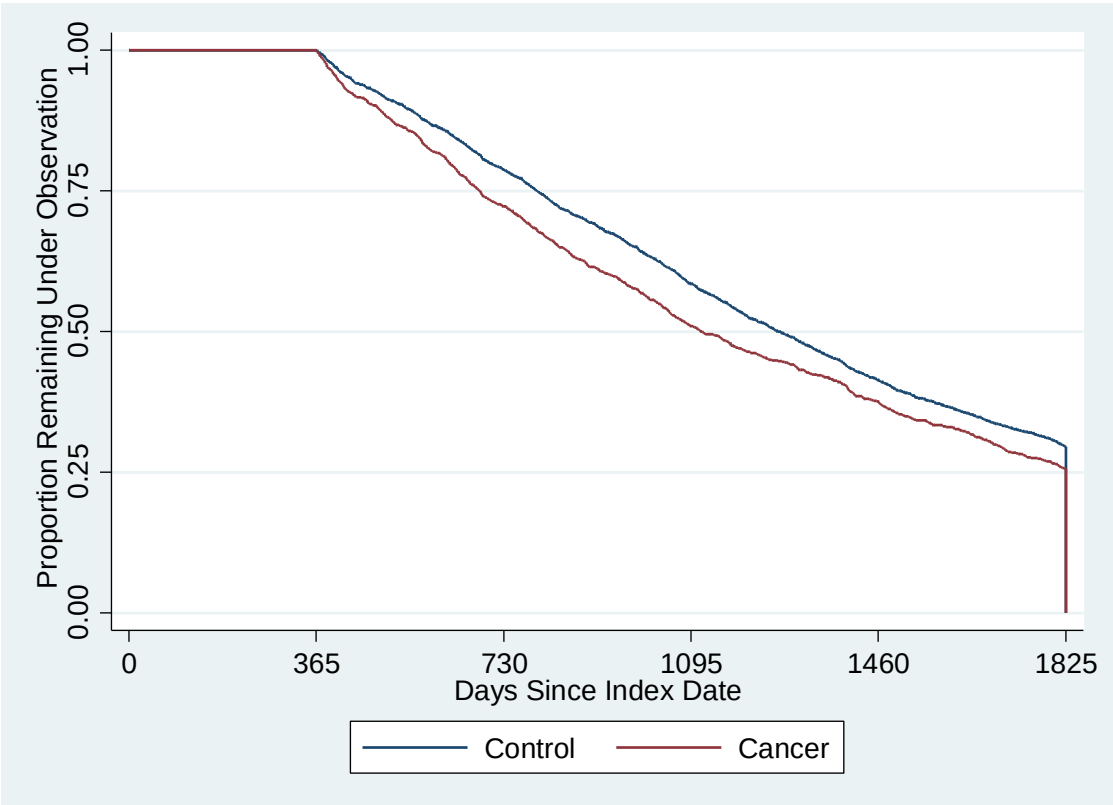
Breast Cancer



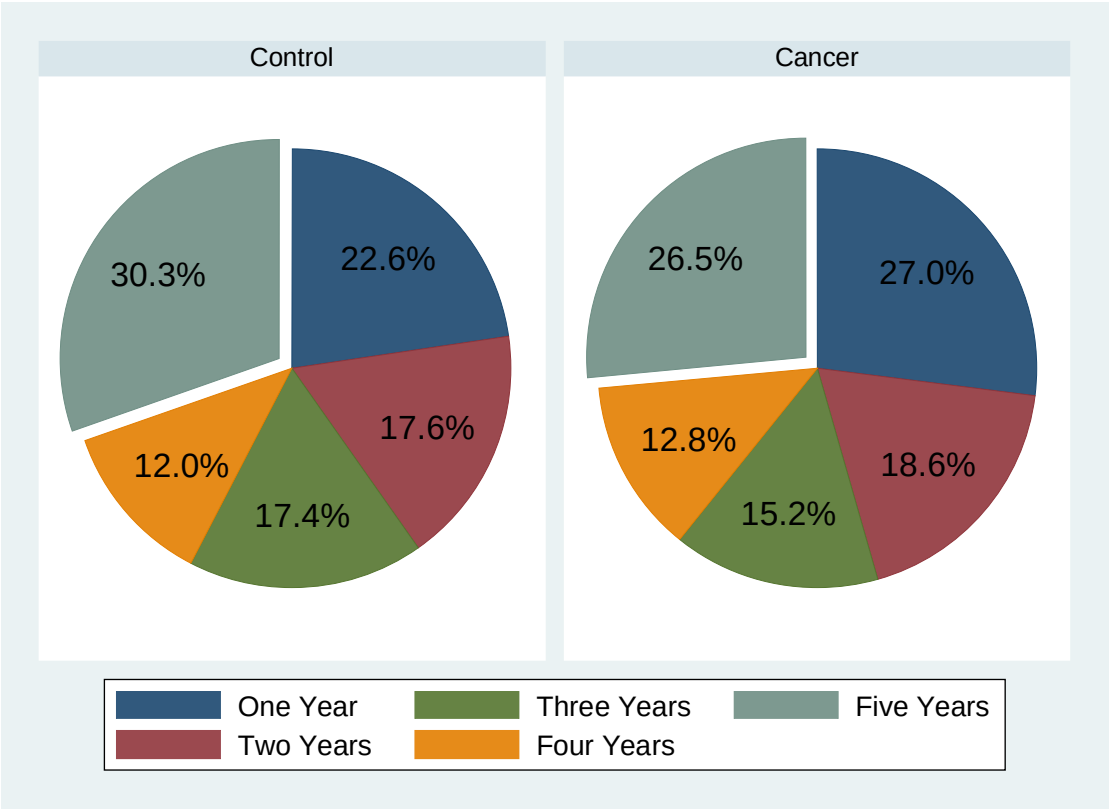


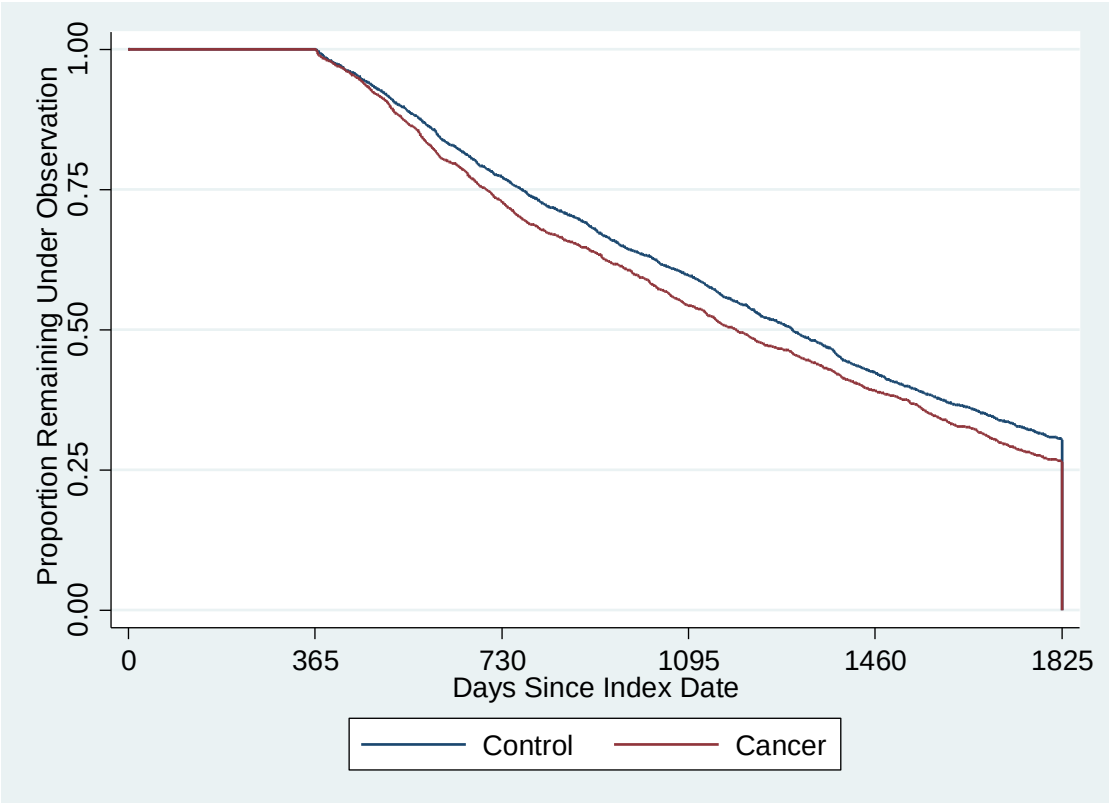
Colorectal Cancer





Prostate Cancer





CHAPTER 4 APPENDIX

Full Results of the Primary Multivariate Analyses

Combined cohorts – Part 1. **(continued on the following four pages)**

	BP ≤150/90 mm/Hg	BP ≤140/80 mm/Hg	TC ≤5 mmol/L	Albumin creatinine test	ACE-I/ARB
	OR* (95% CI)	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Index Year			Reference Category		
Year 2	1.09* (1.01,1.18)	1.12*** (1.05,1.19)	1.12** (1.05,1.21)	1.12*** (1.05,1.20)	0.80 (0.55,1.17)
Year 3	1.30*** (1.19,1.42)	1.27*** (1.19,1.36)	1.25*** (1.15,1.35)	1.25*** (1.16,1.34)	0.64* (0.42,0.97)
Year 4	1.38*** (1.24,1.52)	1.52*** (1.41,1.64)	1.29*** (1.18,1.42)	1.34*** (1.23,1.46)	0.47** (0.28,0.77)
Year 5	1.43*** (1.28,1.61)	1.63*** (1.50,1.78)	1.38*** (1.24,1.53)	1.40*** (1.27,1.55)	0.27*** (0.15,0.49)
Cancer (versus Control)	1.05 (0.96,1.16)	1.04 (0.97,1.12)	0.82*** (0.75,0.90)	0.83*** (0.75,0.91)	0.48 (0.21,1.10)
Age <60			Reference Category		
60 - <70	0.94 (0.80,1.10)	1.04 (0.92,1.18)	1.26** (1.08,1.47)	1.13 (0.95,1.33)	0.08* (0.01,0.85)
70 - <80	0.81** (0.69,0.95)	1.15* (1.02,1.29)	1.25** (1.08,1.45)	1.07 (0.91,1.26)	0.04** (0.00,0.46)
>= 80	0.74*** (0.62,0.87)	1.08 (0.95,1.24)	1.01 (0.86,1.20)	0.97 (0.81,1.17)	0.01*** (0.00,0.13)

Female (versus Male)	0.89	0.87*	0.54***	1.04	1.80
	(0.77,1.02)	(0.78,0.97)	(0.47,0.62)	(0.90,1.20)	(0.51,6.38)
Year of Diagnosis 2000-2004			Reference Category		
2005-2009	1.53***	1.40***	0.97	1.67***	0.59
	(1.37,1.72)	(1.28,1.53)	(0.86,1.09)	(1.47,1.90)	(0.10,3.50)
After 2009	1.89***	1.95***	0.96	2.01***	0.41
	(1.67,2.15)	(1.76,2.16)	(0.84,1.09)	(1.75,2.30)	(0.07,2.46)
Index of Multiple Deprivation = 1			Reference Category		
2	1.04	1.09	1.07	0.98	0.44
	(0.90,1.20)	(0.97,1.21)	(0.93,1.24)	(0.84,1.15)	(0.11,1.81)
3	0.99	1.03	0.99	1.16	0.31
	(0.86,1.14)	(0.92,1.15)	(0.86,1.14)	(1.00,1.36)	(0.08,1.26)
4	0.91	1.04	1.16	0.92	0.37
	(0.79,1.06)	(0.92,1.16)	(1.00,1.34)	(0.78,1.07)	(0.09,1.54)
5	0.92	1.04	1.03	0.99	0.24
	(0.78,1.08)	(0.91,1.18)	(0.88,1.21)	(0.83,1.18)	(0.05,1.10)
Missing	1.08	1.21***	1.15*	1.22**	0.20**
	(0.95,1.22)	(1.10,1.33)	(1.02,1.30)	(1.07,1.39)	(0.06,0.67)
Non Smoker			Reference Category		
Ex Smoker	0.97	1.00	1.04	1.00	0.95
	(0.88,1.06)	(0.94,1.08)	(0.95,1.13)	(0.91,1.11)	(0.40,2.22)
Current Smoker	0.90	0.97	0.88	0.82**	0.62
	(0.78,1.03)	(0.87,1.08)	(0.76,1.00)	(0.71,0.95)	(0.19,2.05)
Missing	0.97	1.07	0.83*	0.77**	1.79
	(0.82,1.14)	(0.93,1.22)	(0.70,0.97)	(0.64,0.92)	(0.27,11.70)

Drinker					
			Reference Category		
Non Drinker	0.88*	1.00	1.02	0.95	0.29*
	(0.78,0.99)	(0.92,1.10)	(0.91,1.15)	(0.84,1.08)	(0.11,0.78)
Missing	0.87**	0.92*	0.90*	0.76***	0.45
	(0.80,0.95)	(0.86,0.98)	(0.83,0.98)	(0.69,0.83)	(0.20,1.01)
Body Mass Index <25 kg/m^2					
			Reference Category		
25 - <30	1.18**	1.05	1.11	1.20**	2.25
	(1.06,1.32)	(0.97,1.15)	(1.00,1.24)	(1.07,1.36)	(0.85,5.97)
>= 30	1.02	0.91*	1.18**	1.10	2.93*
	(0.91,1.14)	(0.84,1.00)	(1.05,1.31)	(0.97,1.24)	(1.09,7.84)
Missing	0.73*	0.88	0.78	0.58***	0.11
	(0.57,0.93)	(0.71,1.08)	(0.61,1.01)	(0.43,0.77)	(0.01,2.09)
Cohort - Breast Cancer					
			Reference Category		
Colorectal Cancer	1.02	0.95	0.88*	1.00	1.32
	(0.90,1.16)	(0.86,1.05)	(0.78,1.00)	(0.87,1.15)	(0.36,4.77)
Prostate Cancer	1.08	0.99	0.80**	1.05	2.92
	(0.91,1.27)	(0.87,1.12)	(0.68,0.94)	(0.88,1.26)	(0.62,13.70)
Charlson Comorbidity Index 1 - 2					
			Reference Category		
3 - 4	0.96	1.04	0.86**	0.88*	0.52
	(0.87,1.05)	(0.97,1.12)	(0.79,0.95)	(0.80,0.97)	(0.22,1.25)
>4	0.98	1.13*	0.85*	0.78**	0.31*
	(0.85,1.13)	(1.01,1.26)	(0.74,0.98)	(0.67,0.91)	(0.10,0.93)

Blood Pressure <= 140/80 mm Hg					
			Reference Category		
>140/80 mm Hg	0.41***	0.38***	0.84***	0.89**	1.42
	(0.38,0.44)	(0.35,0.40)	(0.78,0.91)	(0.82,0.97)	(0.68,2.97)
Missing	0.42***	0.48***	1.17	1.26	4013.88*
	(0.30,0.60)	(0.35,0.66)	(0.81,1.70)	(0.81,1.96)	(4.08,3.95e+06)
Total Cholesterol <= 5 mmol/L					
			Reference Category		
>5 mmol/L	0.71***	0.80***	0.13***	0.82***	0.15***
	(0.64,0.78)	(0.74,0.87)	(0.12,0.14)	(0.73,0.91)	(0.05,0.44)
Missing	0.59***	0.66***	0.15***	0.46***	0.00*
	(0.47,0.74)	(0.55,0.81)	(0.12,0.19)	(0.35,0.60)	(0.00,0.45)
Hemoglobin A1c <= 59 mmol/mol					
			Reference Category		
59 - <=64 mmol/mol	0.87*	0.91	0.93	0.84*	0.74
	(0.76,0.99)	(0.82,1.01)	(0.81,1.06)	(0.73,0.97)	(0.24,2.31)
65 - <=75 mmol/mol	0.81**	0.87**	0.84*	0.74***	2.32
	(0.71,0.92)	(0.79,0.97)	(0.74,0.96)	(0.64,0.85)	(0.72,7.45)
>75 mmol/mol	0.68***	0.81**	0.80**	0.58***	0.96
	(0.58,0.80)	(0.72,0.92)	(0.68,0.94)	(0.49,0.69)	(0.25,3.70)
Missing	0.68***	0.78***	0.65***	0.53***	0.60
	(0.60,0.76)	(0.71,0.86)	(0.58,0.74)	(0.46,0.61)	(0.15,2.43)

Microvascular Complication	0.93	0.94	1.03	0.92	0.54
	(0.84,1.03)	(0.87,1.02)	(0.93,1.13)	(0.83,1.03)	(0.23,1.24)
Macrovascular Complication	1.03	1.15***	1.17**	0.76***	1.78
	(0.93,1.14)	(1.06,1.24)	(1.06,1.30)	(0.69,0.85)	(0.79,4.03)
Any Anti-Diabetic Agent	1.01	1.09*	1.32***	1.02	0.85
	(0.92,1.12)	(1.01,1.17)	(1.20,1.45)	(0.92,1.14)	(0.32,2.26)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Combined cohorts – Part 2. **(continued on the following four pages)**

	HbA1c ≤59 mmol/mol	HbA1c ≤64 mmol/mol	HbA1c ≤75 mmol/mol	Influenza Immunisation	Retinal Screening
	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
Index Year			Reference Category		
Year 2	0.98 (0.91,1.05)	1.00 (0.93,1.08)	1.04 (0.96,1.14)	1.21*** (1.09,1.34)	0.91** (0.86,0.97)
Year 3	0.89** (0.83,0.96)	0.93 (0.86,1.01)	0.94 (0.86,1.03)	1.21** (1.07,1.36)	0.87*** (0.81,0.93)
Year 4	0.88** (0.81,0.96)	0.90* (0.82,0.99)	1.08 (0.97,1.20)	1.32*** (1.15,1.51)	0.78*** (0.72,0.84)
Year 5	0.85*** (0.77,0.93)	0.85** (0.77,0.95)	0.94 (0.84,1.07)	1.29** (1.11,1.51)	0.74*** (0.67,0.81)
Cancer (versus Control)	0.77*** (0.70,0.85)	0.75*** (0.68,0.82)	0.80*** (0.73,0.89)	1.31** (1.07,1.59)	0.99 (0.91,1.08)
Age <60			Reference Category		
60 - <70	1.55*** (1.32,1.82)	1.62*** (1.38,1.89)	1.53*** (1.30,1.81)	1.77*** (1.29,2.43)	1.21* (1.04,1.40)
70 - <80	1.83*** (1.56,2.15)	2.00*** (1.71,2.34)	1.83*** (1.55,2.15)	2.67*** (1.95,3.66)	1.27** (1.09,1.47)
>= 80	1.98*** (1.66,2.37)	1.98*** (1.66,2.36)	1.63*** (1.36,1.96)	2.58*** (1.81,3.68)	1.02 (0.87,1.21)
Female (versus Male)	1.16* (1.00,1.34)	1.16 (1.00,1.34)	1.21* (1.04,1.42)	0.88 (0.66,1.18)	0.92 (0.81,1.05)

Year of Diagnosis 2000-2004			Reference Category		
2005-2009	0.96	0.90	0.85*	0.71**	0.47***
	(0.85,1.09)	(0.80,1.02)	(0.74,0.97)	(0.54,0.92)	(0.42,0.53)
After 2009	0.95	0.88	0.86*	0.89	0.36***
	(0.83,1.09)	(0.77,1.00)	(0.74,0.99)	(0.67,1.17)	(0.32,0.41)
Index of Multiple Deprivation = 1			Reference Category		
2	1.01	1.10	1.04	0.86	0.81**
	(0.87,1.18)	(0.95,1.29)	(0.88,1.22)	(0.63,1.17)	(0.70,0.93)
3	1.03	1.01	0.99	1.00	0.77***
	(0.88,1.20)	(0.86,1.17)	(0.84,1.17)	(0.73,1.37)	(0.67,0.88)
4	1.00	0.96	0.83*	0.77	0.89
	(0.86,1.17)	(0.82,1.12)	(0.70,0.98)	(0.56,1.07)	(0.77,1.02)
5	1.10	1.05	0.98	0.54***	0.79**
	(0.93,1.31)	(0.89,1.25)	(0.81,1.18)	(0.38,0.76)	(0.67,0.92)
Missing	1.10	1.10	1.06	0.87	0.83**
	(0.96,1.25)	(0.96,1.25)	(0.92,1.22)	(0.66,1.14)	(0.73,0.93)
Non Smoker			Reference Category		
Ex Smoker	1.02	1.02	0.96	1.34**	0.94
	(0.93,1.13)	(0.93,1.13)	(0.87,1.07)	(1.10,1.63)	(0.86,1.02)
Current Smoker	0.98	0.89	0.77***	0.61***	0.83**
	(0.85,1.13)	(0.77,1.03)	(0.66,0.90)	(0.46,0.82)	(0.73,0.94)
Missing	0.85	0.87	0.85	1.03	0.87
	(0.71,1.01)	(0.73,1.04)	(0.71,1.03)	(0.72,1.49)	(0.73,1.02)

Drinker					
			Reference Category		
Non Drinker	0.95	0.87*	0.85*	0.63***	0.87*
	(0.84,1.07)	(0.77,0.99)	(0.74,0.97)	(0.49,0.80)	(0.78,0.97)
Missing	0.84***	0.81***	0.80***	0.76**	0.73***
	(0.77,0.92)	(0.74,0.89)	(0.73,0.88)	(0.63,0.91)	(0.67,0.79)
Body Mass Index <25 kg/m^2					
			Reference Category		
25 - <30	0.96	1.00	1.09	0.98	1.06
	(0.86,1.08)	(0.89,1.13)	(0.96,1.24)	(0.77,1.25)	(0.96,1.18)
>= 30	0.90	0.93	0.95	0.92	1.07
	(0.80,1.02)	(0.82,1.05)	(0.84,1.08)	(0.72,1.18)	(0.96,1.19)
Missing	0.61***	0.58***	0.53***	0.28***	0.48***
	(0.46,0.81)	(0.44,0.76)	(0.40,0.70)	(0.16,0.47)	(0.37,0.63)
Cohort - Breast Cancer					
			Reference Category		
Colorectal Cancer	1.20**	1.14	1.21*	1.06	1.00
	(1.05,1.38)	(0.99,1.31)	(1.04,1.41)	(0.80,1.39)	(0.88,1.14)
Prostate Cancer	1.16	1.16	1.27*	1.11	0.96
	(0.98,1.38)	(0.97,1.38)	(1.05,1.53)	(0.78,1.58)	(0.82,1.12)
Charlson Comorbidity Index 1 - 2					
			Reference Category		
3 - 4	0.85**	0.83***	0.90	1.13	1.05
	(0.77,0.94)	(0.75,0.92)	(0.81,1.00)	(0.92,1.38)	(0.95,1.14)
>4	0.80**	0.73***	0.75***	1.66**	0.97
	(0.69,0.93)	(0.64,0.85)	(0.64,0.87)	(1.22,2.25)	(0.85,1.11)

Blood Pressure <= 140/80 mm Hg					
			Reference Category		
>140/80 mm Hg	0.89**	0.87**	0.87**	0.83*	0.99
	(0.82,0.96)	(0.80,0.95)	(0.80,0.95)	(0.70,0.99)	(0.92,1.07)
Missing	0.79	0.84	0.89	0.78	1.05
	(0.52,1.19)	(0.56,1.24)	(0.60,1.31)	(0.35,1.73)	(0.71,1.56)
Total Cholesterol <= 5 mmol/L					
			Reference Category		
>5 mmol/L	0.72***	0.69***	0.70***	0.38***	0.91
	(0.64,0.80)	(0.62,0.77)	(0.62,0.78)	(0.30,0.47)	(0.82,1.01)
Missing	0.56***	0.50***	0.44***	0.34***	0.53***
	(0.43,0.72)	(0.39,0.65)	(0.34,0.56)	(0.20,0.57)	(0.42,0.68)
Hemoglobin A1c <= 59 mmol/mol					
			Reference Category		
59 - <=64 mmol/mol	0.18***	0.28***	0.53***	1.11	1.11
	(0.16,0.21)	(0.25,0.32)	(0.45,0.61)	(0.83,1.49)	(0.98,1.26)
65 - <=75 mmol/mol	0.08***	0.10***	0.26***	0.89	1.05
	(0.07,0.10)	(0.09,0.12)	(0.23,0.30)	(0.67,1.18)	(0.92,1.19)
>75 mmol/mol	0.04***	0.04***	0.08***	0.63**	0.95
	(0.03,0.05)	(0.04,0.05)	(0.07,0.10)	(0.45,0.89)	(0.81,1.12)
Missing	0.29***	0.23***	0.23***	0.63**	0.63***
	(0.25,0.33)	(0.20,0.26)	(0.20,0.27)	(0.48,0.84)	(0.56,0.72)

Microvascular Complication	0.89*	0.89*	0.93	1.13	1.30***
	(0.80,0.99)	(0.80,0.99)	(0.83,1.04)	(0.91,1.40)	(1.18,1.43)
Macrovascular Complication	0.91	0.88*	0.88*	0.94	1.01
	(0.82,1.01)	(0.80,0.98)	(0.79,0.99)	(0.76,1.17)	(0.92,1.11)
Any Anti-Diabetic Agent	0.44***	0.58***	0.96	1.13	1.05
	(0.40,0.49)	(0.52,0.65)	(0.86,1.08)	(0.92,1.39)	(0.96,1.15)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Combined cohorts – Part 3. **(continued on the following four pages)**

	Foot Exam	Dietary Review	Erectile Dysfunction (Asked)	Erectile Dysfunction (Advice)
	OR* (95% CI)	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Index Year		Reference Category		
Year 2	2.52*** (2.31,2.75)	2.37*** (1.84,3.05)	2.04*** (1.58,2.65)	2.56*** (1.70,3.86)
Year 3	7.82*** (7.06,8.67)	12.04*** (7.51,19.32)	7.97*** (5.04,12.62)	10.54*** (5.49,20.23)
Year 4	21.89*** (19.46,24.63)	289.33*** (128.96,649.10)	149.04*** (67.99,326.67)	97.23*** (35.12,269.18)
Year 5	50.30*** (43.83,57.71)	1263.00*** (465.33,3428.06)	558.33*** (214.24,1455.05)	473.82*** (125.06,1795.24)
Cancer (versus Control)	0.94 (0.85,1.04)	1.01 (0.87,1.16)	1.06 (0.89,1.26)	1.60** (1.18,2.18)
Age <60		Reference Category		
60 - <70	0.94 (0.80,1.12)	0.91 (0.71,1.17)	0.79 (0.58,1.10)	1.04 (0.60,1.80)
70 - <80	1.05 (0.89,1.25)	1.08 (0.85,1.39)	0.81 (0.59,1.11)	0.68 (0.39,1.18)
>= 80	0.97 (0.80,1.17)	1.04 (0.79,1.37)	0.81 (0.57,1.16)	0.30*** (0.15,0.59)
Female (versus Male)	1.03 (0.89,1.20)	1.01 (0.81,1.25)	Not Applicable	

Year of Diagnosis 2000-2004				
	Reference Category			
2005-2009	37.66***	144.57***	101.98***	168.81***
	(30.32,46.78)	(42.81,488.23)	(23.95,434.21)	(16.15,1764.83)
After 2009	2698.43***	163589.10***	52432.71***	74789.15***
	(2077.98,3504.13)	(29802.26,897965.43)	(8512.10,322974.08)	(3984.76,1.40e+06)
Index of Multiple Deprivation = 1				
	Reference Category			
2	1.08	0.80	0.80	0.67
	(0.92,1.26)	(0.64,1.00)	(0.61,1.05)	(0.41,1.08)
3	1.15	0.71**	0.67**	0.62
	(0.99,1.35)	(0.56,0.89)	(0.51,0.88)	(0.38,1.00)
4	1.17	0.72**	0.83	0.69
	(1.00,1.38)	(0.57,0.92)	(0.62,1.10)	(0.42,1.14)
5	0.95	0.91	0.75	0.39**
	(0.79,1.13)	(0.70,1.18)	(0.54,1.03)	(0.21,0.72)
Missing	1.02	1.13	0.89	0.80
	(0.89,1.16)	(0.94,1.36)	(0.71,1.11)	(0.54,1.18)
Non Smoker				
	Reference Category			
Ex Smoker	1.06	0.93	0.99	0.88
	(0.96,1.17)	(0.81,1.07)	(0.82,1.18)	(0.64,1.20)
Current Smoker	0.94	0.93	1.01	0.99
	(0.81,1.09)	(0.75,1.15)	(0.77,1.32)	(0.62,1.59)
Missing	1.04	1.39	1.48	1.92
	(0.83,1.31)	(0.98,1.95)	(0.97,2.27)	(0.93,3.97)

Drinker				
Non Drinker	0.99 (0.87,1.12)	0.93 (0.78,1.11)	1.06 (0.83,1.36)	0.92 (0.58,1.46)
Missing	0.79*** (0.72,0.87)	0.85* (0.74,0.97)	0.91 (0.77,1.06)	1.05 (0.80,1.38)
Body Mass Index <25 kg/m^2				
25 - <30	1.11 (0.98,1.25)	1.07 (0.90,1.28)	1.05 (0.85,1.30)	1.70* (1.11,2.60)
>= 30	1.02 (0.90,1.15)	1.01 (0.84,1.20)	0.98 (0.78,1.22)	1.65* (1.07,2.53)
Missing	0.55** (0.36,0.82)	0.64 (0.31,1.30)	0.39 (0.14,1.11)	0.71 (0.11,4.50)
Cohort - Breast Cancer				
Colorectal Cancer	1.20* (1.04,1.38)	1.11 (0.90,1.36)		
Prostate Cancer	1.14 (0.95,1.36)	1.19 (0.92,1.55)	1.17* (1.01,1.36)	1.49** (1.13,1.96)
Charlson Comorbidity Index 1 - 2				
3 - 4	1.15** (1.04,1.27)	1.04 (0.90,1.20)	1.12 (0.94,1.34)	0.96 (0.70,1.32)
>4	1.20* (1.03,1.39)	1.01 (0.81,1.24)	1.06 (0.82,1.37)	0.74 (0.46,1.18)

Blood Pressure <= 140/80 mm Hg				
		Reference Category		
>140/80 mm Hg	0.87**	0.72***	0.79**	0.74*
	(0.80,0.95)	(0.63,0.82)	(0.68,0.92)	(0.56,0.97)
Missing	2.68**	1.74	3.13	1.73
	(1.32,5.44)	(0.46,6.55)	(0.63,15.66)	(0.09,33.21)
Total Cholesterol <= 5 mmol/L				
		Reference Category		
>5 mmol/L	0.84**	0.84	0.91	0.76
	(0.75,0.95)	(0.70,1.01)	(0.71,1.16)	(0.48,1.19)
Missing	0.32***	0.19**	0.23*	0.19
	(0.19,0.53)	(0.06,0.64)	(0.06,0.93)	(0.01,2.78)
Hemoglobin A1c <= 59 mmol/mol				
		Reference Category		
59 - <=64 mmol/mol	0.83*	0.83	0.87	0.63*
	(0.72,0.96)	(0.67,1.02)	(0.68,1.12)	(0.40,0.99)
65 - <=75 mmol/mol	0.81**	0.91	0.91	0.79
	(0.71,0.94)	(0.74,1.12)	(0.71,1.16)	(0.51,1.21)
>75 mmol/mol	0.80*	1.00	1.07	1.03
	(0.67,0.96)	(0.77,1.30)	(0.79,1.47)	(0.60,1.76)
Missing	0.72***	0.66**	0.72	0.35**
	(0.61,0.84)	(0.51,0.86)	(0.52,1.01)	(0.18,0.71)

Microvascular Complication	1.16**	1.23**	1.05	1.19
	(1.04,1.29)	(1.06,1.43)	(0.87,1.25)	(0.86,1.65)
Macrovascular Complication	0.85**	0.82*	0.77**	0.63**
	(0.76,0.94)	(0.70,0.96)	(0.64,0.93)	(0.45,0.89)
Any Anti-Diabetic Agent	1.11*	0.97	1.12	1.95***
	(1.00,1.24)	(0.83,1.13)	(0.93,1.35)	(1.34,2.83)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Breast cancer – Part 1. **(continued on the following four pages)**

	BP ≤150/90 mm/Hg	BP ≤140/80 mm/Hg	TC ≤5 mmol/L	Albumin creatinine test	ACE-I/ARB
	OR* (95% CI)	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Index Year			Reference Category		
Year 2	1.01 (0.88,1.16)	1.08 (0.97,1.20)	1.08 (0.95,1.23)	1.21** (1.07,1.37)	0.80 (0.29,2.20)
Year 3	1.14 (0.98,1.33)	1.14* (1.02,1.29)	1.13 (0.98,1.29)	1.13 (0.99,1.29)	0.39 (0.13,1.16)
Year 4	1.12 (0.94,1.33)	1.39*** (1.21,1.59)	1.14 (0.97,1.33)	1.34*** (1.15,1.56)	0.33 (0.09,1.15)
Year 5	1.15 (0.94,1.40)	1.48*** (1.27,1.72)	1.18 (0.98,1.41)	1.35*** (1.14,1.61)	0.08*** (0.02,0.32)
Cancer (versus Control)	1.00 (0.85,1.18)	1.06 (0.93,1.20)	1.03 (0.88,1.21)	0.80** (0.68,0.95)	0.57 (0.05,5.98)
Age <60			Reference Category		
60 - <70	0.95 (0.75,1.21)	1.02 (0.85,1.23)	1.45** (1.15,1.82)	1.11 (0.87,1.40)	0.03 (0.00,6.46)
70 - <80	0.84 (0.66,1.07)	1.12 (0.94,1.35)	1.15 (0.92,1.45)	1.19 (0.93,1.51)	0.03 (0.00,5.30)
>= 80	0.56*** (0.43,0.74)	0.94 (0.76,1.16)	0.99 (0.76,1.28)	1.05 (0.80,1.38)	0.03 (0.00,5.21)

Year of Diagnosis 2000-2004			Reference Category		
2005-2009	1.39**	1.33***	0.71**	1.62***	0.11
	(1.13,1.71)	(1.12,1.57)	(0.57,0.88)	(1.30,2.02)	(0.00,13.25)
After 2009	1.48***	1.70***	0.60***	1.57***	0.06
	(1.18,1.87)	(1.42,2.05)	(0.48,0.76)	(1.24,2.00)	(0.00,8.37)
Index of Multiple Deprivation = 1			Reference Category		
2	1.08	1.13	1.06	1.03	1.06
	(0.83,1.41)	(0.92,1.39)	(0.82,1.37)	(0.79,1.35)	(0.04,31.39)
3	1.12	1.10	1.05	1.32*	0.21
	(0.86,1.46)	(0.90,1.36)	(0.81,1.36)	(1.01,1.73)	(0.00,13.00)
4	0.95	1.09	1.13	0.99	0.05
	(0.72,1.24)	(0.88,1.34)	(0.86,1.47)	(0.75,1.31)	(0.00,2.05)
5	0.97	1.08	0.99	1.09	0.05
	(0.72,1.31)	(0.86,1.37)	(0.73,1.33)	(0.80,1.48)	(0.00,2.20)
Missing	1.11	1.29**	1.24	1.41**	0.25
	(0.89,1.40)	(1.08,1.54)	(0.99,1.55)	(1.12,1.78)	(0.01,5.05)
Non Smoker			Reference Category		
Ex Smoker	0.98	0.98	1.01	0.98	1.83
	(0.84,1.16)	(0.87,1.11)	(0.86,1.18)	(0.83,1.15)	(0.25,13.24)
Current Smoker	0.78*	0.86	0.85	0.88	2.03
	(0.62,0.99)	(0.71,1.03)	(0.68,1.08)	(0.69,1.12)	(0.11,35.99)
Missing	0.90	0.85	0.79	0.70*	518.23
	(0.68,1.21)	(0.67,1.08)	(0.59,1.06)	(0.52,0.96)	(0.29,925053.08)

Drinker					
			Reference Category		
Non Drinker	0.75**	0.91	1.02	0.93	5.05
	(0.62,0.92)	(0.79,1.06)	(0.84,1.23)	(0.76,1.13)	(0.44,58.42)
Missing	0.81*	0.92	0.82*	0.89	0.57
	(0.68,0.96)	(0.81,1.05)	(0.69,0.96)	(0.75,1.05)	(0.06,5.15)
Body Mass Index <25 kg/m^2					
			Reference Category		
25 - <30	1.09	1.12	1.15	1.20	0.96
	(0.89,1.35)	(0.94,1.32)	(0.93,1.41)	(0.97,1.49)	(0.07,12.88)
>= 30	1.04	0.97	1.34**	1.04	2.86
	(0.85,1.27)	(0.83,1.14)	(1.10,1.63)	(0.85,1.28)	(0.21,39.61)
Missing	0.64*	0.84	0.65	0.46**	0.00***
	(0.42,0.96)	(0.59,1.20)	(0.43,1.00)	(0.29,0.74)	(0.00,0.00)
Charlson Comorbidity Index 1 - 2					
			Reference Category		
3 - 4	0.88	0.96	0.93	0.81*	0.27
	(0.74,1.05)	(0.84,1.10)	(0.79,1.10)	(0.68,0.97)	(0.02,3.01)
>4	0.98	1.09	0.92	0.82	0.27
	(0.75,1.27)	(0.89,1.34)	(0.71,1.19)	(0.63,1.07)	(0.02,4.77)
Blood Pressure <= 140/80 mm Hg					
			Reference Category		
>140/80 mm Hg	0.39***	0.39***	0.76***	0.83*	4.19
	(0.34,0.45)	(0.35,0.44)	(0.66,0.88)	(0.71,0.96)	(0.63,27.97)
Missing	0.25***	0.33**	0.48	0.50	
	(0.12,0.52)	(0.16,0.65)	(0.21,1.09)	(0.19,1.27)	NA

Total Cholesterol <= 5 mmol/L			Reference Category		
>5 mmol/L	0.68***	0.81**	0.11***	0.91	0.00***
	(0.57,0.80)	(0.71,0.93)	(0.09,0.13)	(0.77,1.09)	(0.00,0.01)
Missing	0.48***	0.57**	0.10***	0.42***	0.00***
	(0.32,0.72)	(0.40,0.81)	(0.07,0.16)	(0.27,0.67)	(0.00,0.00)
Hemoglobin A1c <= 59 mmol/mol			Reference Category		
59 - <=64 mmol/mol	0.88	0.81*	0.92	0.76*	0.78
	(0.68,1.13)	(0.67,0.98)	(0.72,1.18)	(0.59,0.98)	(0.02,29.38)
65 - <=75 mmol/mol	0.78*	0.90	0.79	0.64***	13.93
	(0.62,0.99)	(0.75,1.09)	(0.63,1.00)	(0.50,0.81)	(0.59,331.28)
>75 mmol/mol	0.70*	0.87	0.74*	0.62**	1.32
	(0.52,0.94)	(0.68,1.10)	(0.55,1.00)	(0.45,0.84)	(0.04,47.82)
Missing	0.72**	0.85	0.83	0.53***	3.97
	(0.58,0.91)	(0.71,1.03)	(0.66,1.04)	(0.42,0.67)	(0.05,326.03)
Microvascular Complication	0.99	0.95	1.02	1.09	0.23
	(0.82,1.19)	(0.82,1.09)	(0.85,1.23)	(0.90,1.32)	(0.03,1.96)
Macrovascular Complication	0.88	0.97	1.17	0.65***	1.58
	(0.72,1.08)	(0.83,1.14)	(0.96,1.44)	(0.53,0.80)	(0.13,19.02)
Any Anti-Diabetic Agent	0.81*	0.99	1.40***	0.92	3.58
	(0.67,0.97)	(0.86,1.13)	(1.18,1.66)	(0.76,1.10)	(0.30,42.42)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Breast cancer – Part 2. **(continued on the following four pages)**

	HbA1c ≤59 mmol/mol	HbA1c ≤64 mmol/mol	HbA1c ≤75 mmol/mol	Influenza Immunisation	Retinal Screening
	OR* (95% CI)	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Index Year			Reference Category		
Year 2	0.98 (0.87,1.11)	0.98 (0.86,1.12)	1.04 (0.89,1.21)	1.27* (1.05,1.53)	1.00 (0.89,1.12)
Year 3	0.89 (0.78,1.03)	0.91 (0.79,1.05)	0.88 (0.75,1.03)	1.22 (0.99,1.50)	0.94 (0.83,1.06)
Year 4	0.85* (0.73,1.00)	0.84* (0.71,0.99)	1.02 (0.85,1.24)	1.57*** (1.23,1.99)	0.89 (0.77,1.03)
Year 5	0.85 (0.71,1.01)	0.89 (0.74,1.07)	0.91 (0.74,1.13)	1.12 (0.86,1.45)	0.95 (0.81,1.11)
Cancer (versus Control)	0.72*** (0.61,0.85)	0.74*** (0.63,0.88)	0.86 (0.72,1.03)	0.95 (0.68,1.34)	1.03 (0.88,1.19)
Age <60			Reference Category		
60 - <70	1.48** (1.17,1.88)	1.56*** (1.23,1.98)	1.40** (1.10,1.79)	1.91** (1.19,3.07)	1.30* (1.05,1.61)
70 - <80	1.73*** (1.36,2.20)	1.84*** (1.45,2.34)	1.52*** (1.19,1.96)	2.42*** (1.50,3.92)	1.39** (1.13,1.73)
>= 80	2.05*** (1.55,2.69)	2.01*** (1.52,2.64)	1.41* (1.06,1.88)	1.74* (1.01,2.99)	1.19 (0.93,1.51)

Year of Diagnosis 2000-2004			Reference Category		
2005-2009	1.04	1.04	0.81	0.76	0.42***
	(0.83,1.29)	(0.83,1.30)	(0.64,1.03)	(0.48,1.20)	(0.34,0.51)
After 2009	1.05	0.98	0.78	0.90	0.38***
	(0.82,1.33)	(0.77,1.25)	(0.60,1.01)	(0.56,1.47)	(0.30,0.47)
Index of Multiple Deprivation = 1			Reference Category		
2	0.98	1.11	1.07	0.93	0.73**
	(0.74,1.28)	(0.84,1.47)	(0.80,1.43)	(0.53,1.61)	(0.57,0.93)
3	1.38*	1.25	1.21	1.15	0.78*
	(1.05,1.82)	(0.94,1.65)	(0.90,1.63)	(0.66,2.01)	(0.61,1.00)
4	1.15	1.00	0.86	1.02	0.84
	(0.87,1.52)	(0.75,1.32)	(0.64,1.16)	(0.58,1.79)	(0.65,1.07)
5	1.41*	1.26	1.07	0.58	0.83
	(1.03,1.92)	(0.92,1.73)	(0.77,1.49)	(0.31,1.07)	(0.63,1.09)
Missing	1.14	1.15	1.10	0.82	0.73**
	(0.90,1.44)	(0.91,1.46)	(0.86,1.42)	(0.51,1.32)	(0.59,0.90)
Non Smoker			Reference Category		
Ex Smoker	1.08	1.04	0.87	1.19	0.95
	(0.92,1.28)	(0.88,1.23)	(0.73,1.03)	(0.85,1.66)	(0.83,1.10)
Current Smoker	0.99	0.88	0.69**	0.73	0.87
	(0.77,1.26)	(0.68,1.12)	(0.53,0.89)	(0.45,1.18)	(0.70,1.08)
Missing	0.84	0.88	0.77	0.87	0.78
	(0.61,1.15)	(0.64,1.20)	(0.56,1.06)	(0.46,1.63)	(0.59,1.03)

Drinker					
			Reference Category		
Non Drinker	0.87	0.84	0.85	0.65*	0.91
	(0.71,1.06)	(0.69,1.04)	(0.68,1.05)	(0.43,0.96)	(0.77,1.09)
Missing	0.81*	0.76**	0.80*	0.84	0.77***
	(0.68,0.96)	(0.63,0.90)	(0.66,0.96)	(0.59,1.20)	(0.66,0.90)
Body Mass Index <25 kg/m^2					
			Reference Category		
25 - <30	1.00	0.97	1.01	1.07	1.10
	(0.80,1.25)	(0.77,1.22)	(0.79,1.28)	(0.69,1.67)	(0.91,1.33)
>= 30	0.94	0.96	0.94	0.99	1.13
	(0.76,1.16)	(0.77,1.19)	(0.74,1.18)	(0.65,1.51)	(0.94,1.37)
Missing	0.58*	0.53**	0.43***	0.48	0.43***
	(0.37,0.93)	(0.34,0.83)	(0.28,0.67)	(0.20,1.17)	(0.28,0.65)
Charlson Comorbidity Index 1 - 2					
			Reference Category		
3 - 4	0.80*	0.77**	0.94	1.18	0.97
	(0.67,0.96)	(0.65,0.93)	(0.77,1.13)	(0.83,1.70)	(0.83,1.13)
>4	0.77	0.76*	0.82	1.16	0.84
	(0.59,1.01)	(0.58,1.00)	(0.62,1.09)	(0.68,1.99)	(0.66,1.06)
Blood Pressure <= 140/80 mm Hg					
			Reference Category		
>140/80 mm Hg	0.80**	0.79**	0.80**	1.00	0.94
	(0.69,0.93)	(0.68,0.91)	(0.69,0.94)	(0.74,1.36)	(0.83,1.07)
Missing	0.32**	0.33**	0.33**	0.25	0.55
	(0.14,0.75)	(0.15,0.75)	(0.15,0.72)	(0.05,1.21)	(0.24,1.23)

Total Cholesterol <= 5 mmol/L					
			Reference Category		
>5 mmol/L	0.72***	0.71***	0.72***	0.36***	0.92
	(0.61,0.87)	(0.59,0.85)	(0.60,0.87)	(0.25,0.51)	(0.79,1.08)
Missing	0.82	0.69	0.55**	0.32*	0.49***
	(0.52,1.30)	(0.44,1.07)	(0.36,0.85)	(0.13,0.79)	(0.33,0.75)
Hemoglobin A1c <= 59 mmol/mol					
			Reference Category		
59 - <=64 mmol/mol	0.18***	0.26***	0.44***	1.56	1.24
	(0.14,0.23)	(0.20,0.33)	(0.34,0.58)	(0.91,2.68)	(0.99,1.56)
65 - <=75 mmol/mol	0.08***	0.10***	0.27***	0.87	1.22
	(0.06,0.10)	(0.08,0.13)	(0.21,0.35)	(0.53,1.43)	(0.98,1.52)
>75 mmol/mol	0.03***	0.04***	0.07***	0.41**	1.04
	(0.02,0.05)	(0.03,0.05)	(0.05,0.10)	(0.22,0.75)	(0.79,1.38)
Missing	0.29***	0.24***	0.22***	0.66	0.78*
	(0.23,0.37)	(0.19,0.30)	(0.17,0.28)	(0.41,1.07)	(0.63,0.97)
Microvascular Complication	0.90	0.90	0.86	1.00	1.39***
	(0.74,1.09)	(0.74,1.09)	(0.70,1.05)	(0.68,1.46)	(1.17,1.65)
Macrovascular Complication	0.85	0.80*	0.87	0.90	0.95
	(0.69,1.05)	(0.65,0.99)	(0.70,1.09)	(0.59,1.37)	(0.79,1.15)
Any Anti-Diabetic Agent	0.47***	0.68***	1.05	1.29	0.96
	(0.39,0.57)	(0.56,0.83)	(0.85,1.28)	(0.90,1.87)	(0.81,1.12)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Breast cancer – Part 3. **(continued on the following four pages)**

	Foot Exam	Dietary Review
	OR* (95% CI)	**OR* (95% CI)**
Index Year	Reference Category	
Year 2	2.51***	2.34*
	(2.15,2.94)	(1.19,4.61)
Year 3	6.51***	12.89***
	(5.43,7.81)	(3.51,47.30)
Year 4	19.09***	777.58***
	(15.47,23.55)	(65.38,9247.64)
Year 5	42.58***	5120.01***
	(33.37,54.33)	(217.27,120654.67)
Cancer (versus Control)	0.88	0.89
	(0.74,1.04)	(0.66,1.21)
Age <60	Reference Category	
60 - <70	0.94	0.96
	(0.74,1.20)	(0.62,1.48)
70 - <80	1.03	1.49
	(0.81,1.32)	(0.93,2.38)
>= 80	0.86	1.25
	(0.65,1.14)	(0.76,2.05)

Year of Diagnosis 2000-2004	Reference Category	
2005-2009	32.84***	0.00***
	(22.63,47.67)	(0.00,0.00)
After 2009	1722.48***	.
	(1101.72,2692.99)	(1101.72,2692.99)
Index of Multiple Deprivation = 1	Reference Category	
2	1.22	0.80
	(0.93,1.60)	(0.50,1.28)
3	1.15	0.83
	(0.88,1.52)	(0.51,1.35)
4	1.08	0.68
	(0.82,1.43)	(0.41,1.13)
5	0.98	0.88
	(0.72,1.33)	(0.51,1.54)
Missing	1.01	1.34
	(0.80,1.27)	(0.90,1.99)
Non Smoker	Reference Category	
Ex Smoker	0.95	0.80
	(0.81,1.11)	(0.61,1.06)
Current Smoker	0.90	0.89
	(0.71,1.15)	(0.59,1.35)
Missing	0.85	1.18
	(0.57,1.28)	(0.55,2.51)

Drinker		
Non Drinker	1.00	0.82
	(0.83,1.21)	(0.59,1.15)
Missing	0.78**	0.87
	(0.66,0.92)	(0.65,1.16)
Body Mass Index <25 kg/m^2		
25 - <30	0.98	1.09
	(0.79,1.21)	(0.74,1.59)
>= 30	0.88	1.00
	(0.72,1.09)	(0.70,1.43)
Missing	0.46*	0.60
	(0.24,0.91)	(0.15,2.43)
Charlson Comorbidity Index 1 - 2		
3 - 4	1.19*	0.85
	(1.00,1.42)	(0.63,1.15)
>4	1.30*	0.93
	(1.00,1.68)	(0.60,1.44)
Blood Pressure <= 140/80 mm Hg		
>140/80 mm Hg	0.82**	0.56***
	(0.70,0.95)	(0.40,0.79)
Missing	1.71	1.08
	(0.33,8.81)	(0.04,29.80)

Total Cholesterol <= 5 mmol/L	Reference Category	
>5 mmol/L	0.87	0.93
	(0.72,1.04)	(0.67,1.28)
Missing	0.24*	.
	(0.08,0.72)	(0.08,0.72)
Hemoglobin A1c <= 59 mmol/mol	Reference Category	
59 - <=64 mmol/mol	0.69**	0.99
	(0.53,0.89)	(0.64,1.54)
65 - <=75 mmol/mol	0.83	0.96
	(0.65,1.06)	(0.63,1.47)
>75 mmol/mol	0.58**	0.68
	(0.42,0.81)	(0.37,1.25)
Missing	0.63***	0.41**
	(0.48,0.83)	(0.22,0.77)
Microvascular Complication	1.34**	1.53*
	(1.11,1.61)	(1.09,2.15)
Macrovascular Complication	0.81*	0.93
	(0.65,1.00)	(0.64,1.34)
Any Anti-Diabetic Agent	1.21*	0.84
	(1.01,1.45)	(0.61,1.15)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Colorectal cancer – Part 1. **(continued on the following three pages)**

	BP ≤150/90 mm/Hg	BP ≤140/80 mm/Hg	TC ≤5 mmol/L	Albumin creatinine test	ACE-I/ARB
	OR* (95% CI)	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Index Year			Reference Category		
Year 2	1.03 (0.90,1.17)	1.06 (0.96,1.17)	1.22*** (1.09,1.38)	1.06 (0.95,1.19)	0.94 (0.54,1.62)
Year 3	1.42*** (1.22,1.65)	1.29*** (1.15,1.43)	1.41*** (1.23,1.61)	1.28*** (1.12,1.45)	0.85 (0.46,1.57)
Year 4	1.53*** (1.29,1.81)	1.54*** (1.36,1.74)	1.37*** (1.17,1.59)	1.31*** (1.13,1.51)	0.52 (0.25,1.09)
Year 5	1.84*** (1.50,2.25)	1.71*** (1.48,1.97)	1.57*** (1.31,1.88)	1.42*** (1.20,1.67)	0.26** (0.11,0.64)
Cancer (versus Control)	0.96 (0.81,1.13)	0.99 (0.87,1.11)	0.80** (0.68,0.93)	0.81* (0.68,0.97)	0.76 (0.23,2.56)
Age <60			Reference Category		
60 - <70	0.82 (0.61,1.09)	0.93 (0.76,1.15)	1.21 (0.93,1.58)	1.24 (0.92,1.68)	0.08 (0.00,1.49)
70 - <80	0.70* (0.53,0.92)	0.99 (0.81,1.21)	1.36* (1.05,1.76)	1.14 (0.85,1.52)	0.05* (0.00,0.84)
>= 80	0.75 (0.55,1.02)	0.99 (0.80,1.24)	1.10 (0.83,1.46)	1.05 (0.76,1.45)	0.01** (0.00,0.22)
Female (versus Male)	0.88 (0.76,1.02)	0.88* (0.79,0.98)	0.53*** (0.46,0.60)	1.10 (0.94,1.28)	2.01 (0.60,6.71)

Year of Diagnosis 2000-2004					
			Reference Category		
2005-2009	1.78***	1.44***	1.17	1.97***	0.44
	(1.46,2.16)	(1.23,1.68)	(0.96,1.43)	(1.56,2.48)	(0.03,6.57)
After 2009	2.32***	2.08***	1.26*	2.22***	0.20
	(1.86,2.88)	(1.75,2.46)	(1.01,1.56)	(1.74,2.85)	(0.01,3.13)
Index of Multiple Deprivation = 1					
			Reference Category		
2	1.20	1.14	0.97	0.80	1.87
	(0.93,1.54)	(0.95,1.38)	(0.76,1.24)	(0.61,1.06)	(0.23,15.02)
3	1.06	1.04	0.90	0.83	0.74
	(0.83,1.36)	(0.86,1.26)	(0.71,1.15)	(0.63,1.09)	(0.11,5.11)
4	1.22	1.12	1.16	0.70*	0.41
	(0.94,1.58)	(0.92,1.35)	(0.90,1.50)	(0.53,0.93)	(0.06,2.62)
5	1.15	1.14	1.20	0.85	1.12
	(0.87,1.50)	(0.93,1.40)	(0.92,1.57)	(0.63,1.15)	(0.12,10.25)
Missing	1.24*	1.29**	1.00	1.08	0.18*
	(1.01,1.54)	(1.10,1.51)	(0.81,1.23)	(0.85,1.36)	(0.04,0.87)
Non Smoker					
			Reference Category		
Ex Smoker	0.98	1.05	0.92	0.97	1.20
	(0.84,1.15)	(0.93,1.17)	(0.79,1.07)	(0.82,1.15)	(0.35,4.12)
Current Smoker	1.01	1.08	0.80	0.78	0.36
	(0.79,1.28)	(0.90,1.29)	(0.64,1.00)	(0.60,1.01)	(0.06,1.99)
Missing	0.92	1.08	0.82	0.63**	0.18
	(0.70,1.21)	(0.86,1.34)	(0.62,1.07)	(0.46,0.87)	(0.01,2.37)

Drinker					
			Reference Category		
Non Drinker	0.90	1.06	0.96	0.84	0.19*
	(0.73,1.11)	(0.91,1.24)	(0.78,1.17)	(0.67,1.06)	(0.05,0.81)
Missing	0.88	0.92	0.89	0.70***	0.44
	(0.76,1.01)	(0.82,1.02)	(0.77,1.03)	(0.60,0.82)	(0.14,1.38)
Body Mass Index <25 kg/m^2			Reference Category		
25 - <30	1.37**	1.11	1.09	1.28*	2.44
	(1.13,1.65)	(0.97,1.28)	(0.91,1.31)	(1.05,1.57)	(0.64,9.24)
>= 30	1.05	0.95	1.13	1.30*	6.32**
	(0.87,1.26)	(0.82,1.09)	(0.94,1.36)	(1.06,1.60)	(1.62,24.65)
Missing	0.86	0.97	0.87	0.84	1.50
	(0.56,1.32)	(0.68,1.39)	(0.56,1.34)	(0.50,1.40)	(0.01,301.86)
Charlson Comorbidity Index 1 - 2			Reference Category		
3 - 4	1.02	1.16*	0.92	0.82*	0.55
	(0.87,1.20)	(1.03,1.31)	(0.79,1.07)	(0.69,0.98)	(0.15,1.95)
>4	0.90	1.11	0.89	0.63***	0.25
	(0.72,1.14)	(0.94,1.33)	(0.71,1.12)	(0.49,0.81)	(0.05,1.23)
Blood Pressure <= 140/80 mm Hg			Reference Category		
>140/80 mm Hg	0.40***	0.39***	0.84**	0.91	1.51
	(0.35,0.45)	(0.35,0.43)	(0.73,0.95)	(0.79,1.06)	(0.53,4.28)
Missing	0.38***	0.46**	0.76	1.20	8.24e+17
	(0.22,0.66)	(0.28,0.75)	(0.43,1.36)	(0.59,2.47)	(0.00,.)

Total Cholesterol <= 5 mmol/L					
			Reference Category		
>5 mmol/L	0.75**	0.82**	0.13***	0.78*	0.47
	(0.62,0.89)	(0.71,0.94)	(0.11,0.15)	(0.64,0.95)	(0.10,2.17)
Missing	0.61*	0.63**	0.19***	0.50**	0.00
	(0.41,0.89)	(0.45,0.88)	(0.13,0.28)	(0.31,0.81)	(0.00,.)
Hemoglobin A1c <= 59 mmol/mol					
			Reference Category		
59 - <=64 mmol/mol	0.85	0.90	0.86	0.83	0.49
	(0.68,1.07)	(0.76,1.07)	(0.69,1.07)	(0.65,1.06)	(0.10,2.28)
65 - <=75 mmol/mol	0.76*	0.81*	0.79*	0.69**	0.85
	(0.61,0.96)	(0.68,0.96)	(0.63,0.99)	(0.54,0.88)	(0.18,4.04)
>75 mmol/mol	0.70**	0.77**	0.89	0.52***	4.42
	(0.54,0.91)	(0.63,0.94)	(0.69,1.15)	(0.39,0.69)	(0.58,33.72)
Missing	0.71**	0.77**	0.62***	0.53***	0.29
	(0.58,0.87)	(0.65,0.90)	(0.51,0.76)	(0.42,0.67)	(0.04,2.07)
Microvascular Complication	0.90	0.93	1.05	0.96	0.57
	(0.76,1.07)	(0.82,1.06)	(0.89,1.23)	(0.80,1.15)	(0.18,1.88)
Macrovascular Complication	0.93	1.09	1.04	0.72***	1.31
	(0.79,1.09)	(0.96,1.23)	(0.88,1.22)	(0.60,0.86)	(0.43,4.00)
Any Anti-Diabetic Agent	1.17	1.12	1.28**	0.98	0.44
	(1.00,1.38)	(0.99,1.27)	(1.09,1.49)	(0.82,1.17)	(0.10,1.89)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Colorectal cancer – Part 2. **(continued on the following three pages)**

	HbA1c ≤59 mmol/mol	HbA1c ≤64 mmol/mol	HbA1c ≤75 mmol/mol	Influenza Immunisation	Retinal Screening
	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
Index Year			Reference Category		
Year 2	0.93 (0.83,1.04)	0.99 (0.87,1.12)	0.98 (0.85,1.14)	1.19* (1.00,1.42)	0.88* (0.79,0.98)
Year 3	0.80*** (0.70,0.91)	0.89 (0.77,1.02)	0.86 (0.73,1.01)	1.23* (1.00,1.50)	0.85** (0.76,0.96)
Year 4	0.74*** (0.64,0.86)	0.80** (0.69,0.94)	0.93 (0.77,1.11)	1.23 (0.98,1.55)	0.77*** (0.67,0.88)
Year 5	0.74*** (0.63,0.87)	0.78** (0.65,0.93)	0.90 (0.73,1.11)	1.30 (1.00,1.69)	0.69*** (0.59,0.81)
Cancer (versus Control)	0.80* (0.68,0.95)	0.77** (0.65,0.91)	0.76** (0.63,0.91)	0.96 (0.67,1.36)	1.03 (0.88,1.20)
Age <60			Reference Category		
60 - <70	1.61** (1.21,2.16)	1.84*** (1.39,2.44)	1.78*** (1.33,2.39)	1.39 (0.79,2.45)	1.09 (0.83,1.43)
70 - <80	1.96*** (1.48,2.59)	2.31*** (1.76,3.03)	2.17*** (1.63,2.89)	2.44** (1.40,4.24)	1.08 (0.83,1.40)
>= 80	2.00*** (1.46,2.72)	2.28*** (1.68,3.09)	1.97*** (1.43,2.71)	2.98*** (1.61,5.53)	0.96 (0.72,1.29)
Female (versus Male)	1.16 (0.99,1.35)	1.16 (0.99,1.35)	1.22* (1.03,1.44)	0.86 (0.63,1.18)	0.94 (0.81,1.08)

Year of Diagnosis 2000-2004			Reference Category		
2005-2009	0.98	0.87	0.93	0.64	0.54***
	(0.78,1.23)	(0.70,1.09)	(0.74,1.19)	(0.40,1.03)	(0.44,0.67)
After 2009	0.97	0.89	1.00	0.81	0.43***
	(0.76,1.23)	(0.69,1.13)	(0.77,1.30)	(0.50,1.33)	(0.34,0.54)
Index of Multiple Deprivation = 1			Reference Category		
2	1.05	1.20	1.27	1.00	0.84
	(0.81,1.38)	(0.92,1.57)	(0.94,1.70)	(0.58,1.75)	(0.66,1.07)
3	1.00	1.07	1.13	1.17	0.86
	(0.76,1.31)	(0.81,1.40)	(0.85,1.52)	(0.67,2.04)	(0.67,1.11)
4	0.90	0.88	0.80	0.77	0.91
	(0.68,1.18)	(0.67,1.15)	(0.59,1.07)	(0.44,1.34)	(0.71,1.18)
5	1.23	1.20	1.25	0.58	0.83
	(0.91,1.65)	(0.89,1.61)	(0.90,1.72)	(0.32,1.04)	(0.63,1.09)
Missing	1.20	1.20	1.21	1.02	0.85
	(0.95,1.50)	(0.96,1.51)	(0.94,1.55)	(0.64,1.62)	(0.69,1.05)
Non Smoker			Reference Category		
Ex Smoker	0.96	0.98	0.97	1.26	0.93
	(0.82,1.14)	(0.83,1.16)	(0.81,1.16)	(0.90,1.77)	(0.80,1.08)
Current Smoker	0.91	0.84	0.77	0.73	0.70**
	(0.71,1.17)	(0.65,1.08)	(0.59,1.01)	(0.44,1.19)	(0.55,0.88)
Missing	0.76	0.81	0.82	1.38	0.90
	(0.55,1.04)	(0.59,1.10)	(0.59,1.14)	(0.72,2.63)	(0.67,1.21)

Drinker					
			Reference Category		
Non Drinker	0.96	0.88	0.88	0.54**	0.78*
	(0.77,1.19)	(0.71,1.10)	(0.69,1.12)	(0.34,0.83)	(0.64,0.96)
Missing	0.89	0.89	0.79**	0.58***	0.67***
	(0.76,1.04)	(0.76,1.04)	(0.67,0.94)	(0.42,0.79)	(0.58,0.77)
Body Mass Index <25 kg/m^2					
			Reference Category		
25 - <30	1.01	1.17	1.36**	0.90	0.99
	(0.83,1.24)	(0.95,1.43)	(1.10,1.70)	(0.59,1.35)	(0.83,1.19)
>= 30	0.88	0.96	1.11	0.82	1.05
	(0.72,1.08)	(0.79,1.18)	(0.89,1.38)	(0.54,1.25)	(0.87,1.26)
Missing	0.68	0.72	0.73	0.21**	0.52**
	(0.41,1.12)	(0.44,1.17)	(0.44,1.20)	(0.08,0.55)	(0.33,0.84)
Charlson Comorbidity Index 1 - 2					
			Reference Category		
3 - 4	0.82*	0.82*	0.89	1.45*	1.04
	(0.69,0.97)	(0.70,0.98)	(0.74,1.07)	(1.03,2.05)	(0.89,1.21)
>4	0.83	0.74*	0.77*	2.37***	0.92
	(0.65,1.06)	(0.58,0.95)	(0.59,1.00)	(1.42,3.94)	(0.74,1.15)
Blood Pressure <= 140/80 mm Hg					
			Reference Category		
>140/80 mm Hg	0.94	0.96	0.96	0.76	1.02
	(0.82,1.09)	(0.83,1.10)	(0.82,1.12)	(0.57,1.02)	(0.89,1.16)
Missing	1.14	0.98	1.10	0.58	0.90
	(0.57,2.27)	(0.51,1.89)	(0.57,2.10)	(0.16,2.10)	(0.47,1.72)

Total Cholesterol <= 5 mmol/L			Reference Category		
>5 mmol/L	0.78*	0.70***	0.72**	0.39***	0.94
	(0.64,0.96)	(0.58,0.85)	(0.58,0.88)	(0.27,0.58)	(0.79,1.13)
Missing	0.35***	0.34***	0.35***	0.35*	0.61*
	(0.22,0.56)	(0.22,0.53)	(0.22,0.55)	(0.14,0.87)	(0.39,0.95)
Hemoglobin A1c <= 59 mmol/mol			Reference Category		
59 - <=64 mmol/mol	0.18***	0.27***	0.54***	0.87	1.08
	(0.14,0.23)	(0.22,0.34)	(0.42,0.70)	(0.53,1.41)	(0.87,1.34)
65 - <=75 mmol/mol	0.09***	0.11***	0.27***	0.80	0.90
	(0.07,0.12)	(0.09,0.14)	(0.21,0.34)	(0.49,1.31)	(0.72,1.13)
>75 mmol/mol	0.04***	0.04***	0.08***	0.82	0.89
	(0.03,0.05)	(0.03,0.05)	(0.06,0.11)	(0.47,1.44)	(0.69,1.15)
Missing	0.34***	0.29***	0.30***	0.64	0.55***
	(0.27,0.42)	(0.23,0.37)	(0.24,0.38)	(0.40,1.01)	(0.45,0.69)
Microvascular Complication	0.90	0.88	0.94	0.96	1.41***
	(0.75,1.07)	(0.74,1.05)	(0.78,1.14)	(0.67,1.38)	(1.20,1.66)
Macrovascular Complication	0.91	0.86	0.81*	0.72	0.99
	(0.76,1.08)	(0.72,1.02)	(0.67,0.97)	(0.50,1.02)	(0.85,1.16)
Any Anti-Diabetic Agent	0.42***	0.53***	0.94	1.13	1.05
	(0.35,0.50)	(0.44,0.65)	(0.77,1.15)	(0.79,1.62)	(0.89,1.23)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Colorectal cancer – Part 3. **(continued on the following three pages)**

	Foot Exam	Dietary Review	Erectile Dysfunction (Asked)	Erectile Dysfunction (Advice)
	OR* (95% CI)	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Index Year		Reference Category		
Year 2	2.14*** (1.86,2.46)	2.35*** (1.51,3.64)	1.91** (1.22,3.00)	3.04** (1.31,7.02)
Year 3	7.76*** (6.57,9.16)	10.80*** (4.51,25.84)	6.07*** (2.60,14.16)	9.48*** (2.51,35.86)
Year 4	20.39*** (16.87,24.64)	462.71*** (97.28,2200.83)	223.34*** (44.80,1113.42)	173.69*** (18.25,1652.98)
Year 5	51.13*** (40.92,63.90)	2135.18*** (320.12,14241.40)	1090.06*** (156.98,7569.39)	2172.66*** (91.61,51527.19)
Cancer (versus Control)	0.92 (0.78,1.09)	1.02 (0.80,1.28)	1.00 (0.75,1.32)	1.26 (0.71,2.26)
Age <60		Reference Category		
60 - <70	0.78 (0.59,1.03)	0.62* (0.42,0.93)	0.62* (0.40,0.95)	0.85 (0.37,1.98)
70 - <80	1.01 (0.77,1.33)	0.69 (0.47,1.01)	0.64* (0.42,0.97)	0.52 (0.22,1.26)
>= 80	0.96 (0.71,1.30)	0.65* (0.43,0.99)	0.64 (0.40,1.03)	0.16** (0.05,0.56)
Female (versus Male)	1.02 (0.88,1.19)	1.01 (0.82,1.25)	Not Applicable	

Year of Diagnosis 2000-2004	Reference Category			
2005-2009	43.17*** (29.67,62.81)	All data 0.		
After 2009	3171.19*** (2033.45,4945.51)			
Index of Multiple Deprivation = 1		Reference Category		
2	1.09 (0.85,1.41)	1.12 (0.78,1.60)	1.13 (0.75,1.72)	0.82 (0.32,2.12)
3	1.25 (0.97,1.61)	0.86 (0.59,1.25)	0.85 (0.55,1.33)	1.44 (0.56,3.68)
4	1.41** (1.09,1.82)	1.13 (0.78,1.63)	1.39 (0.89,2.16)	2.73* (1.02,7.32)
5	1.26 (0.95,1.66)	1.34 (0.90,2.00)	1.07 (0.65,1.74)	0.96 (0.32,2.88)
Missing	1.21 (0.98,1.50)	1.29 (0.96,1.75)	1.18 (0.83,1.67)	1.55 (0.73,3.32)
Non Smoker		Reference Category		
Ex Smoker	0.99 (0.85,1.16)	0.99 (0.80,1.23)	0.86 (0.66,1.14)	0.90 (0.51,1.60)
Current Smoker	0.90 (0.71,1.14)	0.93 (0.66,1.30)	1.05 (0.70,1.57)	1.01 (0.43,2.36)
Missing	1.06 (0.74,1.53)	1.52 (0.90,2.57)	0.93 (0.43,1.97)	1.00 (0.19,5.25)

Drinker				
	Reference Category			
Non Drinker	0.90	1.04	0.96	0.62
	(0.73,1.10)	(0.79,1.37)	(0.66,1.41)	(0.26,1.48)
Missing	0.78***	0.92	0.95	1.02
	(0.67,0.90)	(0.75,1.13)	(0.75,1.20)	(0.63,1.67)
Body Mass Index <25 kg/m^2				
	Reference Category			
25 - <30	1.03	1.11	1.10	1.61
	(0.85,1.24)	(0.84,1.45)	(0.79,1.53)	(0.74,3.48)
>= 30	0.99	1.04	1.04	1.55
	(0.82,1.20)	(0.79,1.36)	(0.74,1.47)	(0.71,3.40)
Missing	0.56	0.55	0.19	0.25
	(0.29,1.09)	(0.19,1.61)	(0.03,1.17)	(0.01,11.56)
Charlson Comorbidity Index 1 - 2				
	Reference Category			
3 - 4	1.08	1.09	0.94	0.72
	(0.92,1.27)	(0.87,1.36)	(0.71,1.23)	(0.40,1.30)
>4	1.16	1.23	1.14	1.20
	(0.92,1.46)	(0.89,1.70)	(0.78,1.66)	(0.54,2.66)
Blood Pressure <= 140/80 mm Hg				
	Reference Category			
>140/80 mm Hg	0.87	0.84	0.96	1.10
	(0.76,1.00)	(0.69,1.02)	(0.76,1.21)	(0.68,1.77)
Missing	2.24	0.86	11.77*	24.18
	(0.77,6.51)	(0.11,6.48)	(1.11,125.23)	(0.18,3200.97)

Total Cholesterol <= 5 mmol/L		Reference Category		
>5 mmol/L	0.79*	1.01	0.89	0.92
	(0.65,0.96)	(0.77,1.34)	(0.61,1.30)	(0.42,2.03)
Missing	0.31**	0.21	0.12	0.02
	(0.14,0.69)	(0.04,1.23)	(0.01,1.30)	(0.00,10.39)
Hemoglobin A1c <= 59 mmol/mol		Reference Category		
59 - <=64 mmol/mol	0.85	0.79	0.93	0.42
	(0.68,1.07)	(0.57,1.08)	(0.65,1.34)	(0.18,1.01)
65 - <=75 mmol/mol	0.77*	0.96	0.90	1.10
	(0.61,0.98)	(0.70,1.33)	(0.63,1.30)	(0.54,2.24)
>75 mmol/mol	0.93	0.84	0.73	0.56
	(0.70,1.23)	(0.57,1.26)	(0.45,1.19)	(0.21,1.55)
Missing	0.82	0.82	0.70	0.29
	(0.64,1.05)	(0.56,1.19)	(0.42,1.18)	(0.08,1.02)
Microvascular Complication	1.07	1.06	0.99	1.08
	(0.91,1.27)	(0.84,1.33)	(0.76,1.30)	(0.61,1.91)
Macrovascular Complication	0.93	0.85	0.83	0.45*
	(0.78,1.10)	(0.67,1.07)	(0.63,1.09)	(0.23,0.88)
Any Anti-Diabetic Agent	1.09	0.95	1.05	2.17*
	(0.92,1.29)	(0.76,1.20)	(0.79,1.40)	(1.06,4.43)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Prostate cancer – Part 1. **(continued on the following three pages)**

	BP ≤150/90 mm/Hg	BP ≤140/80 mm/Hg	TC ≤5 mmol/L	Albumin creatinine test	ACE-I/ARB
	OR* (95% CI)	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Index Year			Reference Category		
Year 2	1.20** (1.05,1.37)	1.22*** (1.10,1.34)	1.08 (0.95,1.22)	1.08 (0.97,1.21)	0.64 (0.34,1.20)
Year 3	1.31*** (1.13,1.51)	1.36*** (1.22,1.52)	1.21** (1.06,1.39)	1.31*** (1.16,1.49)	0.51 (0.25,1.03)
Year 4	1.48*** (1.25,1.75)	1.62*** (1.43,1.84)	1.39*** (1.19,1.63)	1.34*** (1.16,1.54)	0.46 (0.20,1.04)
Year 5	1.45*** (1.19,1.75)	1.73*** (1.50,2.00)	1.39*** (1.16,1.67)	1.40*** (1.19,1.65)	0.47 (0.18,1.25)
Cancer (versus Control)	1.16 (1.00,1.35)	1.06 (0.95,1.19)	0.66*** (0.57,0.76)	0.86 (0.73,1.01)	0.33 (0.09,1.14)
Age <60			Reference Category		
60 - <70	1.34 (0.96,1.89)	1.50** (1.15,1.97)	1.27 (0.90,1.77)	1.00 (0.68,1.46)	0.52 (0.00,58.49)
70 - <80	1.20 (0.86,1.67)	1.67*** (1.28,2.18)	1.39 (0.99,1.94)	0.87 (0.59,1.26)	0.18 (0.00,18.51)
>= 80	1.18 (0.82,1.70)	1.65*** (1.24,2.21)	1.07 (0.75,1.54)	0.81 (0.54,1.22)	0.01 (0.00,1.73)

Year of Diagnosis 2000-2004			Reference Category		
2005-2009	1.45***	1.38***	1.09	1.46***	0.48
	(1.20,1.74)	(1.19,1.61)	(0.90,1.32)	(1.18,1.80)	(0.03,7.44)
After 2009	1.91***	1.99***	1.09	2.09***	0.48
	(1.55,2.34)	(1.69,2.34)	(0.89,1.34)	(1.67,2.62)	(0.03,7.55)
Index of Multiple Deprivation = 1			Reference Category		
2	0.87	0.97	1.17	1.13	0.08*
	(0.68,1.10)	(0.81,1.16)	(0.93,1.46)	(0.88,1.44)	(0.01,0.70)
3	0.79	0.90	1.05	1.41**	0.32
	(0.63,1.00)	(0.75,1.07)	(0.84,1.32)	(1.10,1.81)	(0.04,2.88)
4	0.67**	0.88	1.15	1.06	0.89
	(0.52,0.85)	(0.73,1.07)	(0.90,1.46)	(0.81,1.37)	(0.08,9.67)
5	0.74*	0.90	0.93	1.09	0.10
	(0.56,0.98)	(0.73,1.12)	(0.71,1.21)	(0.81,1.47)	(0.01,1.07)
Missing	0.90	1.05	1.24*	1.17	0.25
	(0.73,1.10)	(0.89,1.22)	(1.02,1.50)	(0.94,1.44)	(0.04,1.69)
Non Smoker			Reference Category		
Ex Smoker	0.97	1.02	1.19*	1.09	0.82
	(0.83,1.14)	(0.90,1.16)	(1.02,1.39)	(0.92,1.29)	(0.21,3.29)
Current Smoker	0.90	1.00	1.00	0.83	0.95
	(0.71,1.15)	(0.82,1.20)	(0.79,1.27)	(0.64,1.08)	(0.12,7.46)
Missing	1.03	1.25*	0.89	0.98	4.86
	(0.78,1.35)	(1.00,1.57)	(0.68,1.16)	(0.72,1.33)	(0.14,163.72)

Drinker					
			Reference Category		
Non Drinker	1.09	1.07	1.02	1.22	0.09**
	(0.86,1.39)	(0.90,1.28)	(0.81,1.28)	(0.95,1.57)	(0.02,0.49)
Missing	0.90	0.92	1.00	0.73***	0.65
	(0.78,1.03)	(0.83,1.03)	(0.87,1.15)	(0.63,0.84)	(0.20,2.12)
Body Mass Index <25 kg/m^2					
			Reference Category		
25 - <30	1.04	0.95	1.08	1.18	3.38
	(0.87,1.25)	(0.83,1.10)	(0.91,1.29)	(0.97,1.43)	(0.68,16.92)
>= 30	0.95	0.85*	1.06	1.01	1.64
	(0.78,1.15)	(0.73,0.99)	(0.88,1.28)	(0.82,1.24)	(0.32,8.41)
Missing	0.70	0.88	0.83	0.51**	5.56
	(0.46,1.09)	(0.60,1.29)	(0.54,1.29)	(0.30,0.85)	(0.00,18667.21)
Charlson Comorbidity Index 1 - 2					
			Reference Category		
3 - 4	0.95	1.02	0.77***	0.94	0.70
	(0.81,1.11)	(0.90,1.15)	(0.66,0.89)	(0.79,1.11)	(0.18,2.70)
>4	1.06	1.19	0.78*	0.90	0.36
	(0.84,1.35)	(0.99,1.43)	(0.62,0.98)	(0.70,1.16)	(0.07,1.93)
Blood Pressure <= 140/80 mm Hg					
			Reference Category		
>140/80 mm Hg	0.42***	0.35***	0.92	0.91	0.82
	(0.36,0.47)	(0.32,0.39)	(0.81,1.04)	(0.79,1.04)	(0.26,2.55)
Missing	0.47*	0.45**	2.44**	1.66	4.01
	(0.26,0.87)	(0.26,0.78)	(1.31,4.53)	(0.79,3.52)	(0.00,97994.62)

Total Cholesterol <= 5 mmol/L			Reference Category		
>5 mmol/L	0.71***	0.80***	0.13***	0.82***	0.15***
	(0.64,0.78)	(0.74,0.87)	(0.12,0.14)	(0.73,0.91)	(0.05,0.44)
Missing	0.59***	0.66***	0.15***	0.46***	0.00*
	(0.47,0.74)	(0.55,0.81)	(0.12,0.19)	(0.35,0.60)	(0.00,0.45)
Hemoglobin A1c <= 59 mmol/mol			Reference Category		
59 - <=64 mmol/mol	0.82	0.93	1.01	0.93	1.98
	(0.66,1.02)	(0.78,1.11)	(0.81,1.27)	(0.74,1.19)	(0.30,13.34)
65 - <=75 mmol/mol	0.83	0.90	0.96	0.90	2.30
	(0.67,1.04)	(0.76,1.07)	(0.77,1.20)	(0.71,1.14)	(0.34,15.71)
>75 mmol/mol	0.63***	0.84	0.74*	0.62**	0.18
	(0.48,0.82)	(0.67,1.05)	(0.57,0.97)	(0.46,0.84)	(0.02,1.45)
Missing	0.61***	0.72***	0.55***	0.58***	0.47
	(0.50,0.76)	(0.61,0.85)	(0.45,0.68)	(0.46,0.74)	(0.05,4.65)
Microvascular Complication	0.91	0.94	1.02	0.81*	0.64
	(0.77,1.08)	(0.83,1.08)	(0.87,1.20)	(0.68,0.96)	(0.17,2.36)
Macrovascular Complication	1.30**	1.35***	1.36***	0.89	3.19
	(1.11,1.53)	(1.20,1.53)	(1.17,1.59)	(0.76,1.05)	(0.88,11.61)
Any Anti-Diabetic Agent	1.07	1.08	1.26**	1.12	0.73
	(0.92,1.26)	(0.96,1.23)	(1.08,1.46)	(0.94,1.32)	(0.16,3.31)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

Prostate cancer – Part 2. **(continued on the following three pages)**

	HbA1c ≤59 mmol/mol	HbA1c ≤64 mmol/mol	HbA1c ≤75 mmol/mol	Influenza Immunisation	Retinal Screening
	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
Index Year			Reference Category		
Year 2	1.01 (0.90,1.13)	1.00 (0.89,1.13)	1.07 (0.93,1.24)	1.20* (1.00,1.44)	0.86** (0.78,0.96)
Year 3	1.00 (0.88,1.13)	0.98 (0.86,1.12)	1.08 (0.93,1.27)	1.14 (0.94,1.40)	0.81*** (0.72,0.91)
Year 4	1.02 (0.89,1.18)	1.05 (0.90,1.23)	1.26* (1.05,1.51)	1.25 (1.00,1.58)	0.70*** (0.61,0.80)
Year 5	0.95 (0.81,1.12)	0.86 (0.72,1.02)	0.97 (0.79,1.19)	1.61*** (1.23,2.11)	0.62*** (0.53,0.72)
Cancer (versus Control)	0.79** (0.68,0.92)	0.73*** (0.63,0.85)	0.79** (0.67,0.93)	2.18*** (1.56,3.06)	0.91 (0.79,1.05)
Age <60			Reference Category		
60 - <70	1.56* (1.09,2.23)	1.47* (1.04,2.09)	1.60* (1.11,2.29)	3.00** (1.50,6.01)	1.14 (0.82,1.59)
70 - <80	1.79** (1.26,2.55)	1.84*** (1.31,2.61)	1.99*** (1.39,2.84)	4.72*** (2.37,9.39)	1.23 (0.88,1.71)
>= 80	1.83** (1.25,2.68)	1.67** (1.14,2.43)	1.66* (1.12,2.45)	5.12*** (2.39,10.93)	0.84 (0.59,1.20)

Year of Diagnosis 2000-2004			Reference Category		
2005-2009	0.84	0.79*	0.80*	0.73	0.43***
	(0.68,1.03)	(0.64,0.96)	(0.65,1.00)	(0.47,1.13)	(0.35,0.52)
After 2009	0.84	0.76*	0.80	1.02	0.28***
	(0.67,1.04)	(0.61,0.94)	(0.63,1.01)	(0.65,1.60)	(0.23,0.34)
Index of Multiple Deprivation = 1			Reference Category		
2	1.01	1.00	0.81	0.71	0.79*
	(0.79,1.28)	(0.79,1.28)	(0.62,1.06)	(0.42,1.18)	(0.63,0.99)
3	0.84	0.79	0.76*	0.82	0.69**
	(0.66,1.07)	(0.62,1.01)	(0.58,0.99)	(0.49,1.37)	(0.55,0.87)
4	0.94	0.94	0.81	0.67	0.84
	(0.73,1.21)	(0.73,1.22)	(0.61,1.06)	(0.39,1.15)	(0.66,1.06)
5	0.78	0.77	0.71*	0.36***	0.72*
	(0.59,1.04)	(0.58,1.03)	(0.52,0.96)	(0.20,0.66)	(0.55,0.95)
Missing	0.99	0.97	0.90	0.78	0.87
	(0.81,1.22)	(0.79,1.19)	(0.71,1.13)	(0.50,1.21)	(0.72,1.06)
Non Smoker			Reference Category		
Ex Smoker	1.04	1.07	1.07	1.48*	0.89
	(0.89,1.23)	(0.91,1.26)	(0.89,1.27)	(1.05,2.09)	(0.77,1.04)
Current Smoker	1.02	0.94	0.89	0.45**	0.93
	(0.80,1.32)	(0.74,1.21)	(0.69,1.16)	(0.27,0.73)	(0.74,1.18)
Missing	0.86	0.85	0.88	0.83	0.85
	(0.64,1.15)	(0.64,1.14)	(0.65,1.19)	(0.45,1.54)	(0.64,1.13)

Drinker					
			Reference Category		
Non Drinker	1.00	0.80	0.75*	0.80	0.92
	(0.79,1.27)	(0.63,1.01)	(0.58,0.96)	(0.49,1.31)	(0.74,1.15)
Missing	0.83*	0.79**	0.82*	0.89	0.74***
	(0.72,0.96)	(0.69,0.92)	(0.70,0.96)	(0.66,1.21)	(0.64,0.84)
Body Mass Index <25 kg/m^2					
			Reference Category		
25 - <30	0.87	0.87	0.96	0.97	1.19*
	(0.72,1.05)	(0.72,1.06)	(0.78,1.18)	(0.65,1.44)	(1.00,1.42)
>= 30	0.87	0.84	0.82	0.96	1.06
	(0.71,1.06)	(0.69,1.03)	(0.66,1.02)	(0.63,1.45)	(0.89,1.28)
Missing	0.55*	0.50**	0.47**	0.19***	0.55*
	(0.34,0.90)	(0.31,0.80)	(0.30,0.76)	(0.07,0.49)	(0.34,0.88)
Charlson Comorbidity Index 1 - 2					
			Reference Category		
3 - 4	0.91	0.87	0.87	0.81	1.09
	(0.77,1.07)	(0.74,1.03)	(0.74,1.04)	(0.58,1.13)	(0.94,1.26)
>4	0.80	0.72**	0.71**	1.91*	1.07
	(0.63,1.02)	(0.57,0.91)	(0.55,0.91)	(1.12,3.24)	(0.86,1.34)
Blood Pressure <= 140/80 mm Hg					
			Reference Category		
>140/80 mm Hg	0.89	0.87*	0.83*	0.80	0.99
	(0.77,1.01)	(0.76,0.99)	(0.72,0.96)	(0.60,1.06)	(0.88,1.13)
Missing	1.01	1.25	1.22	1.97	1.37
	(0.50,2.03)	(0.64,2.45)	(0.64,2.33)	(0.50,7.78)	(0.69,2.69)

Total Cholesterol <= 5 mmol/L			Reference Category		
>5 mmol/L	0.68***	0.68***	0.65***	0.38***	0.87
	(0.56,0.84)	(0.55,0.83)	(0.53,0.80)	(0.25,0.57)	(0.71,1.05)
Missing	0.57**	0.52**	0.42***	0.39*	0.52**
	(0.38,0.86)	(0.35,0.77)	(0.29,0.62)	(0.17,0.88)	(0.35,0.77)
Hemoglobin A1c <= 59 mmol/mol			Reference Category		
59 - <=64 mmol/mol	0.20***	0.31***	0.59***	1.02	1.07
	(0.16,0.24)	(0.25,0.38)	(0.46,0.76)	(0.62,1.66)	(0.87,1.33)
65 - <=75 mmol/mol	0.08***	0.10***	0.24***	1.01	0.99
	(0.06,0.10)	(0.08,0.12)	(0.19,0.30)	(0.62,1.65)	(0.80,1.23)
>75 mmol/mol	0.05***	0.05***	0.08***	0.64	0.90
	(0.04,0.07)	(0.04,0.07)	(0.06,0.11)	(0.35,1.16)	(0.68,1.18)
Missing	0.26***	0.19***	0.21***	0.69	0.57***
	(0.20,0.32)	(0.15,0.23)	(0.16,0.26)	(0.43,1.10)	(0.46,0.71)
Microvascular Complication	0.90	0.91	0.93	1.47*	1.21*
	(0.76,1.06)	(0.76,1.07)	(0.77,1.11)	(1.02,2.12)	(1.04,1.42)
Macrovascular Complication	0.91	0.92	0.91	1.21	1.05
	(0.78,1.07)	(0.79,1.08)	(0.77,1.07)	(0.86,1.69)	(0.90,1.22)
Any Anti-Diabetic Agent	0.45***	0.57***	0.94	0.97	1.11
	(0.38,0.54)	(0.48,0.68)	(0.78,1.13)	(0.69,1.36)	(0.95,1.29)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.00

Prostate cancer – Part 3. **(continued on the following three pages)**

	Foot Exam	Dietary Review	Erectile Dysfunction (Asked)	Erectile Dysfunction (Advice)
	OR* (95% CI)	**OR* (95% CI)**	**OR* (95% CI)**	**OR* (95% CI)**
Index Year		Reference Category		
Year 2	3.17*** (2.73,3.69)	3.04*** (1.85,4.99)	2.17*** (1.53,3.08)	2.33*** (1.51,3.59)
Year 3	10.28*** (8.60,12.29)	23.16*** (8.96,59.85)	10.33*** (5.44,19.60)	10.12*** (5.23,19.61)
Year 4	31.24*** (25.40,38.43)	1493.78*** (258.94,8617.53)	350.23*** (110.54,1109.66)	87.70*** (31.38,245.10)
Year 5	65.49*** (51.55,83.20)	8746.32*** (979.20,78122.79)	1462.86*** (354.64,6034.15)	380.48*** (101.02,1433.07)
Cancer (versus Control)	1.03 (0.87,1.21)	1.08 (0.83,1.41)	1.08 (0.86,1.35)	1.71** (1.21,2.41)
Age <60		Reference Category		
60 - <70	1.19 (0.82,1.75)	1.38 (0.75,2.54)	1.12 (0.68,1.85)	1.23 (0.59,2.56)
70 - <80	1.19 (0.82,1.74)	1.48 (0.81,2.71)	1.12 (0.68,1.83)	0.83 (0.40,1.73)
>= 80	1.13 (0.75,1.71)	1.58 (0.82,3.07)	1.15 (0.66,1.98)	0.42* (0.18,0.98)

Year of Diagnosis 2000-2004	Reference Category			
2005-2009	38.52*** (26.94,55.10)	Not Applicable		
After 2009	3862.34*** (2481.49,6011.56)			
Index of Multiple Deprivation = 1		Reference Category		
2	1.00 (0.77,1.30)	0.67 (0.44,1.01)	0.72 (0.51,1.01)	0.62 (0.37,1.05)
3	1.10 (0.85,1.43)	0.54** (0.35,0.83)	0.62** (0.43,0.88)	0.48** (0.28,0.82)
4	1.07 (0.82,1.42)	0.47** (0.29,0.75)	0.59** (0.40,0.86)	0.37** (0.20,0.67)
5	0.71* (0.52,0.96)	0.71 (0.44,1.15)	0.69 (0.46,1.03)	0.38** (0.19,0.74)
Missing	0.85 (0.68,1.06)	0.89 (0.63,1.24)	0.73* (0.54,0.98)	0.62* (0.40,0.96)
Non Smoker		Reference Category		
Ex Smoker	1.24* (1.04,1.48)	0.99 (0.75,1.30)	1.05 (0.83,1.33)	0.84 (0.59,1.20)
Current Smoker	1.04 (0.79,1.36)	0.94 (0.62,1.44)	0.95 (0.66,1.36)	0.94 (0.55,1.62)
Missing	1.22 (0.83,1.78)	1.61 (0.85,3.05)	1.90* (1.12,3.24)	2.11 (0.98,4.57)

Drinker				
	Reference Category			
Non Drinker	1.01	0.87	1.03	0.97
	(0.78,1.29)	(0.59,1.28)	(0.74,1.42)	(0.57,1.63)
Missing	0.83*	0.74*	0.85	1.00
	(0.71,0.97)	(0.57,0.95)	(0.69,1.04)	(0.73,1.37)
Body Mass Index <25 kg/m^2				
	Reference Category			
25 - <30	1.23*	0.91	0.93	1.55
	(1.00,1.52)	(0.65,1.26)	(0.70,1.22)	(0.97,2.49)
>= 30	1.14	0.91	0.89	1.48
	(0.92,1.42)	(0.65,1.28)	(0.67,1.19)	(0.92,2.41)
Missing	0.52	0.48	0.53	1.24
	(0.24,1.15)	(0.11,2.20)	(0.15,1.95)	(0.17,9.02)
Charlson Comorbidity Index 1 - 2				
	Reference Category			
3 - 4	1.16	1.09	1.29*	1.17
	(0.98,1.38)	(0.83,1.43)	(1.02,1.63)	(0.82,1.68)
>4	1.15	0.84	1.03	0.58
	(0.89,1.49)	(0.56,1.26)	(0.73,1.45)	(0.33,1.02)
Blood Pressure <= 140/80 mm Hg				
	Reference Category			
>140/80 mm Hg	0.89	0.65***	0.65***	0.59**
	(0.77,1.04)	(0.50,0.84)	(0.52,0.80)	(0.42,0.81)
Missing	3.88*	2.20	0.74	0.21
	(1.17,12.89)	(0.19,25.18)	(0.08,6.94)	(0.00,11.64)

Total Cholesterol <= 5 mmol/L		Reference Category		
>5 mmol/L	0.94	0.60*	0.91	0.76
	(0.74,1.19)	(0.40,0.91)	(0.65,1.26)	(0.45,1.28)
Missing	0.34**	0.43	0.53	0.66
	(0.15,0.75)	(0.07,2.74)	(0.11,2.60)	(0.04,11.14)
Hemoglobin A1c <= 59 mmol/mol		Reference Category		
59 - <=64 mmol/mol	0.99	0.81	0.81	0.72
	(0.77,1.27)	(0.54,1.21)	(0.57,1.14)	(0.43,1.23)
65 - <=75 mmol/mol	0.98	0.98	0.99	0.68
	(0.76,1.25)	(0.67,1.42)	(0.72,1.37)	(0.41,1.14)
>75 mmol/mol	0.89	1.53	1.40	1.32
	(0.65,1.22)	(0.94,2.49)	(0.94,2.10)	(0.72,2.41)
Missing	0.81	0.77	0.75	0.38*
	(0.61,1.08)	(0.46,1.29)	(0.48,1.17)	(0.17,0.87)
Microvascular Complication	1.08	1.30	1.06	1.17
	(0.90,1.29)	(0.98,1.74)	(0.84,1.35)	(0.81,1.69)
Macrovascular Complication	0.86	0.78	0.80	0.79
	(0.72,1.02)	(0.59,1.04)	(0.63,1.02)	(0.54,1.15)
Any Anti-Diabetic Agent	1.19	1.33	1.30*	1.98**
	(1.00,1.42)	(0.99,1.79)	(1.01,1.67)	(1.30,2.99)

BP blood pressure. TC total cholesterol. ACE-I Angiotensin converting enzyme inhibitor. ARB Angiotensin receptor blocker. OR odds ratio. CI confidence interval. * p <0.05, ** p <0.01, *** p <0.001

CHAPTER 5 APPENDIX

Development of the Longitudinal Models for the Secondary Analyses

Development of the longitudinal models for the secondary analyses that included all seven years of data was undertaken with the goal of reproducing the shapes of the longitudinal weight trajectories for colorectal cancer patients and their controls, as shown in the plot in Figure 5.7 of the main body of the thesis (lower left panel).

In the first two longitudinal models developed (**Models A and B below**), cancer was included as a binary, time-dependent variable, which was equal to zero at all time points for control patients, equal to zero for Q1-8 in cancer patients, and equal to one for Q9-28 in cancer patients. This variable was constructed to pick up the incremental impact (in the form of a vertical shift in the weight trajectory) of cancer on patient weight in Q9. Therefore, it ignores any impact cancer may have had prior to Q9. This specification represents the first step in a textbook approach to modelling discontinuous change associated with a time-dependent exposure, and it is a useful place to start if only to illustrate the risks of not conducting exploratory data analysis prior to developing the longitudinal models.

Model A includes a linear term for time (in quarters), the cancer variable described above, and the cancer*time "interaction" term described above.

Level 1 Sub-Model

The level 1 sub-model addresses questions about changes in test results *within patients*, and it includes all the predictors that vary over time. It takes the following form:

$\mathbf{Y_{ij}=\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(cancer_{ij}) + \pi_{3i}(cancer\_time_{ij}) + \varepsilon_{ij}}$, where

Y_{ij} is the observed patient weight (kg) for patient i at time=j (quarter j)

π_{0i} is the intercept of the *true* change trajectory for patient i

π_{1i} is the slope of the *true* change trajectory for patient i

$time_{ij}$ is calendar quarters 1-28 j in which weight was measured in patient i

π_{2i} is the incremental impact on the intercept of the true change trajectory of cancer for patient i

$cancer_i$ is a binary time-dependent variable, which is equal to zero at all time points if patient i is a control patient, or is equal to zero for Q1-8 if patient i is a cancer patient, and equal to one for Q9-28 if patient i is a cancer patient

π_{3i} is the incremental impact on the slope of the true change trajectory of cancer for patient i

$cancer\_time_{ij}$ is an "interaction term" between cancer and time, which is equal to zero at all time points if patient i is a control patient, or is equal to zero for Q1-9 if patient i is a cancer patient, and equal to 1-19 for Q10-28 if patient i is a cancer patient

ε_{ij} is the difference between patient i's observed and *true* weight at time j – also known as the level 1 residual variance

In order to further understand how the level 1 sub-model works, it can be assessed at three critical time points for cancer patients: Q1-8, Q9, and Q10-28.

From Q1-8, cancer and control patients share the same intercept and slope because, for cancer patients, $cancer_i$ and $cancer\_time_{ij}$ both equal zero during this interval:

$$\mathbf{Y_{ij}=\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(0) + \pi_{3i}(0) + \varepsilon_{ij}}$$

In Q9, the incremental impact on the intercept of the true change trajectory for cancer patients (π_{2i}) is added to the intercept of the true change trajectory for *control patients (*π_{0i}).

$$\mathbf{Y_{ij}=\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(1) + \pi_{3i}(0) + \varepsilon_{ij}}$$

From Q10-28, the incremental impact on the slope of the true change trajectory for cancer patients (π_{3i}) is added to the slope of the true change trajectory for *control patients (*π_{1i}).

$\mathbf{Y_{ij}=\pi_{0i} + \pi_{1i}(time_{ij}) + \pi_{2i}(1) + \pi_{3i}(cancer\_time_{ij}) + \varepsilon_{ij}}$, where

$cancer\_time_{ij}$ for cancer patients i takes the value 1-19 during Q10-28

Level 2 Sub-Models

Level 2 sub-models address questions about between-person differences in change. In this instance, since the cancer patients and controls are propensity score matched, there are no predictor variables in the level 2 sub-models. However, there are random effects, which allow individual patient coefficients from the level 1 sub-model to vary around the population mean of that coefficient.

$\mathbf{\pi_{0i}= \gamma_{00}+\zeta_{0i}}$

π_{0i} (from the level 1 sub-model) is the intercept of the true change trajectory for patient i

γ_{00} is the population intercept (average of the π_{0i}'s from the level 1 sub-model)

ζ_{0i} is the difference between the population intercept (γ_{00}) and the true intercept (π_{0i}) for patient i. *This is a random effect.*

$\mathbf{\pi_{1i}= \gamma_{10}+\zeta_{1i}}$

π_{1i} (from the level 1 sub-model) is the slope of the true change trajectory for patient i

γ_{10} is the population slope (average of the π_{1i}'s from the level 1 sub-model)

ζ_{1i} is the difference between the population slope (γ_{10}) and the true slope (π_{1i}) for patient i.

This is a random effect.

$\mathbf{\pi_{2i}= \gamma_{20}+\zeta_{2i}}$

π_{2i} (from the level 1 sub-model) is the incremental intercept of the true change trajectory for *cancer patient* i

γ_{20} is the population incremental intercept for cancer (average of the π_{2i}'s from the level 1 sub-model)

ζ_{2i} is the difference between the population incremental intercept for cancer (γ_{20}) and the true incremental intercept for cancer (π_{2i}) for patient i. *This is a random effect.*

$$\pi_{3i} = \gamma_{30} + \zeta_{3i}$$

π_{3i} (from the level 1 sub-model) is the incremental slope of the true change trajectory for *cancer patient* i

γ_{30} is the population incremental slope for cancer (average of the π_{3i}'s from the level 1 sub-model)

ζ_{3i} is the difference between the population incremental slope for cancer (γ_{30}) and the true incremental slope for cancer (π_{3i}) for patient i. *This is a random effect.*

Composite Specification of Longitudinal Model

The level 1 and level 2 sub-models can be combined to form the **composite specification** of the longitudinal model. (Box A5.1)

Box A5.1: Composite Specification of Longitudinal Model

$$Y_{ij} = (\gamma_{00}+\zeta_{0i}) + (\gamma_{10}+\zeta_{1i})(time_{ij}) + (\gamma_{20}+\zeta_{2i})(cancer_{ij}) + (\gamma_{30}+\zeta_{3i})(cancer\_time_{ij}) + \varepsilon_{ij}$$

$$= \{\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(cancer_{ij}) + \gamma_{30}(cancer\_time_{ij})\} +$$

$$\{\zeta_{0i} + \zeta_{1i}(time_{ij}) + \zeta_{2i}(cancer_{ij}) + \zeta_{3i}(cancer\_time_{ij}) + \varepsilon_{ij}\}, \text{ where}$$

$\{\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(cancer_{ij}) + \gamma_{30}(cancer\_time_{ij})\}$ **is the structural component** of the composite model, consisting of the fixed effects, and

$\{\zeta_{0i} + \zeta_{1i}(time_{ij}) + \zeta_{2i}(cancer_{ij}) + \zeta_{3i}(cancer\_time_{ij}) + \varepsilon_{ij}\}$ **is the stochastic component** containing the random effects and the level 1 residual variance.

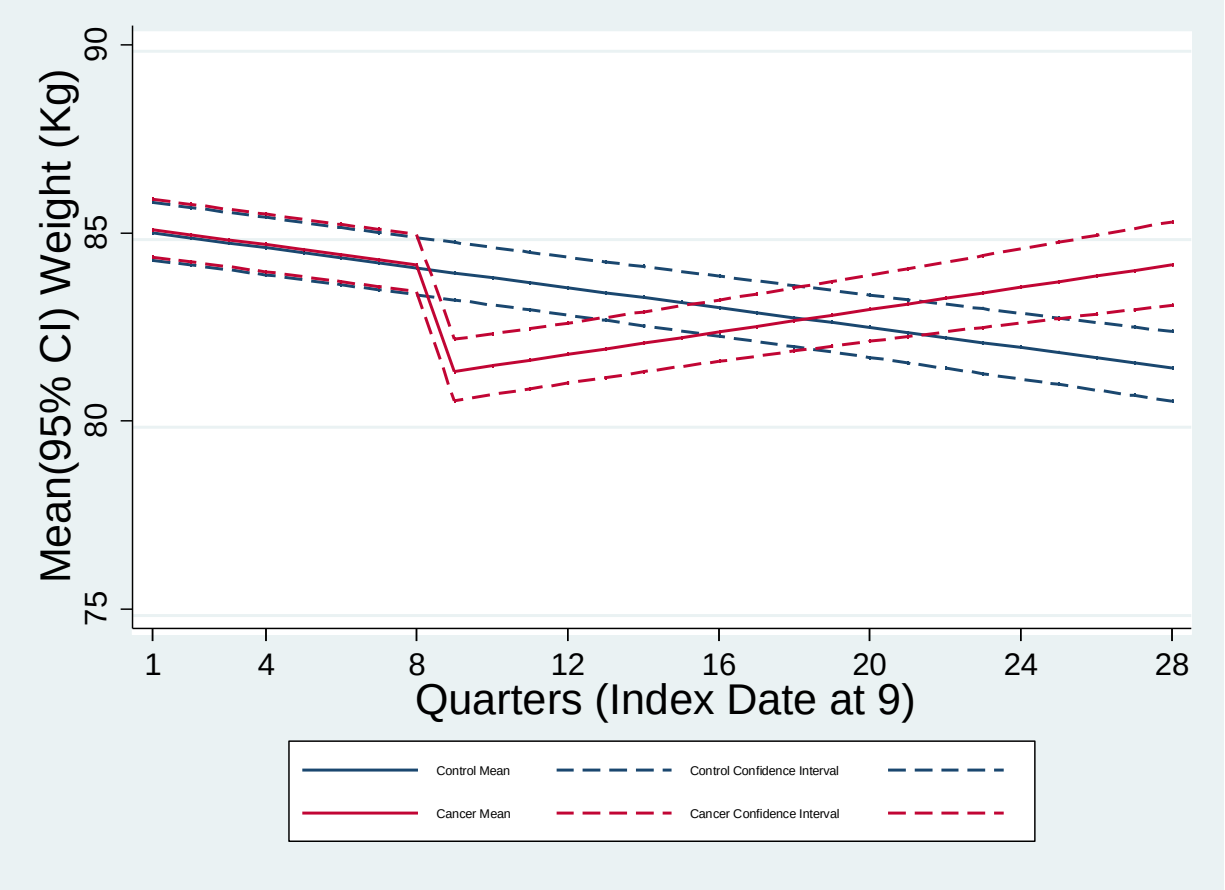
This is an important step since STATA requires the composite specification of the model in the command <xtmixed>, which was the one used for longitudinal modelling of the laboratory test results.

The STATA code for the composite model specified above is as follows:

xtmixed weight time cancer cancer_time||patid: time cancer cancer_time, cov(un) mle

Comparison of the predicted values for this model (Figure A5.1) to the plot in Figure 5.7 (lower left panel) in the main body of the thesis indicates that this model begins to approximate the shapes of the trajectories for unadjusted weight in the cancer and control patients. It captures the difference between cancer cases and controls in the index quarter, and it captures the reversal in the slope of the trajectory in the cancer patients after the quarter of the index date. However, there are some limitations which suggest improvements are required. First, because the intercepts and slopes of the trajectories for cancer and control patients are constrained to be identical prior to Q9, the model fails to pick up the separation of cancer and control trajectories prior to cancer. Second, since the trajectories of cancer patients and controls are constrained to be linear, the model does not pick up the non-linear trajectory of the cancer patients after the index date.

Figure A5.1: Predicted Patient Weight (Kg) from Model A.



Model B added squared and cubic terms for both time and cancer*time. Random effects for the higher order terms were not included for the sake of computational efficiency. The composite specification for this model is as follows:

$$\{\gamma_{00} + \gamma_{10}(time_{ij}) + \gamma_{20}(cancer_{ij}) + \gamma_{30}(cancer\_time_{ij}) + \gamma_{40}(time^2_{ij}) + \gamma_{40}(time^3_{ij})$$

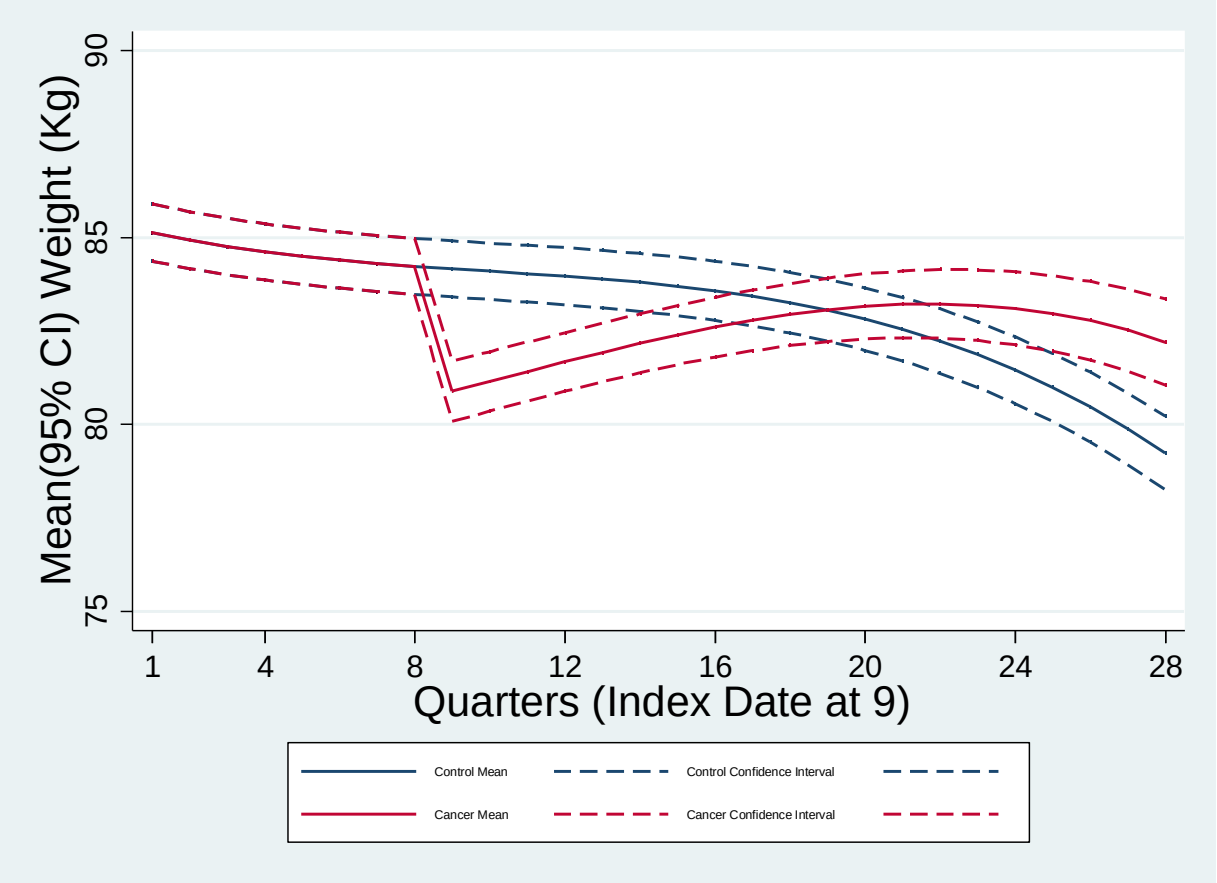
$$+ \gamma_{50}(cancer\_time^2_{ij}) + \gamma_{60}(cancer\_time^3_{ij})\}$$

$$+ \{\zeta_{0i} + \zeta_{1i}(time_{ij}) + \zeta_{2i}(cancer_{ij}) + \zeta_{3i}(cancer\_time_{ij}) + \varepsilon_{ij}\}$$

Comparison of the predicted values for this model (Figure A5.2) to the plot in Figure 5.7 (lower left panel) in the main body of the thesis indicates that adding higher order terms improves the shape of the trajectory in the cancer patients after the index date. One

important issue is that cancer and control patients are still constrained to share the same slope and intercept prior to Q9.

Figure A5.2: Predicted Patient Weight (Kg) from Model B.

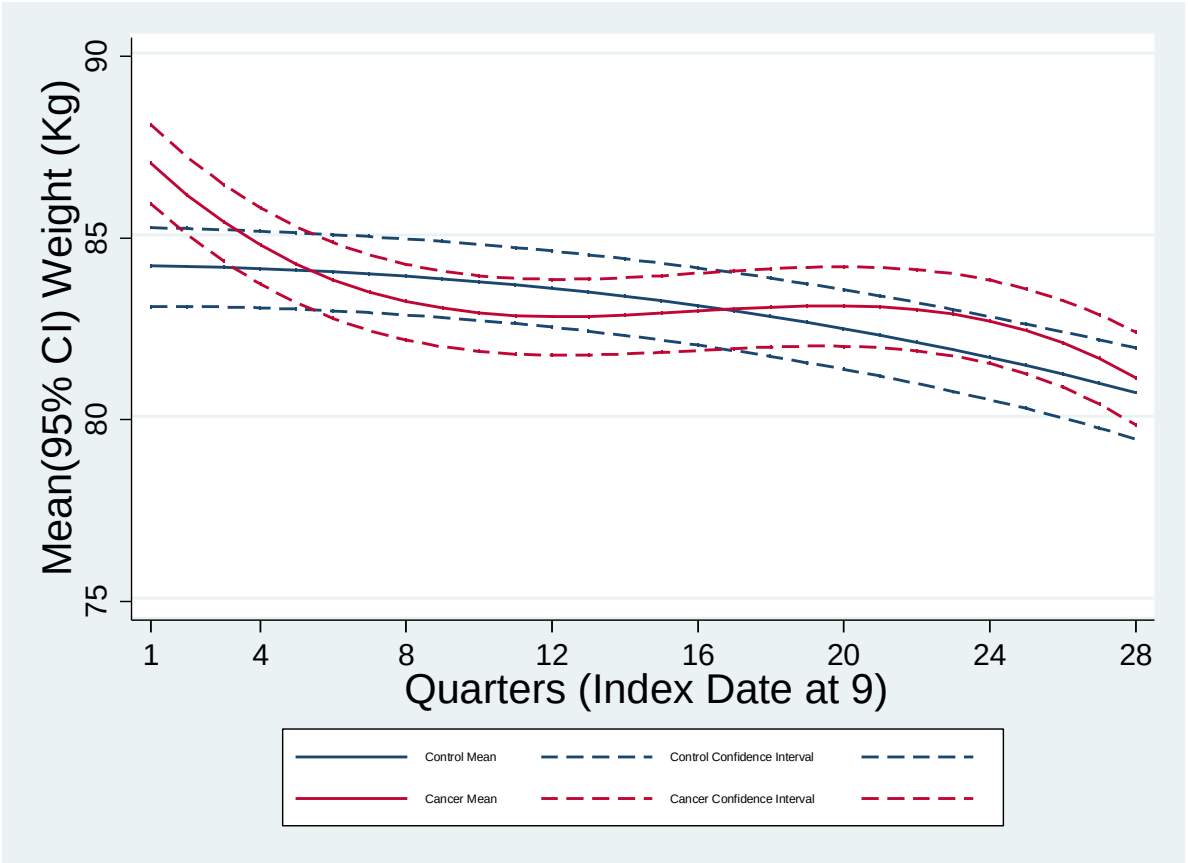


In an attempt to address the remaining limitations of the previous models, **Model C** changes the specification of the cancer variable from a time-dependent predictor to one that is fixed for the entire observation period, i.e., equal to one for cancer patients over the entire period. It also changes the specification of the "interaction" term for cancer*time to a conventional time*cancer term, with values of 1-28 for cancer patients.

As shown in Figure A5.3, this specification considerably improves the shape of the population predicted trajectories for both cancer patients and controls. The predicted

trajectory for the control patients has a negative slope, and is fairly linear even though there are quadratic and cubic terms included in the model. The predicted trajectory for cancer patients has an intercept which is slightly higher than for controls, which is consistent with the plot in Figure 5.7 (lower left panel) in the main body of the thesis. The slope of the trajectory in the cancer cohort is negative until around Q9, which also is reasonably consistent with the plot in Figure 5.7 (lower left panel). However, Model C fails to pick up the abrupt reversal in slope after Q9 shown in the plot of the raw data. Instead, the predicted trajectory for cancer patients is relatively flat between Q9-Q23, and then it is negative after Q23.

Figure A5.3: Predicted Patient Weight (Kg) from Model C.



One important limitation of Model C is that it fails to pick up the abrupt reversal in trajectory that occurs in cancer patients around Q9. **Model D** was designed to address

that limitation by partitioning the observation period into two discrete time intervals: one up to and including Q9, and a second after Q9. Model D also includes quadratic terms for both discrete time intervals, a cubic term for Q10-Q28, and interaction terms (with cancer) for each of these time variables.

The level 1 sub-model for Model D is as follows:

$$Y_{ij}=\pi_{0i} + \pi_{1i}(time\_before_{ij}) + \pi_{2i}(time\_before_{ij}^2) + \pi_{3i}(time\_after_{ij}) + \pi_{4i}(time\_after_{ij}^2) + \pi_{5i}(time\_after_{ij}^3) + \varepsilon_{ij}$$

The level 2 sub-models are as follows:

$$\pi_{0i}= \gamma_{00} + \gamma_{01}(cancer_i) + \zeta_{0i}$$

$$\pi_{1i}= \gamma_{10} + \gamma_{11}(cancer_i) + \zeta_{1i}$$

$$\pi_{2i}= \gamma_{20} + \gamma_{21}(cancer_i)$$

$$\pi_{3i}= \gamma_{30} + \gamma_{31}(cancer_i) + \zeta_{3i}$$

$$\pi_{4i}= \gamma_{40} + \gamma_{41}(cancer_i)$$

$$\pi_{5i}= \gamma_{50} + \gamma_{51}(cancer_i)$$

Note that since cancer is now time-invariant, it is included in the level 2 sub-model instead of the level 1 sub-model. Also, the only random effects included in this model are for the intercept, linear slope from Q1-Q9, and linear slope for Q10-Q28.

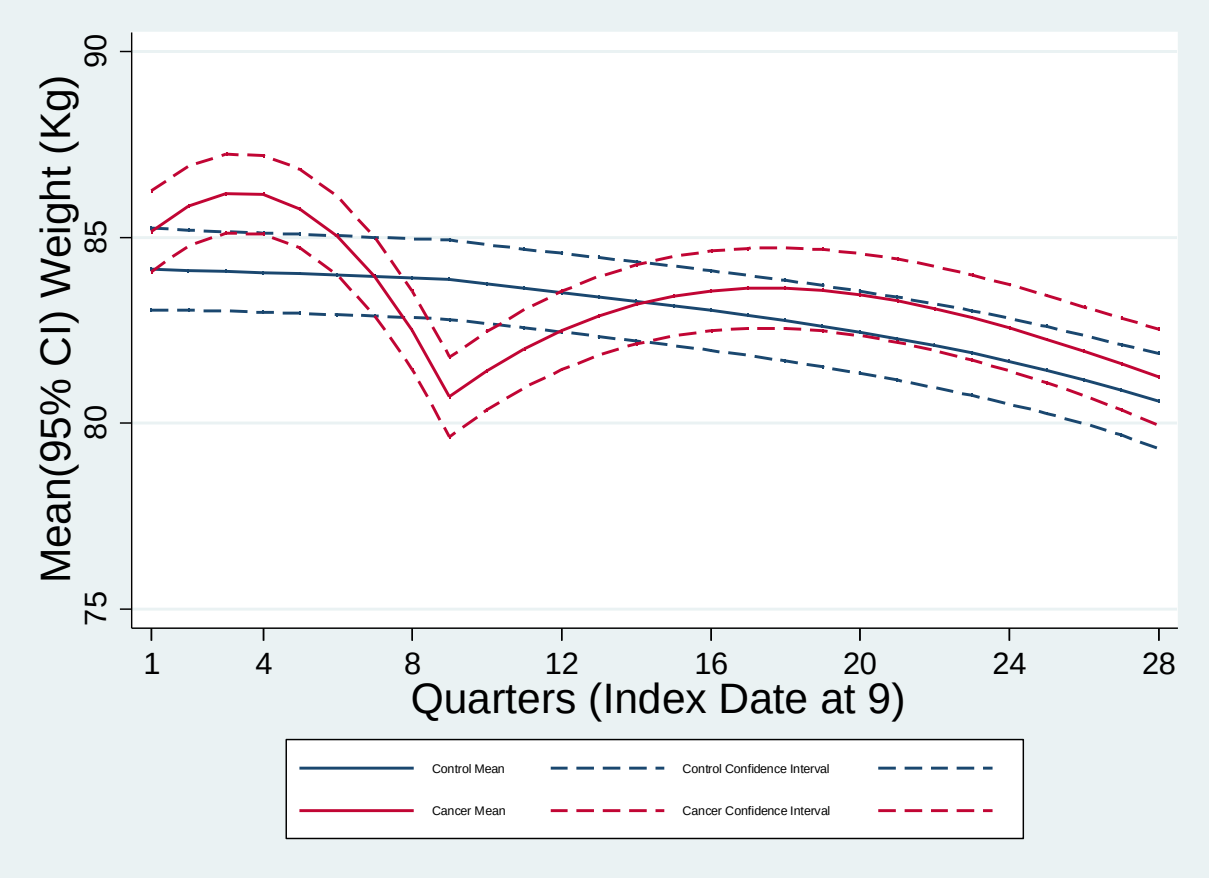
As shown below, although the interaction terms do not appear in the level 1 or level 2 sub-models, they do appear in the **composite specification**.

$$Y_{ij}= \{\gamma_{00} + \gamma_{10}(time\_before_{ij}) + \gamma_{20}(time\_before_{ij}^2) + \gamma_{30}(time\_after_{ij}) + \gamma_{40}(time\_after_{ij}^2) + \gamma_{50}(time\_after_{ij}^3) + \gamma_{11}(time\_before_{ij}*cancer_i) + \gamma_{21}(time\_before_{ij}^{2}*cancer_i) + \gamma_{31}(time\_after_{ij}*cancer_i) + \gamma_{41}(time\_after_{ij}^{2}*cancer_i) + \gamma_{51}(time\_after_{ij}^{3}*cancer_i)\} + \{\zeta_{0i} + \zeta_{1i}(time_{ij}) + \zeta_{3i}(time\_after_{ij}) + \varepsilon_{ij}\}$$

The trajectories of predicted values from this model (Figure A5.4) are much more consistent with the plot of mean values in Figure 5.7. Specifically, fitting the spline

model had little impact on the negative sloping linear trajectory in the control group. The biggest difference is in the cancer group, where the spline now picks up the abrupt change in the direction of the slope at Q9, the rapid increase in weight in the quarters after Q9, and the attenuation of this increase at around Q13-Q14.

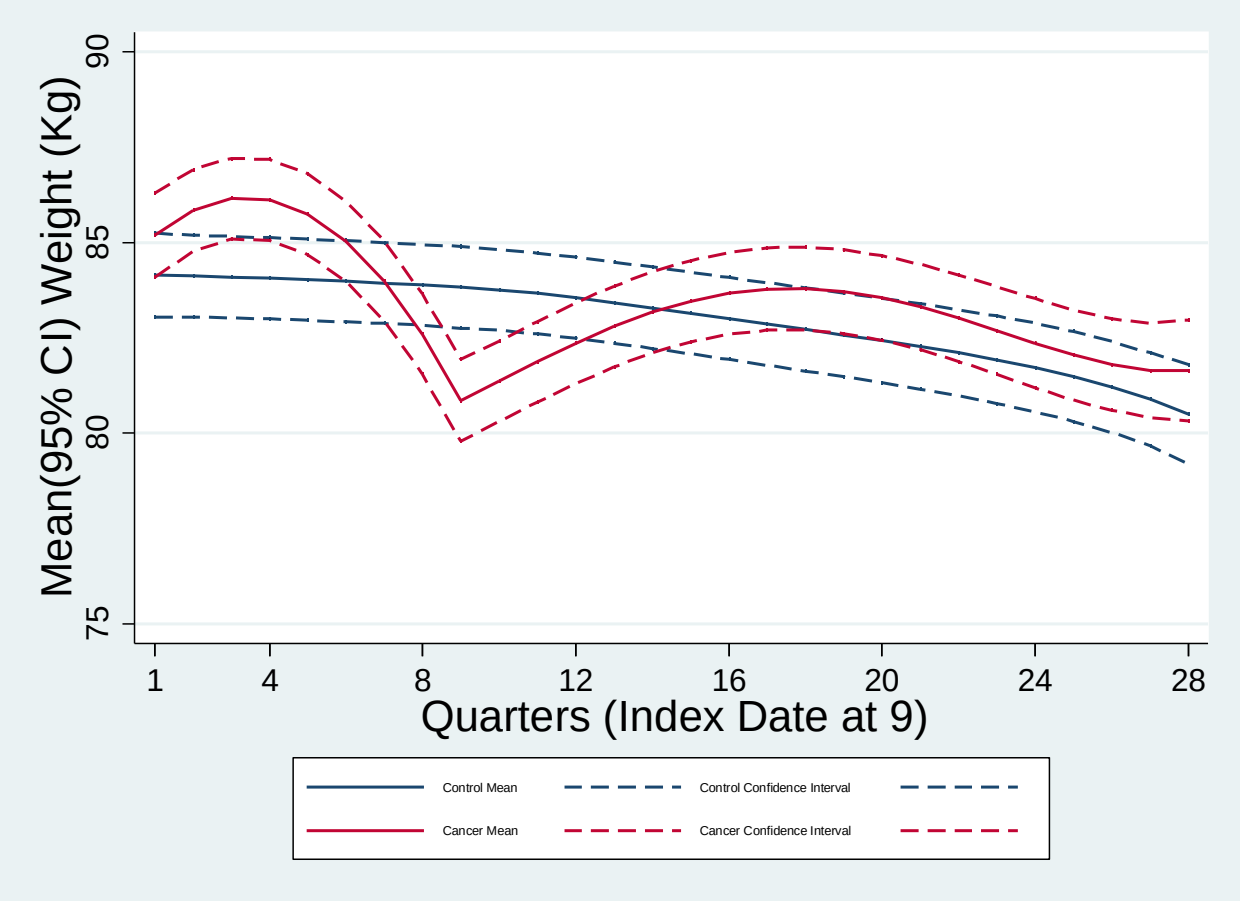
Figure A5.4: Predicted Patient Weight (Kg) from Model D.



Model E is identical to Model D except that two quartic terms have been added: **$time\_after_{ij}^4$ and $time\_after_{ij}^4$*$cancer_i$.** (Figure A5.5) According to the likelihood ratio test, Model E resulted in a statistically significantly improved fit compared to Model D (p=0.03). As shown in Figure A5.5, adding the quartic terms had little impact on the predicted trajectories other than to smooth them out slightly. The predicted trajectory

was statistically significantly lower in cancer patients than controls at all time points Q4-Q28.

Figure A5.5: Predicted Patient Weight (Kg) from Model E.



STATA output from Model E is shown in Box A5.2. There were 16,990 weight measurements during the observation period among 2,071 (99.4% of 2,084 in the colorectal cancer propensity score matched cohort used for developing the model) patients who had at least one weight measurement. The average number of quarters per patient in which there was at least one weight measurement was 8.2, with a range of 1-28. In the output, quarters1 and quarters1_sq are the linear and quadratic terms (respectively) for time Q1-Q9; quarters2, quarters2_sq, quarters2_cube, and quarters2_quart are the polynomial terms for time Q10-Q28; patient_type is the binary

variable for cancer; and the cancerq… terms are the interaction terms between cancer and time. Interestingly, none of the first or second order time covariates (quarters1 quarters1_sq quarters2 quarters2_sq) were statistically significant. However, with so many time coefficients in one model, it is difficult to interpret the importance of individual ones. In such circumstances a graphical depiction of the predicted trajectories with 95% confidence intervals, e.g. Figure A5.5, proves to be much more informative than inspecting the values of individual coefficients from the model output.

Model E was used in all the multivariate analyses using all seven years of data. The results from these models are reported as margins plots of the predicted values.

Box A5.2: STATA Output for Model E.

Mixed-effects ML regression — Number of obs = 16,990
Group variable: **patid** — Number of groups = 2,071

Obs per group:
min = 1
avg = 8.2
max = 28

Wald chi2(13) = 1162.65
Log likelihood = -52005.571 — Prob > chi2 = 0.0000

ave_test_result	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
patient_type	.0503	.8360363	0.06	0.952	-1.588301	1.688901
quarters1	-.0135119	.1051295	-0.13	0.898	-.219562	.1925382
cancerq1	1.171984	.1479772	7.92	0.000	.8819543	1.462014
quarters1_sq	-.002521	.0099452	-0.25	0.800	-.0220133	.0169712
cancerq1_sq	-.1674803	.0141025	-11.88	0.000	-.1951208	-.1398399
quarters2	-.0542128	.1186164	-0.46	0.648	-.2866967	.1782711
cancerq2	.5420376	.1716027	3.16	0.002	.2057025	.8783726
quarters2_sq	-.0168699	.0291808	-0.58	0.563	-.0740633	.0403235
cancerq2_sq	.0362399	.0421423	0.86	0.390	-.0463574	.1188372
quarters2_cube	.0014473	.0025091	0.58	0.564	-.0034704	.0063649
cancerq2_cube	-.0073087	.0036234	-2.02	0.044	-.0144104	-.000207
quarters2_quart	-.0000471	.0000691	-0.68	0.495	-.0001824	.0000883
cancerq2_quart	.0002368	.0000998	2.37	0.018	.0000412	.0004323
_cons	84.15566	.5934459	141.81	0.000	82.99253	85.31879

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
patid: Unstructured				
sd(quarter)	.4028268	.0092484	.3851019	.4213674
sd(_cons)	17.47203	.2792197	16.93325	18.02795
corr(quarter,_cons)	-.2029971	.0255124	-.2524323	-.152505
sd(Residual)	3.433308	.0215487	3.391332	3.475803

LR test vs. linear model: chi2(3) = 41584.96 — Prob > chi2 = 0.0000

Marginal Predicted Values - Propensity-Matched Cohorts, Extended Follow-Up

Figure A5.6: Systolic Blood Pressure (mm Hg).

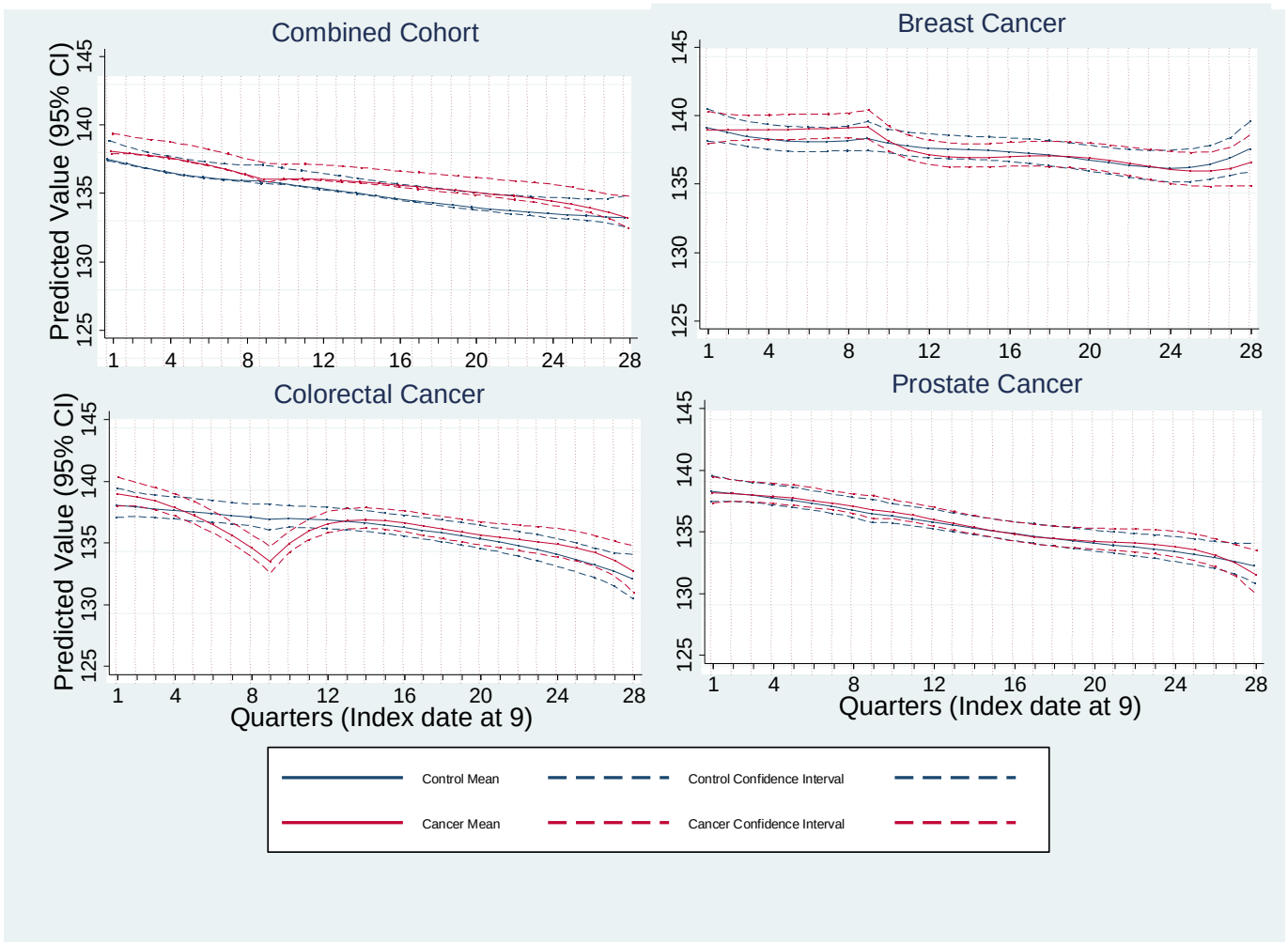


Figure A5.7: Diastolic Blood Pressure (mm Hg).

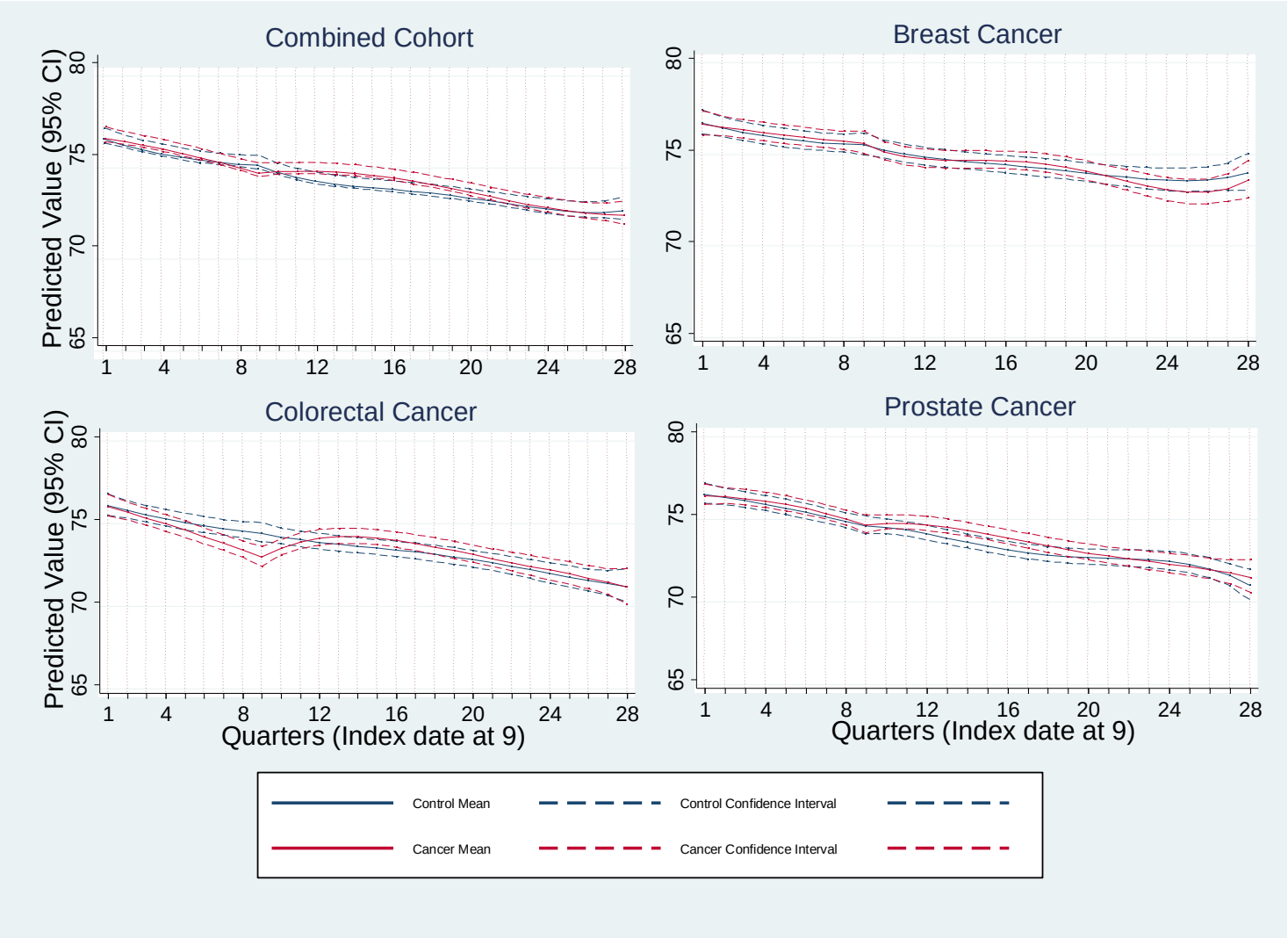


Figure A5.8: Total Cholesterol (mmol/L).

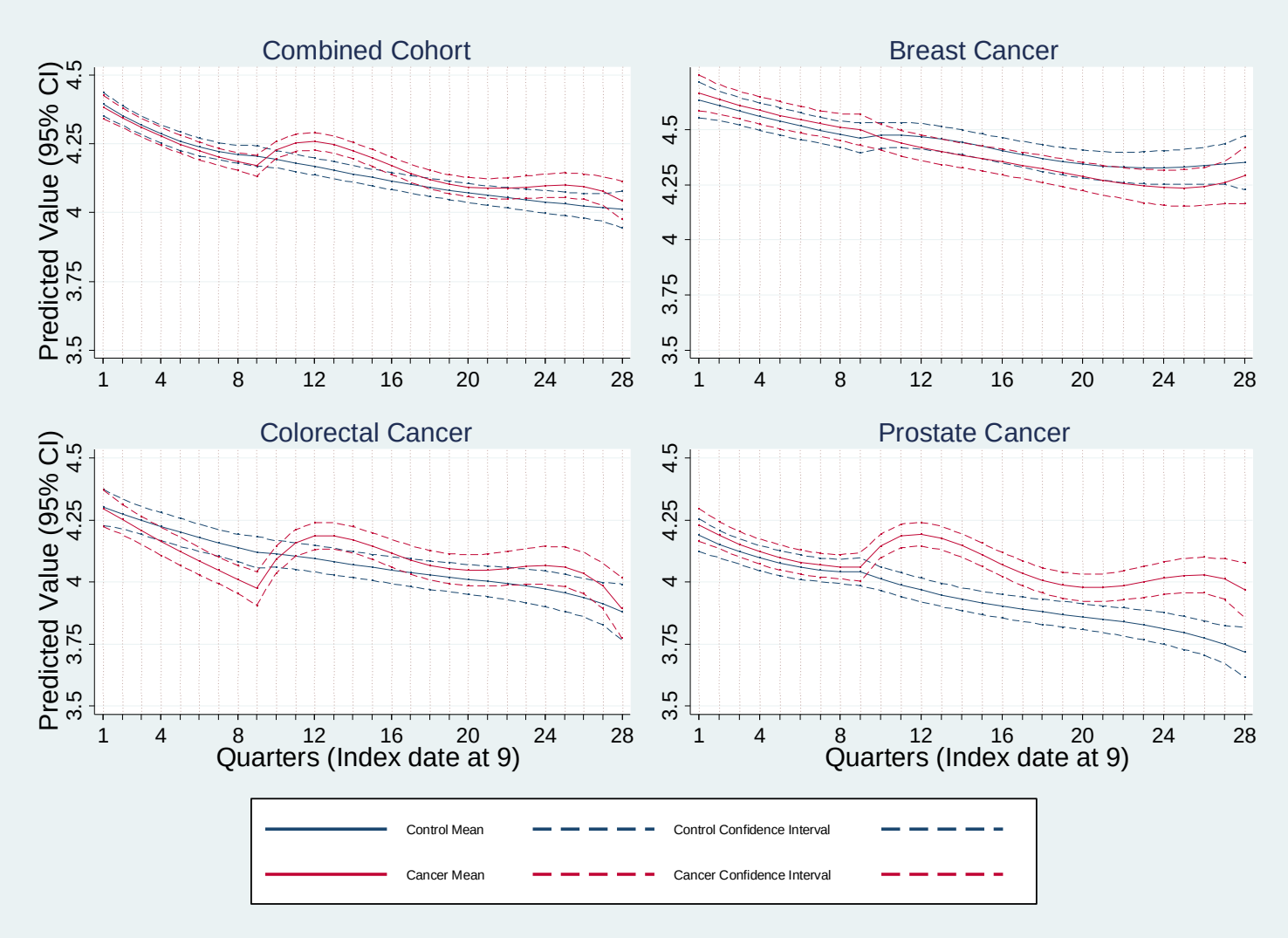


Figure A5.9: Low Density Lipoprotein Cholesterol (mmol/L).

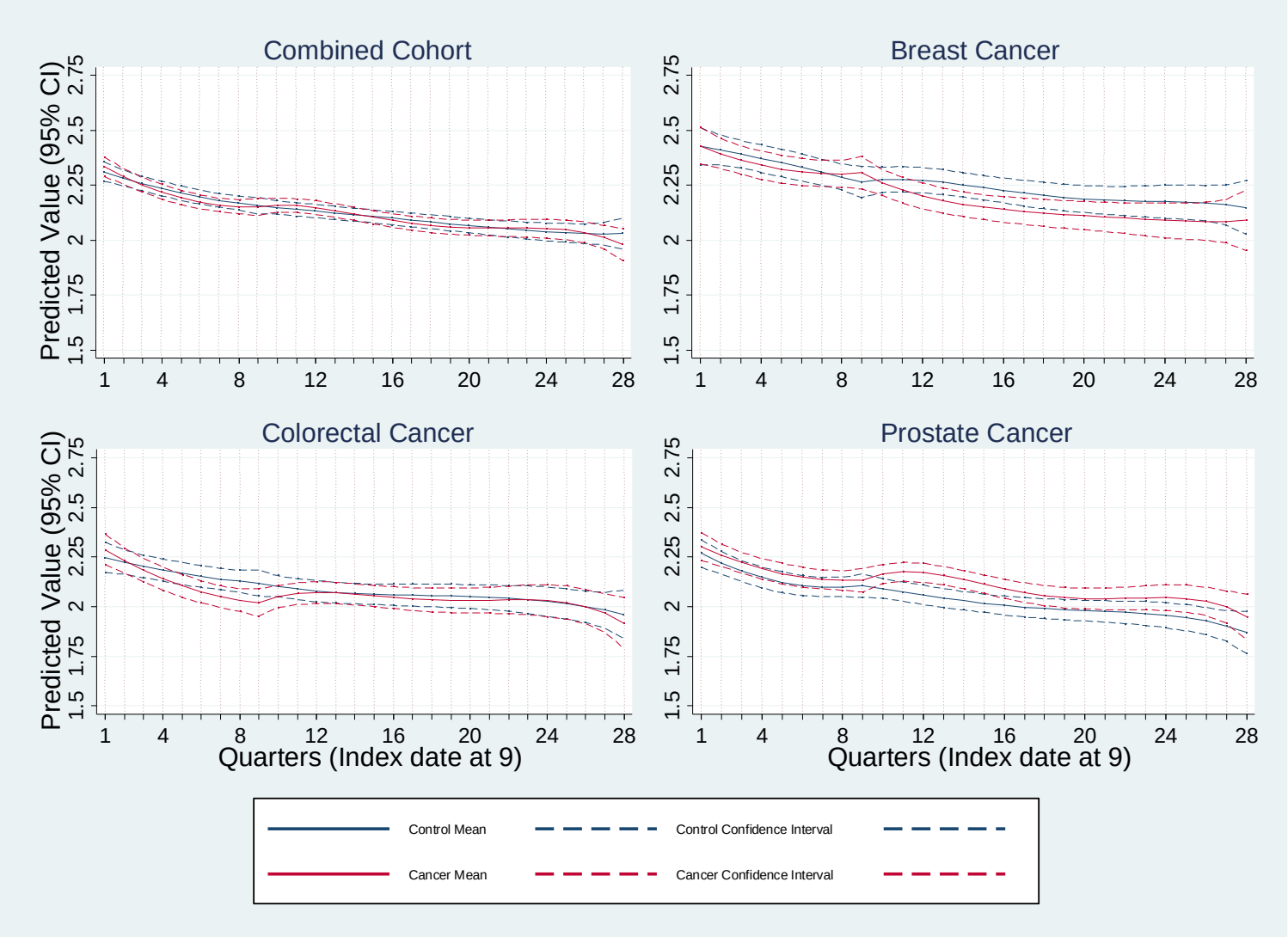


Figure A5.10: High Density Lipoprotein Cholesterol (mmol/L).

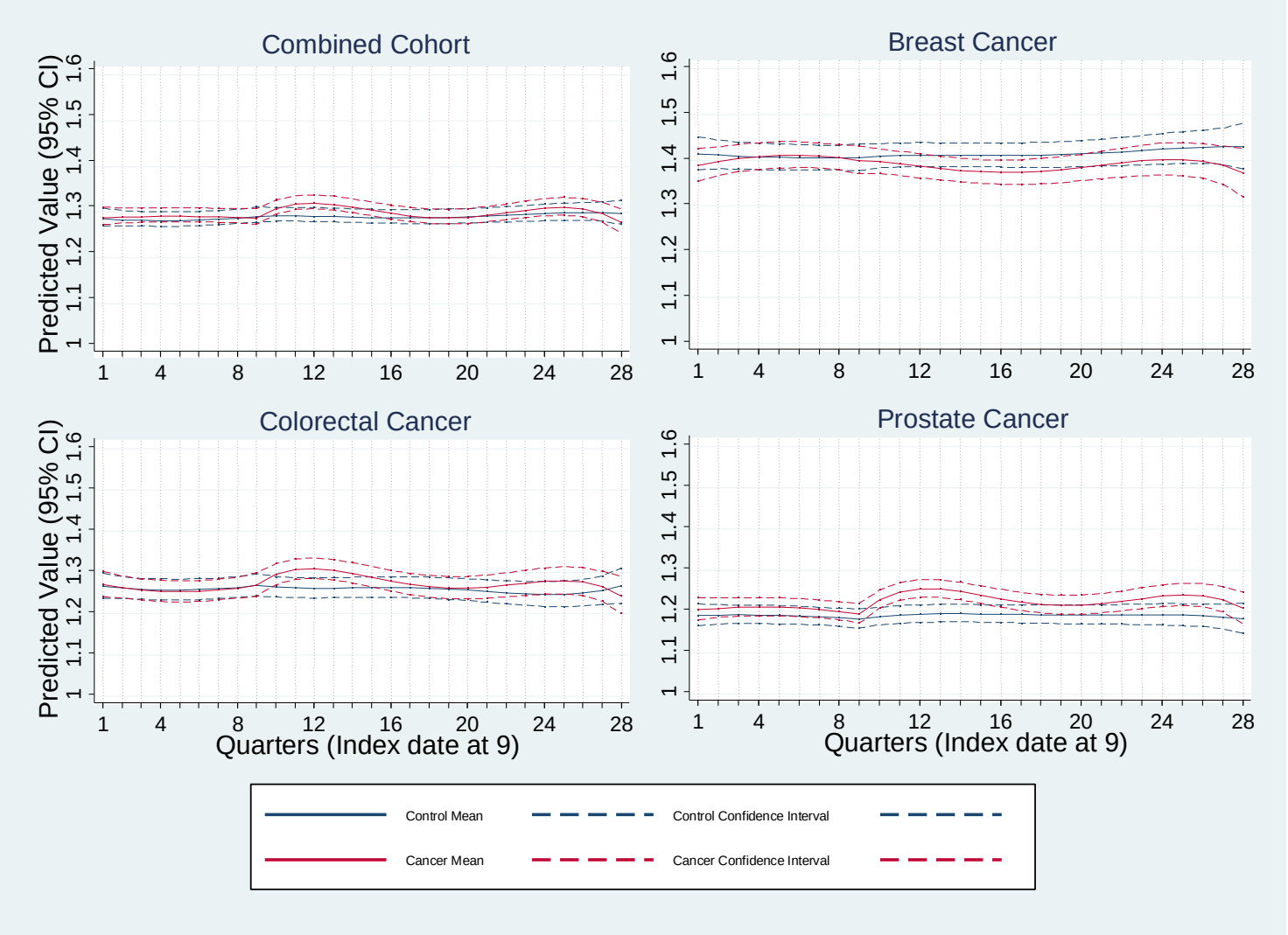


Figure A5.11: Haemoglobin A1c (mmol/mol).

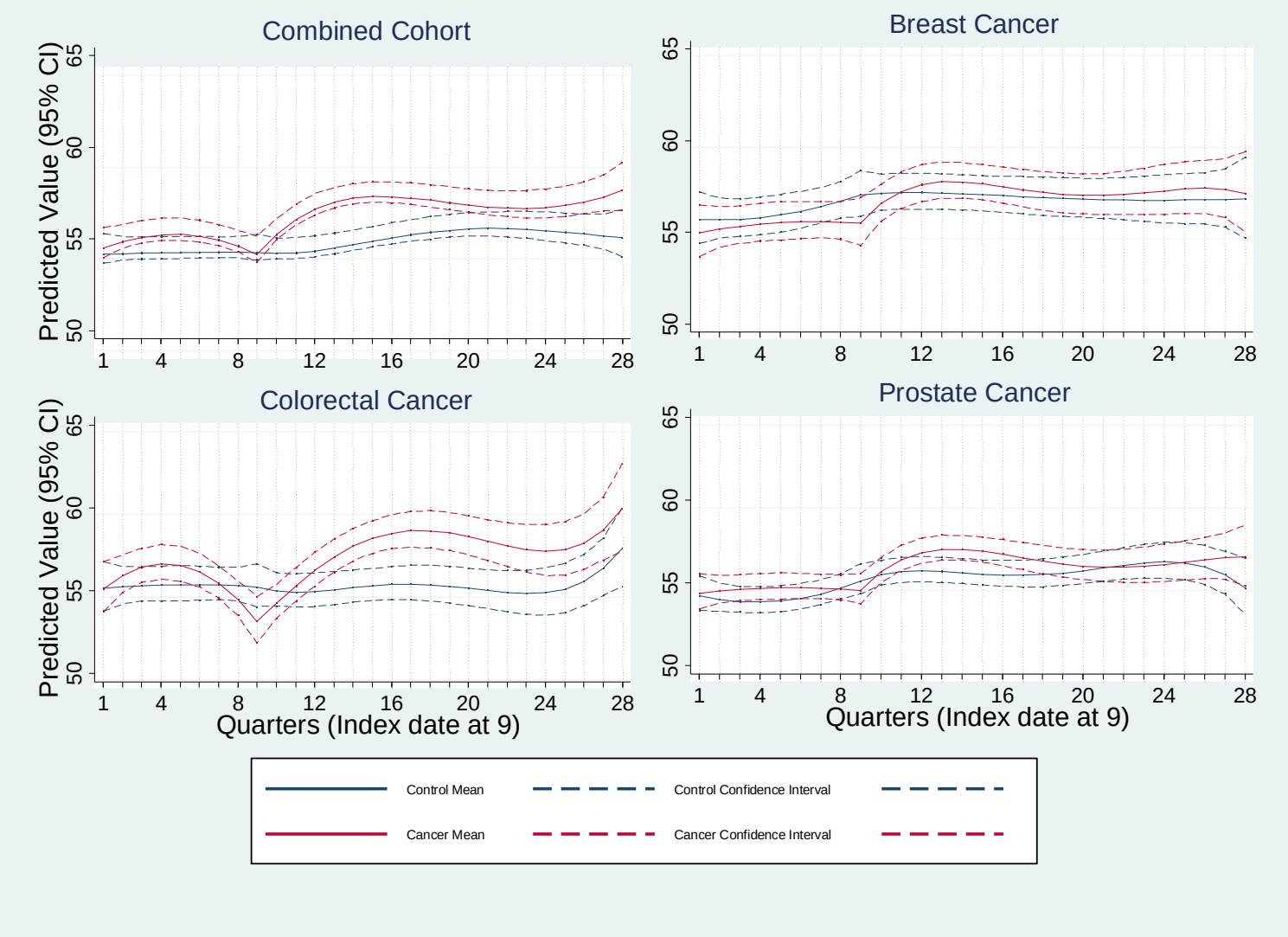
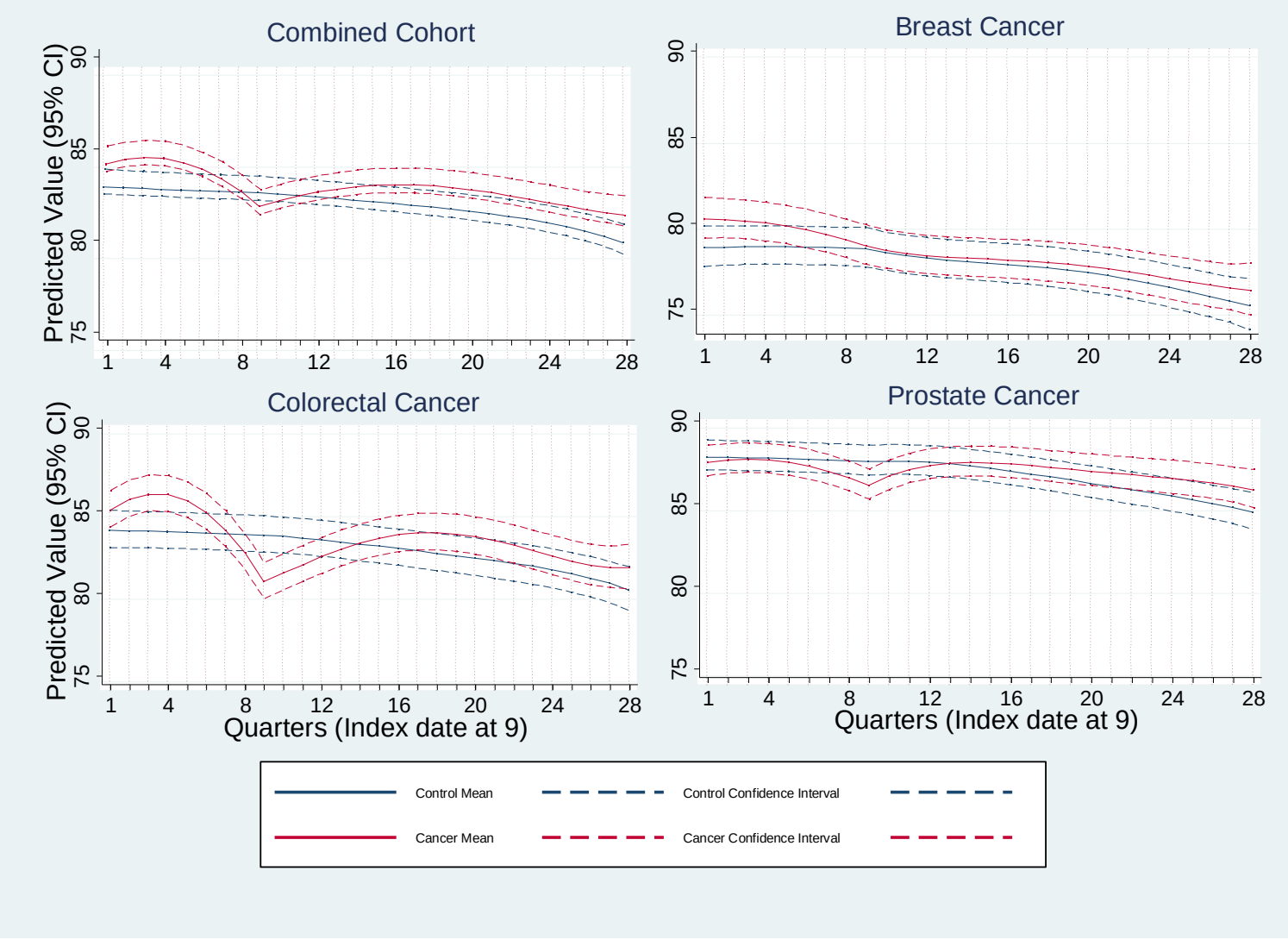


Figure A5.12: Weight (Kg).



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