The association between pre-existing type 2 diabetes on breast cancer-related and all-cause mortality among women with breast cancer

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ABSTRACT

Background: Breast cancer is one of the most common cancers among women in Canada, as an estimated 1 in 8 women will develop this disease. While overall breast cancer mortality has declined in recent decades, differences in treatment effectiveness have been observed in patients with certain pre-existing health conditions, such as type 2 diabetes (T2D). However, the association between T2D and breast cancer mortality outcomes, compared with non-diabetes, remains inconsistent. Moreover, patients with T2D are a heterogeneous group due to various factors including lifestyle behaviours, drug interventions, and comorbidities. To date, however, few studies have investigated the relationship between glycemic control and breast cancer outcomes. Finally, there is evidence that T2D is associated with an increased risk of advanced-stage breast cancer at diagnosis, yet the impact of T2D on breast cancer outcomes in metastatic disease is understudied. Thus, to address this knowledge gap, there is an important need to investigate the effects of T2D on breast cancer outcomes, as well as to assess the impact of glycemic levels, in both patients with and without metastatic disease.

Objectives: The objective of this thesis is to investigate whether pre-existing T2D is associated with an increased risk of breast cancer-related and all-cause mortality, compared with non-diabetes, among women newly diagnosed with non-metastatic and metastatic breast cancer, separately.

Methods: Using the Clinical Practice Research Datalink, we assembled a cohort of patients at least 18 years old, newly diagnosed with invasive breast cancer between 1998 and 2020, with follow-up until March 2021. Separate cohorts were constructed for patients with metastatic and non-metastatic disease. Patients with T2D were identified by recorded diabetes diagnoses,

antihyperglycemic drug prescriptions, and elevated glycemic lab values. Multivariable Cox proportional hazards models were fit to estimate the hazard ratios (HRs) and 95% confidence intervals (CI) of the study outcomes. In a secondary analysis, we estimated the HRs for the outcomes across HbA1c categories (<6.5%, 6.5-7.0%, 7.1-8.0%, >8.0%), comparing women with T2D to non-diabetes.

Results: We identified 157,298 patients with newly diagnosed breast cancer, including 13,908 (8.8%) with T2D. Among patients with non-metastatic disease, T2D was associated with a 12% increased risk of breast cancer mortality (2.19 v 1.43 per 100 person years; HR: 1.12, 95% CI: 1.04-2.10) and a 21% increased risk of all-cause mortality (6.43 v 3.15 per 100 person years; HR: 1.21, 95% CI 1.16-1.26). Among patients with metastatic disease, T2D was associated with a 22% increased risk of breast cancer mortality (5.76 v 3.68 per 100 person years; HR: 1.22, 95% CI 1.11-1.35) and a 24% increased risk of all-cause mortality (9.25 v 5.20 per 100 person years; HR: 1.24, 95% CI: 1.15-1.33). The secondary analysis showed that the risk of the outcomes was increased in the highest HbA1c category (>8.0%) in both the non-metastatic and metastatic group.

Conclusion: In this large population-based cohort study, T2D was associated with a greater risk of breast cancer-related and all-cause mortality, with an increased risk among patients in the highest HbA1c category. Our findings may be important to understand the prognostic differences of patients with T2D, which may indicate the need for more targeted clinical care guidelines to manage both diseases concurrently.

RÉSUMÉ

Contexte: Le cancer du sein est l'un des cancers les plus courants chez les femmes au Canada, car on estime que 1 femme sur 8 développera cette maladie. Alors que la mortalité globale par cancer du sein a diminué au cours des dernières décennies, des différences dans l'efficacité du traitement ont été observées chez les patientes atteintes de certains problèmes de santé préexistants, comme le diabète de type 2 (DT2). Cependant, l'association entre le DT2 et la mortalité par cancer du sein, par rapport aux non-diabétiques, n'est pas concluant. De plus, les patients atteints de DT2 s'agissent d'un groupe hétérogène en termes de facteurs liés au mode de vie, de médicaments et de comorbidités. Cependant, peu d'études ont étudié la relation entre le contrôle glycémique et les la mortalité par du cancer du sein. Enfin, il existe des preuves que le DT2 est associé à un risque accru de cancer du sein à un stade avancé au moment du diagnostic, mais l'impact du DT2 sur les résultats du cancer du sein métastatique est sous-étudié. Ainsi, pour combler ce manque de connaissances, il est important d'étudier les effets du DT2 sur les résultats du cancer du sein, ainsi que d'évaluer l'impact des niveaux glycémiques, chez les patientes avec et sans maladie métastatique.

Objectifs: Déterminer si le DT2 préexistant est associé à un risque accru de mortalité liée au cancer du sein et toutes causes confondues, par rapport au non-diabétique, chez les femmes nouvellement diagnostiquées avec un cancer du sein non métastatique et métastatique, séparément.

Méthodes: En utilisant le Clinical Practice Research Datalink, nous avons rassemblé une cohorte de patientes âgées d'au moins 18 ans, nouvellement diagnostiquées d'un cancer du sein invasif entre 1998 et 2020, avec un suivi jusqu'en mars 2021. Des cohortes distinctes ont été construites pour les patientes atteintes d'un cancer métastatique et non-métastatique. Les patients atteints de DT2 ont été identifiés par des diagnostics de diabète, des prescriptions de médicaments

antihyperglycémiants et des valeurs de laboratoire glycémiques. Des modèles de risques proportionnels de Cox ont été ajustés pour estimer les rapports de risque (RR) ajustés et les intervalles de confiance (IC) à 95% des résultats de l'étude. Dans une analyse secondaire, nous avons estimé les RR pour les résultats dans toutes les catégories d'HbA1c (<6,5 %, 6,5-7,0 %, 7,1-8,0 %, >8,0 %), comparant le DT2 au non-diabétique.

Résultats: Nous avons identifié 157 298 patientes atteintes d'un cancer du sein, dont 13 908 (8,8 %) atteintes de DT2. Parmi les patientes atteintes de cancer non-métastatique, le DT2 était associé à un risque accru de 12 % de mortalité par cancer du sein (2,19 contre 1,43 pour 100 années-personnes; RR: 1,12, IC 95 %: 1,04-2,10) et à un risque accru de 21 % de mortalité toute cause confondues (6,43 contre 3,15 pour 100 années-personnes; RR: 1,21, IC 95 %: 1,16-1,26). Parmi les patientes atteintes de cancer métastatique, le DT2 était associé à un risque accru de 22 % de mortalité par cancer du sein (5,76 contre 3,68 pour 100 années-personnes ; RR: 1,22, IC 95 %: 1,11-1,35) et à un risque accru de 24 % de mortalité toutes causes confondues (9,25 contre 5,20 pour 100 années-personnes; RR: 1,24, IC 95 %: 1,15-1,33). L'analyse secondaire a montré que le risque des résultats était augmenté dans la catégorie d'HbA1c la plus élevée (>8,0 %) dans le groupe non-métastatique et métastatique.

Conclusion: Dans cette vaste étude de cohorte basée sur la population, le DT2 était associé à un risque accru de mortalité spécifique au cancer du sein et toutes causes confondues, avec un risque accru chez les patientes de la catégorie d'HbA1c la plus élevée. Nos résultats peuvent être importants pour comprendre les différences pronostiques des patients atteints de DT2, ce qui peut indiquer la nécessité de directives de soins cliniques plus ciblées pour gérer les deux maladies.

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CONTRIBUTIONS OF AUTHORS

Kristina Parsons drafted the thesis and corresponding manuscript. All authors contributed to the study concept and design. Kristina Parsons, Hui Yin and Dr. Laurent Azoulay contributed to the statistical analyses. Dr. Oriana Yu (diabetologist) and Farzin Khosrow-Khavar (breast cancer specialist) contributed to the methods, interpretation of results and expertise on the biological plausibility. All authors critically revised the manuscript for important intellectual content. Dr. Laurent Azoulay acquired the data, supervised the study and is the guarantor.

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ABBREVIATIONS

2hrPG	2-hour Postprandial Plasma Glucose
AI	Aromatase inhibitor
BMI	Body mass index
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
DPP-4	Dipeptidyl peptidase-4
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide 1
GOLD	Gp OnLine Data
HbA1c	Hemoglobin A1c
HR-positive	Hormone receptor-positive
HES APC	Hospital Episode Statistics Admitted Patient Care
HR	Hazard ratio
HER2	Human epidermal growth factor receptor 2
IGF-1	Insulin-like growth factor 1
ICD-10	International Classification of Diseases, Tenth Revision
OR	Odds ratio
ONS	Office for National Statistics
OGTT	Oral glucose tolerance test
PCOS	Polycystic ovary syndrome
RBG	Random blood glucose
RR	Relative risk
SERM	Selective estrogen receptor modulator
SGLT-2	Sodium-Glucose Cotransporter-2
SNOMED-CT	Systematized Nomenclature of Medicine – Clinical Terms
UK	United Kingdom
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Breast cancer is a significant global health concern as one of the most prevalent cancers worldwide, with 2.3 million newly diagnosed cases in 2020 alone.[1] In Canada, an estimated 1 in 8 women will develop this disease.[2] While improved screening and treatment methods have improved breast cancer survival in recent decades,[1] worse outcomes have been observed in patients with certain pre-existing health conditions, such as diabetes.[3]

Type 2 diabetes is characterized by chronic high blood glucose levels that can lead to serious health consequences including micro- and macrovascular complications, increased risk of mortality, reduced quality of life, and increased risk of certain cancers.[3-5] Approximately 543 million adults aged 20 to 79 are living with diabetes worldwide, with type 2 diabetes accounting for 90% of all cases.[5] In Canada, there are approximately 5.1 million people living with type 2 diabetes, which is expected to rise to over 6.5 million people by 2032.[4] Given the increasing number of breast cancer patients who will also have type 2 diabetes, understanding the prognostic impact of diabetes will become increasingly clinically relevant.

Type 2 diabetes has been associated with an increased risk of breast cancer, with an estimated 10 to 20% of patients having type 2 diabetes at breast cancer diagnosis.[6] Type 2 diabetes may promote breast cancer cell growth through complex endocrinological changes that include increased levels of growth factors, insulin, and inflammatory markers.[7] While several studies have shown that type 2 diabetes is associated with worse overall survival among patients with breast cancer,[3 8] this association with breast cancer-related mortality remains inconclusive.[9] This may be due to inconsistencies across studies in terms of diabetes status ascertainment, sample size and adjustment for covariates, particularly for comorbidities. Additionally, few studies have investigated the impact of type 2 diabetes on mortality outcomes among patients with metastatic

breast cancer, thus is it not well known if this patient population experiences different outcomes.[3] [10] Finally, there is significant heterogeneity in glycemic control within diabetic populations due to various factors including lifestyle behaviours, drug interventions, and comorbidities.[11] To date, however, the association between level of glycemic control and breast cancer outcomes has not been thoroughly investigated.

Thus, to address this knowledge gap, there is an important need to investigate the effects of pre-existing type 2 diabetes on breast cancer outcomes among patients with and without metastatic disease, separately, as well as the impact of glycemic control. These findings will be important to understand the prognostic differences between those with pre-existing type 2 diabetes, compared to non-diabetes, which may indicate the need for more targeted clinical care guidelines to manage diabetes and breast cancer concurrently.

CHAPTER 2: LITERATURE REVIEW

The following chapter is divided into four sections. The first section provides an overview of type 2 diabetes, including its epidemiology, pathophysiology, diagnosis, and clinical management. The second section provides an overview of breast cancer, including its epidemiology, pathophysiology, screening and diagnosis, and treatment. The third section provides an overview of the association between type 2 diabetes and cancer. Finally, the fourth section describes previous research on type 2 diabetes and breast cancer mortality outcomes, including the biological basis of the potential association and knowledge gaps.

2.2 Type 2 Diabetes Mellitus

2.2.1 Epidemiology and Risk Factors

Diabetes is a globally prevalent disease that continues to increase dramatically.[11] The International Diabetes Federation estimates that 543 million adults aged 20 to 79 are living with diabetes worldwide and this number is expected to rise by over 100 million by 2030.[12] Type 2 diabetes is the most common type, as it accounts for approximately 90% of all cases.[5] Diabetes Canada estimates that there are approximately 5.1 million Canadians living with type 2 diabetes, with an increasing incidence trend.[4] By 2032, the number of people in Canada living with diabetes is expected to rise by over 1.5 million people, to approximately 17% of the population.[4]

Type 2 diabetes is a complex metabolic disease that arises from environmental risk factors, predominantly related to lifestyle, which may also interact with genetic factors that may predispose some to this disease.[13] Modifiable risk factors for type 2 diabetes are related to lifestyle, and include poor diet, physical inactivity, smoking, and being overweight or obese.[5] Additionally, prediabetes, which is the intermediate metabolic state that develops before type 2 diabetes, is also

a risk factor.[14] Other health conditions related to elevated blood glucose, such as polycystic ovary syndrome (PCOS) and gestational diabetes, also increase the risk of developing type 2 diabetes.[11] Non-modifiable risk factors include age, as well as factors related to genetic predisposition, such as ethnicity and family history of diabetes.[5 15] Over time, type 2 diabetes can lead to serious health consequences including microvascular complications, such as nephropathy, neuropathy and retinopathy, as well as macrovascular damage of the cardiovascular system, which may result in premature death and reduced quality of life.[5]

2.2.2 Pathophysiology

Type 2 diabetes is a metabolic disorder characterized by chronic hyperglycemia secondary to dysfunctional insulin production and/or response.[11] In non-diabetes, beta cells in the pancreas produce insulin in response to rising blood glucose, allowing glucose uptake from the blood into target cells for energy use, thereby maintaining glycemic homeostasis.[16] Metabolic dysregulation begins to develop when this process is disrupted by complex endocrinological changes that may arise from genetic, lifestyle and other environmental factors.[13]

Prior to the development of type 2 diabetes, there is a distinct intermediate metabolic state known as prediabetes, where blood glucose levels are above the normal range but do not reach the threshold for a diabetes diagnosis.[17] In prediabetes, chronic hyperglycemia leads to increased levels of insulin circulating in the blood.[18] Though there is no global consensus on the definition of prediabetes, **Table 1** summarizes the glycemic tests and lab ranges used for diagnosis, as defined by Diabetes Canada. Over time, target cells in skeletal muscle, liver and adipose tissue become less sensitive to insulin, exacerbating hyperglycemia and, consequently, hyperinsulinemia.[14 18 19] Eventually, this insulin resistance results in decreased function of the pancreatic beta cells.[18]

Concurrently, there is further metabolic dysregulation with increased lipolysis which promotes insulin resistance, stifles glucose uptake, and promotes hepatic glucose production, contributing to hyperglycemia.[18 19] These pathophysiological mechanisms are exacerbated by weight gain, particularly abdominal obesity, as it elicits chronic low-grade inflammation and oxidative stress.[19] Over time, weight gain, insulin resistance and worsening beta cell function is associated with the progression from prediabetes to type 2 diabetes.[14] Prediabetes will progress to type 2 diabetes in up to 70% of cases, with 25% of cases occurring within 3 to 5 years of diagnosis.[14 20]

Table 1. Diabetes Canada Lab Value Ranges for Diagnosis of Prediabetes[21]

Test	**Lab Value**
Fasting Plasma Glucose (FPG) (mmol/L)	6.1-6.9
2-Hour Postprandial Plasma Glucose (2hrPG) (mmol/L)	7.8-11.0
Hemoglobin A1c (HbA1c) (%)	6.0-6.4

Over time, this persistent hyperglycemia, insulin resistance, and oxidative pressure that characterizes type 2 diabetes can lead to serious damage to several organs systems.[5 11] Heart and vascular damage secondary to diabetes-related dyslipidemia and hyperglycemia increases the risk of coronary artery disease, peripheral vascular disease and cerebrovascular disease.[5 22] Indeed, those with type 2 diabetes are 2 to 4 times at risk of developing cardiovascular disease compared to those without diabetes.[11] Furthermore, these metabolic manifestations in type 2 diabetes may also cause long-term microvascular damage, which may result in nephropathy, retinopathy and neuropathy.[5] Therefore, type 2 diabetes is a condition that can have many devastating long-term complications.[5]

2.2.3 Diagnosis

Type 2 diabetes may remain asymptomatic for months or even years.[22] When symptoms do occur, patients may experience polydipsia (excessive thirst), polyuria (excessive urination), fatigue, unintentional weight change, recurring infections, blurred vision or nerve pain in the feet.[11] [22] [23] Because chronic hyperglycemia may cause severe long-term health consequences, screening and diagnosing type 2 diabetes among high-risk populations is essential.[11]

The World Health Organization (WHO) recognizes multiple diagnostic glycemic tests for type 2 diabetes,[24] which are aligned with those used in Canada, the United States and the United Kingdom (UK), as summarized in **Table 2**. For patients with asymptomatic type 2 diabetes, a second glycemic test should be conducted on a separate date to confirm the diagnosis.[21] For patients with symptomatic diabetes, a single lab value within the diabetic range is sufficient for a diagnosis.[24]

Table 2. WHO Lab Value Ranges for Diagnosis of Type 2 Diabetes[24]

Test	**Lab Value**
FPG (mmol/L)	≥7.0
2hrPG (mmol/L)	≥11.1
HbA1c (%)	≥6.5
Random Blood Glucose (RBG) (mmol/L)	≥11.1

Glycated Hemoglobin A1c

Since the 1990s, glycated HbA1c has emerged as an important measure for diabetes screening and diagnosis.[25] The findings of two large prospective randomized studies, the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study, highlighted the

importance of HbA1c as a predictor of outcomes in patients with diabetes.[25] These studies helped establish preliminary HbA1c target values, and the HbA1c test would later be standardized by The National Glycohemoglobin Standardization Program starting in 1996.[25] A HbA1c test measures the amount of glycated hemoglobin in the blood, thereby reflecting average glycemia from the preceding 2 to 3 months.[21 26] This test provides several advantages since it provides reliable information on long-term blood glucose control with less daily variability in measurement compared to FPG and 2hPG.[21] Furthermore, it is more convenient to administer since it may be tested at any time in a non-fasting state.[21] In addition to screening and diagnosis, HbA1c values are also used to inform treatment strategy and efficacy as well as monitor disease progression to prevent or delay health complications.[27]

2.2.4 Clinical Management

There are many treatment options available for type 2 diabetes. Treatment often includes lifestyle behaviour changes in combination with drug interventions to maintain blood glucose within a target range.[28] In general, a HbA1c value of ≤7% is recommended for those with type 2 diabetes since a HbA1c >7% is associated with increased risk of macrovascular and microvascular complications.[28] However, this target should be tailored to the individual treatment plan and may evolve over the course of the disease according to patient risk factors, diabetes complications, hypoglycemia risk, frailty, and life expectancy.[28]

Lifestyle Interventions

Lifestyle interventions can significantly impact glycemia and are therefore essential to type 2 diabetes treatment.[11] Healthy dietary habits and increased physical activity may improve

glycemic control and help achieve or maintain a healthy body weight, especially when coupled with patient-centered counselling, structured programs, and education.[29 30] Nutrition therapy may reduce HbA1c by up to 2% with additional benefits when combined with other interventions, such as pharmacological therapies.[29] Physical activity may induce multiple metabolic improvements, including improved glycemic control, insulin sensitivity, lipidemia and hypertension.[30] Moreover, up to 90% of patients with type 2 diabetes are overweight or obese, thus weight loss is often a focus of disease management.[31] A modest decrease of 5 to 10% of body weight can improve glycemia by increasing insulin sensitivity and glucose uptake while reducing hepatic glucose production.[31] Additionally, smoking cessation and moderate alcohol consumption are also important recommendations for type 2 diabetes management.[11] In patients with a HbA1c <1.5% above of their glycemic target, lifestyle interventions are the recommended first-line treatment.[32] If lifestyle interventions are not sufficient to reach glycemic targets, pharmacological treatment is indicated.[32]

Pharmacological Interventions

A wide array of antihyperglycemic drugs is available as part of pharmacological management of type 2 diabetes. Pharmacological interventions should be patient-centred, considering the individual's glycemic target and preferences alongside drug efficacy, cost, side effects, weight gain, comorbidities and risk of hypoglycemia.[32 33] If glycemic targets are not achieved within 3 months of initiating lifestyle interventions, or if HbA1c is ≥1.5% above the target, antihyperglycemic drugs should be initiated.[32]

First-Line Drug Treatment

Biguanides

Metformin is an oral antihyperglycemic drug that is part of the biguanides drug class.[34] Though approved in Canada in 1972, metformin's use only became widespread after 1998 after the large UK Prospective Diabetes Study demonstrated its glucose-lowering efficacy and safety.[34] Since then, metformin has been widely used as the recommended first-line drug treatment for type 2 diabetes and as well as for other indications such as prediabetes and PCOS.[35]

Metformin impacts hyperglycemia through several mechanisms of action on multiple target tissues.[36] First, metformin alters cellular signalling pathways in the liver, reducing hepatic gluconeogenesis and lipogenesis while also increasing insulin sensitivity.[36] Second, metformin may decrease systemic inflammation by suppressing macrophage generation and secretion of proinflammatory cytokines.[36] Third, there is emerging evidence that metformin acts on the intestines to modify the gut microbiome and incretin hormone secretion, resulting in reduced glucose uptake.[36] Lastly, there is evidence that metformin may act on the gut-brain-liver axis to indirectly suppress hepatic glucose production.[36]

Metformin is a favourable first choice drug intervention due to its cost efficiency, low risk of adverse effects, long-term safety and potential additional benefits, such as cardiovascular benefits.[14 32 37] The UK Prospective Diabetes Study Group found that patients using metformin had a 39% lower risk of myocardial infarction compared to non-users.[38] Similarly, a systematic review and meta-analysis pooling 40 studies of over 1 million patients found that metformin reduced cardiovascular mortality, all-cause mortality and cardiovascular events in coronary artery disease patients.[39] Additional benefits of metformin are that it is generally well tolerated and poses a low risk of hypoglycemia and weight gain.[32] Possible side effects include nausea and diarrhea,

which are usually temporary and resolve within weeks.[32] However, metformin is contraindicated for patients with cardiac failure, hepatic failure or chronic kidney disease stage 4 or more severe as it presents an elevated risk of lactic acidosis.[32 40] If target HbA1c levels are not achieved within 3 months of initiating metformin or if HbA1c is ≥1.5% above target, it is recommended that a second pharmacological agent is initiated.[32]

Second- & Third-Line Drug Treatment

Due to the progressive nature of type 2 diabetes, over time monotherapy often becomes insufficient to manage hyperglycemia, thus additional therapeutic agents may be indicated.[32] Several types of pharmacological agents exist as second- and third-line therapies for type 2 diabetes, which may be selected for use based on individual patient risk factors and tolerance.[41] Sulfonylureas stimulate insulin production by the pancreas but pose a risk of hypoglycemia and so are not recommended for certain patients, namely the elderly.[41] Similarly, meglitinides also stimulate insulin secretion but carry a lower risk of hypoglycemia.[41] On the other hand, thiazolidinediones increase insulin sensitivity to allow better glucose uptake by skeletal muscle and adipose tissue.[41 42] However, use of thiazolidinediones has been limited since this drug class has been associated with several types of adverse outcomes, namely cardiovascular events, liver damage, weight gain, fractures and bladder cancer.[41 42] Alpha-glucosidase inhibitors, such as Acarbose, slow glucose absorption from the gut, eliciting a more gradual rise in blood glucose in response to food intake.[17] However, this drug class has not been used widely due to the gastrointestinal side effects.[17 41] Newer second- and third-line therapies have been developed for glycemic control and may provide additional benefits in the management of type 2 diabetes.

Incretin-based therapies, including glucagon-like peptide 1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors, are a newer drug class that may be used alone or in combination with other antihyperglycemic drugs.[41] GLP-1 analogues improve glycemic control through several mechanisms, including delaying gastric emptying, supporting pancreatic insulin production, decreasing pancreatic glucagon production, and decreasing hepatic gluconeogenesis.[43] GLP-1 analogues also have shown added benefits of weight loss, reduced risk of hypoglycemia, and potential cardiovascular benefits.[43] DPP-4 inhibitors increase levels of incretin hormones which help improve pancreatic insulin production for better glycemic control.[41] Moreover, they do not pose a high risk of hypoglycemia and do not cause weight gain.[41]

The most recent drug class to be approved for the management of type 2 diabetes are sodium-glucose cotransporter-2 (SGLT-2) inhibitors.[44] Unlike many other antihyperglycemic therapies, the mechanism of action for this drug is independent of insulin, lowering blood glucose by decreasing renal glucose reabsorption.[44] For this reason, SGLT-2 inhibitors may be indicated in patients regardless of diabetes duration with adequate renal function and may also provide blood pressure and weight reducing benefits.[44]

If oral or injectable antihyperglycemic drugs are not sufficient to reach glycemic targets, such as in cases of severe hyperglycemia or worsening disease progression, insulin therapy may be indicated to manage type 2 diabetes.

Insulin Treatment

Though there are no unanimous criteria for insulin initiation, insulin therapy does provide the greatest potential reduction in HbA1c and is usually initiated when non-insulin treatments are no longer sufficient to reach glycemic targets.[32]

Insulin therapy is typically initiated using basal insulin, often in addition to existing oral antihyperglycemic drugs, provided that pancreatic beta cell exhaustion has not yet occurred.[41] Basal insulin consists of intermediate or long acting insulins, though the latter is preferable to reduce the risk of hypoglycemia.[45] The goal of basal insulin is to control FPG.[45] If basal insulin is not sufficient to control FPG levels, or if type 2 diabetes has progressed to pancreatic beta cell exhaustion, the addition of a bolus insulin regimen is required.[41] [45] Traditionally, this intensification of insulin therapy consists of the addition of rapid-acting insulin as an injection at meals or as part of a premixed insulin formula according to individual patient needs.[45] The goal of the added bolus insulin is to imitate meal-stimulated insulin secretion to improve post-prandial glucose levels.[45] More recently, there is evidence that the addition of GLP-1 analogues to basal insulin therapy is similar in efficacy as adding bolus insulin before meals, emerging as another treatment strategy.[45]

Patients and clinicians alike may be hesitant to initiate therapy due to risk of adverse events, such as hypoglycemia and weight gain.[45] [46] Moreover, insulin therapy may increase complexity of treatment as it requires additional monitoring and adjustment by both the patient and clinician, and the patient may have negative perceptions of insulin therapy, including inconvenience, painful injections, and worsened disease severity.[45] [46]

While pharmacotherapy is an effective strategy to improve glycemic control of patients with diabetes, all antihyperglycemic drugs have risks and contraindications that must be considered for each individual patient. Therefore, continuous monitoring as part of a patient-centered diabetes care plan is essential to safely reach glycemic targets while minimizing the risk of adverse events.

2.3 Breast Cancer

2.3.1 Epidemiology and Risk Factors

Breast cancer is the most common cancer in women globally, with 2.3 million incident cases and 685,000 deaths in 2020.[1] Breast cancer is also the most common cancers among women in Canada, with 1 in 8 women developing this disease within their lifetime.[2] In 2022, breast cancer accounted for an estimated 25% of all new cancer diagnoses and 14% of all cancer deaths in Canada.[47] Breast cancer is expected to remain an increasingly significant global health burden as it is projected that by 2030, 2.7 million new cases and 870,000 deaths will occur worldwide each year.[48]

Certain factors increase the risk of developing breast cancer, however approximately half of patients have no other risk factors other than being female or over the age of 40 years.[1] Indeed, the risk increases with age as most breast cancer cases occur among women between the ages of 50 to 69.[47] Risk factors related to lifestyle include obesity, alcohol consumption, tobacco use and physical inactivity.[48] Family history is also an important risk factor, as the risk is doubled if a first-degree relative has had breast cancer.[49] Certain inherited genetic mutations, such as the BRCA1 and BRCA2 gene mutations, increase the risk of breast cancer by up to 87% and 85%, respectively.[48] Reproductive history related to exposure to estrogen influences risk since most breast cancers are responsive to estrogen.[49] Accordingly, early menarche, later menopause, later age pregnancy or nulliparity are risk factors.[49] Finally, use of oral contraceptives and hormonal replacement therapy present a small risk due to the exposure to exogenous hormones.[49] Other known risk factors include previous radiation exposure, non-malignant breast diseases, density of breast tissue and previous history of breast cancer.[48]

2.3.2 Pathophysiology

Breast cancer cells arise when DNA damage or genetic mutations cause cells in the breast to behave malignantly, and these cells are often responsive to certain hormones.[49] If the typical immune response fails to destroy these abnormal cells, tumour growth continues, eventually destroying nearby tissues with the possibility of spreading to other areas of the body.[49] In 85% of breast cancer cases, cancerous cells begin to develop in the epithelium of the ducts, known as ductal carcinoma.[1] The remaining 15% of cases originate in the lobules of the glandular tissue, known as lobular carcinoma.[1] In the initial stages of the disease, cancer cells are confined to the tissue of origin, and is referred to as in situ.[1] Over time, these cells may continue to develop and invade nearby breast tissues, becoming invasive breast cancer.[1] Metastasis may occur if cancer cells spread to nearby lymph nodes (regional metastasis) or other organs (distant metastasis) via the lymphatic system or the bloodstream.[1] In the context of distant metastasis, cancer will most commonly spread to the bones, liver, brain and lungs.[50]

2.3.3 Screening and Diagnosis

Screening

In its early stages, breast cancer is a largely asymptomatic disease, thus screening may play an important role to detect early disease when prognosis is better.[51] In high income countries, breast cancer mortality rates have declined by 40% since 1980.[1] This is in part due to widely implemented screening programs that use mammography, a low-dose x-ray of the breast, that can detect breast cancer in its early stages when treatment is most effective.[1] The WHO recommends mammograms every 2 years for women between the ages of 50 to 69 years.[52] Mammograms may be recommended in women outside of this age range, or more frequently in high-risk populations,

based on individual patient risk factors.[52] Mammograms are more likely to detect early-stage breast cancer when tumours are smaller and less likely to have spread, which influences treatment options and prognosis.[53] Indeed, the 5-year survival rate for localized breast cancer is 99%, compared to 84% and 23% for breast cancer that has regional or metastatic spread, respectively.[53] Furthermore, patients who are subsequently diagnosed after mammogram screening are less likely to undergo invasive or toxic treatments.[53] Thus, breast cancer screening is associated with better disease outcomes as well as decreased morbidity related to cancer therapies.[53]

Diagnosis

Breast cancer diagnosis is typically confirmed by a biopsy in response to suspected malignancy following breast imaging tests.[54] During a needle biopsy, cells are removed from suspicious lesions and then analyzed for malignancy.[54] Upon confirmation of a breast cancer diagnosis, additional prognostic tests are conducted, including tests to detect if metastasis has occurred.[49]

Stage and Grade

Breast cancer is a complex disease with various grades, stages and other histological characteristics.[54] Staging indicates the severity of invasiveness, where stage 0 corresponds to pre-invasive in situ disease while stage 4 corresponds to advanced disease of distant metastasis.[54,55] At the time of diagnosis, approximately 65% of patients have localized invasive breast cancer, while only 6% are diagnosed with metastatic disease.[56] Invasive breast cancers are further classified by grade.[54] Several grading systems exists, including a numerical scale from 1 (low) to 3 (high) based

on how differentiated the breast cancer cells are from normal cells, as well as the Tumour Node Metastasis scale which describes the size and spread of the malignancy.[55] Higher grading indicates a more aggressive cancer with a rapid rate of growth and spread compared to lower grades.[54 55]

Hormone Receptor Status

Breast cancer can also be further categorized according to which endogenous hormones will stimulate growth, as determined by the which receptor proteins are present on the cells.[57] Hormone receptor-positive (HR-positive) cancer cells may be stimulated by one or more endogenous hormones, specifically estrogen or progesterone.[57] Estrogen receptor-positive and progesterone receptor-positive breast cancers are stimulated by estrogen and progesterone, respectively.[57] Triple-positive breast cancer possesses receptors for both estrogen and progesterone in addition to the human epidermal growth factor receptor 2 (HER2), while triple-negative cancer does not possess any of these hormone receptors.[57] Up to 80% of breast cancers are HR-positive, with estrogen dependent cancer being the most common.[58]

These malignancy characteristics of grade, stage and hormone receptor status are important prognostic indicators of the disease, thus are a crucial part of the diagnostic process to be able to determine the course of treatment.[59]

2.3.4 Treatment

Breast cancer treatment will be informed by the predictive factors including grade, stage and receptor status, as well as patient characteristics and preferences.[60]

Surgery

In the case of localized and non-invasive breast cancer, breast conservation surgery is the preferred treatment approach.[54 61] In more advanced disease, or when breast conservation surgery is not possible, mastectomy may be indicated.[54 62] Before surgery, neoadjuvant therapy may be used to reduce tumour size.[54] Once the tumour is removed, adjuvant therapy in the form of radiation therapy, sometimes in combination with chemotherapy, is used to maximize the chance of a full recovery.[54]

Adjuvant Therapy

Adjuvant therapy is used reduce the risk of recurrence and metastasis after primary treatment, and may include radiation therapy, chemotherapy, hormone therapy or targeted therapy.[60] Choice of adjuvant treatment depends on the prognostic factors of disease, risks associated with the therapy, and patient risk of relapse.[60]

Chemotherapy

Chemotherapy as adjuvant treatment for breast cancer has been recommended in high-risk patients, particularly those with hormone receptor-negative cancer or those with spread to lymph nodes.[60] In such cases, adjuvant chemotherapy has been shown to provide greater benefits in terms of reduced risk of recurrence and breast cancer mortality.[60] Chemotherapy may be also used in combination with other adjuvant therapies.[60]

Targeted Therapy

Targeted agents are often used as part of adjuvant therapy for HER2 positive breast cancer.[60] These agents target the HER2 receptor on breast cancer cells, diminishing their ability to proliferate and spread.[63] When combined with chemotherapy, the use of HER2 targeted agents has been shown to greatly improve prognosis.[60]

Endocrine Therapy

Endocrine therapy is indicated for patients with HR-positive breast cancer to reduce signalling between endogenous hormones and cancer cells.[64] The three main endocrine therapy strategies are selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs) and ovarian suppression.[65]

SERMs bind to estrogen to prevent it from stimulating cancer cells, thereby preventing cancer growth.[64] SERMS, such as tamoxifen, are used as initial endocrine therapy in premenopausal women, or in postmenopausal women when AIs are not well tolerated or contraindicated.[66] Tamoxifen is typically taken for 5 to 10 years, depending on recurrence risk, and may be used in combination with AIs or ovarian suppression, depending on age, menopausal status, disease risk level, and tolerance.[60 66]

Alternatively, AIs prevent estrogen production by aromatase, making it less available to promote cancer growth or recurrence.[64] AIs are the preferred adjuvant treatment strategy in women without ovarian estrogen production, thus are most effective in postmenopausal women or in premenopausal women who are also undergoing ovarian suppression.[64 67]

Ovarian suppression aims to stop estrogen production by the ovaries by either surgical removal, ovarian ablation by radiation, drug interventions or chemotherapy.[68] Ovarian

suppression may be used in combination with other endocrine therapies, such as tamoxifen and AIs, if risk of recurrence is high.[67] Because ovarian suppression may cause permanent menopause and other serious side effects, careful assessment of the risks and benefits should be considered for each individual patient.[60 68]

2.4 Type 2 Diabetes Mellitus and Cancer

Type 2 diabetes is associated with an increased risk of long-term health complications, including certain cancers.[11 69] Several studies have shown that type 2 diabetes is associated with an increased risk of cancer at several sites, including the liver, pancreas, endometrium, colon, rectum, breast and bladder, but a lower risk of prostate cancer.[70] Similarly, there is increasing evidence that patients with diabetes also have an elevated risk of cancer mortality compared to their non-diabetes counterparts, however fewer studies have analyzed cancer site-specific mortality outcomes, with less robust results.[71] Tsilidis et al. conducted a meta-analyses analyzing the association between type 2 diabetes and cancer incidence and mortality for 20 cancer sites, finding a robust association between type 2 diabetes and incidence of breast, intrahepatic cholangiocarcinoma, colorectal, and endometrial cancer.[71] Conversely, all associations with cancer mortality did not meet the criteria for robustness and had indications of bias, suggesting that there remains substantial uncertainty regarding cancer mortality outcomes among patients with type 2 diabetes.[71]

A pooled analyses of 19 prospective population-based cohorts, comprising of 771,297 individuals from the Asia Cohort Consortium found a 26% increased risk of death from any cancer in those with type 2 diabetes compared to those without diabetes within an Asian population.[72] However, diabetes status was self-reported and the distinction between type 1 and type 2 was not

available.[72] In 2020, another meta-analysis conducted by Ling et al., including over 3.5 million patients from 17 cohorts, found that patients with type 2 diabetes had a pooled relative risk (RR) of 1.25 (95% CI: 1.18-1.33) for all-site cancer mortality, however the heterogeneity across cohorts was significant (I^2 = 80.4%, P <0.001).[73] Similarly, a systematic review and meta-analysis by Noto et al. also found an increased risk of total cancer mortality among the type 2 diabetes group compared to non-diabetes (RR: 1.16; 95% CI: 1.03-1.30), with significant heterogeneity across the 14 cohorts (I^2=82%, P<0.00001).[74] This may be partly due to differences in response to insulin across cancer sites, such as the pancreas, liver, colorectum and breast.[72 74] Meanwhile, the Emerging Risk Factors Collaboration conducted a pooled analysis of 97 prospective cohort studies and found moderate associations between diabetes and mortality from several cancers, namely liver, pancreas, ovary, colorectum, lung, bladder, and breast.[75] However, this study evaluated numerous cancer and noncancer outcomes and had restricted data on cancer site-specific death.[71 75] Despite these findings, the underlying mechanism between type 2 diabetes and cancer mortality remains unclear, but it is suggested that shared risk factors (age, body mass index (BMI), physical activity level, alcohol intake and smoking) may play a role as well as the metabolic abnormalities (hyperinsulinemia, hyperglycemia, systemic inflammation) that characterize diabetes.[69 71 73 75] Therefore, with concerns of bias and methodological issues within the existing literature, further studies with cancer site-specific mortality outcomes is warranted.[71 73] The next section of this thesis will focus on breast cancer mortality outcomes and its association with type 2 diabetes.

2.5 Type 2 Diabetes Mellitus and Breast Cancer Outcomes

There is existing evidence that suggests that type 2 diabetes may have an effect on breast cancer outcomes. This section outlines what is currently known about the association between type 2 diabetes and breast cancer mortality outcomes in the scientific literature.

2.5.1 Association Between Type 2 Diabetes and Breast Cancer Mortality Outcomes

Systematic Reviews & Meta-Analyses

To date, there are 4 key systematic reviews and meta-analyses that investigate the relationship between type 2 diabetes and breast cancer mortality outcomes (summarized in **Table 3**).[3 8 76 77] However, these have several methodological concerns, including evidence of publication bias and significant heterogeneity across studies which may be due to inconsistent measurement and adjustment of covariates, population demographics, ascertainment of diabetes status, study quality, and sample size.

In 2011, Peairs et al. pooled the results of 6 studies to investigate the association between pre-existing diabetes and all-cause mortality, finding a 49% increased risk among women with diabetes compared to non-diabetes (HR: 1.49; 95% CI: 1.35-1.65).[3] Additionally, 2 of the included studies reported on breast cancer-related mortality, however these had inconsistent results.[3] Similarly, Zhou et al. also found an increased risk of all-cause mortality among breast cancer patients with pre-existing diabetes, compared to non-diabetes, after pooling results from 16 studies (HR: 1.37; 95% CI: 1.34-1.41).[8] They also pooled results from 12 studies that reported on breast cancer-related mortality, finding a 17% increased risk for breast cancer mortality in the diabetes group (HR: 1.17; 95% CI: 1.11-1.22).[8] In a sensitivity analysis, the HRs were recalculated by excluding one study per iteration, ranging from 1.07 (95% CI: 0.87-1.04) to 1.32 (95% CI: 1.05-

1.67) for breast cancer mortality.[8] Both of these meta-analyses had indications of publication bias for all-cause mortality.[3 8] Meanwhile, in a meta-analysis including 15 studies, Zhao et al. found a 51% increased risk (HR: 1.51; 95% CI: 1.34-1.70) in overall mortality among patients with diabetes, though there was significant heterogeneity across studies.[77] Additionally, 5 of the pooled studies gave a HR of 1.28 (95% CI: 1.09-1.50) for disease-free survival.[77] Lastly, De Bruijn et al. investigated the effect of diabetes on incidence and mortality of breast and colon cancer, separately.[76] A random-effects model including 8 pooled studies showed a 38% increased risk of breast cancer-related mortality among patients with diabetes compared to non-diabetes (HR: 1.38; 95% CI: 1.20-1.58).[76] The studies included had variations in covariate adjustment, including multivariable adjusted models, age-only adjusted models and unadjusted models.[76]

A concern across all systematic reviews and meta-analyses was the variation in exposure definition. First, none of these meta-analyses differentiated between type 2 diabetes and other forms of diabetes. Second, the included studies used varying methods to identify patients with diabetes, including hospital admission data, medical records, glycemic blood values, insulin levels, antihyperglycemic drug use, as well as self-reported diabetes, leading to potential misclassification bias. Furthermore, breast cancer-related mortality was not the primary outcome in any of the meta-analyses.[3 8 76 77] Another common limitation of these meta-analyses was the inconsistent measurement and adjustment for covariates across the included studies, leaving the results susceptible to residual confounding.

Observational Studies

To date, there have been 13 key observational studies assessing the association between diabetes and breast cancer mortality (summarized in **Table 3**). However, these studies vary greatly

in terms of sample size, diabetes status ascertainment, and covariate inclusion and measurement. Thus, these studies have important methodological limitations, including inadequate cofounder adjustment, potential exposure and outcome misclassification, and limited power, potentially affecting the interpretability of the published literature.

Several studies have found an association between diabetes and an increased risk of all-cause mortality, but not breast cancer-related mortality.[78-81] Zhou et al. pooled data from 17 prospective studies, including 44,655 patients, assessing the risk of total cancer mortality among those with any diabetes compared to non-diabetes, according to glucose tolerance as defined by an OGTT.[81] While they found an association between diabetes status and the risk of total cancer mortality (HR: 1.44; 95% CI: 1.21-1.70), a sub-group analyses found that diabetes was not associated with an increased risk of breast cancer mortality (HR: 1.65; 95% CI: 0.93-2.93).[81] Furthermore, because total cancer mortality was the main outcome, there was limited study power for breast cancer mortality as a small number of events, 85 breast cancer deaths, were observed.[81] Additionally, few lifestyle and comorbidity covariates were included in the model, and diabetes type was not specified.[81] Another large study by Lam et al. pooled individual data from 36 cohort studies conducted in the Asia-Pacific region totalling 367,361 participants, analyzing the relationship between any diabetes and site-specific cancer mortality.[78] After adjusting for age, sex, and study, those with diabetes had 23% greater risk of all-cancer mortality compared to non-diabetes (HR: 1.23; 95% CI: 1.12-1.35), while there was no such association with breast cancer-related mortality (HR: 0.75; 95% CI: 0.39-1.47).[78] There was a total of 299 breast cancer deaths, however the total number of breast cases was not reported.[78] Nechuta et al. investigated the association of all diabetes and other major comorbidities with breast cancer outcomes, including all-cause mortality and breast cancer-related mortality.[82] A total of 4,664 women diagnosed with

stage I-III incident breast cancer were included, with 6.2% of patients having diabetes.[82] Data on comorbidities, including diabetes, was determined via in-person interviews, and was not validated using medical records.[82] Patients reporting diabetes had a 40% increased risk of all-cause mortality (HR: 1.40; 95% CI: 1.06-1.85) but no statistically significant increase in risk of breast cancer-related mortality (HR: 0.98; 95% CI: 0.68-1.41), compared to non-diabetes.[82] Similarly, in 2014, Luo et al. conducted a prospective cohort study of 8,108 patients with breast cancer, finding a 26% increased risk of all-cause mortality (HR: 1.26; 95% CI: 1.06-1.48) but no statistically significant increase in risk of breast cancer-related mortality (HR: 0.74; 95% CI: 0.53-1.02) among the self-reported type 2 diabetes group, compared to non-diabetes, however only 550 breast cancer deaths were recorded.[83] A year later, another prospective study by Luo et al. found similar conclusions among a cohort of 2,833 elderly women, with HRs for the risk of all-cause mortality and breast cancer-related mortality of 1.46 (95% CI: 1.12-1.86) and 1.13 (95% CI: 0.70-1.84), respectively, among patients with type 2 diabetes.[84] However, only 194 breast cancer deaths were recorded and these findings may not be generalizable to patients under 65 years of age.[84] Many of the studies used exposure definitions that did not differentiate between type 2 diabetes and other types of diabetes[78 81 82] and some studies had limited power to assess mortality outcomes, in particular breast cancer-related mortality, due to a small number of breast cancer deaths.[78 81 83 84]

More recently, in 2020, a prospective cohort study by Tao et al. analyzed the effect of pre- and post-diagnosis type 2 diabetes on all-cause mortality and site-specific mortality for breast, prostate and colorectal cancer, including 37,993 cancer patients, of which 6,330 were breast cancer cases.[9] This study found a 31% increase in all-cause mortality in women diagnosed with type 2 diabetes prior to cancer diagnosis (HR: 1.30; 95% CI: 1.10-1.57), but the association with breast cancer mortality was not significant (HR: 0.98; 95% CI: 0.77-1.25).[9] Methodological concerns

for this study are that breast cancer mortality was not the primary outcome of the study, limited comorbidities were considered (hypertension, coronary artery disease and stroke), and self-reported data was used to identify both diabetes status and breast cancer cases.[9]

Among retrospective studies that aimed to quantify the association between type 2 diabetes and breast cancer mortality outcomes, the results have again remained inconsistent with variation in study size, population, and covariate adjustment.

Srokowski et al. analyzed the effect of all types of diabetes on chemotherapy use, treatment-related toxicities and breast cancer outcomes.[85] The study population included 70,781 men and women over 65 years of age with Stage I-III breast cancer from 1992 to 2002 using patient data collected from Medicare database linked to tumour registries.[85] While patients with any diabetes had significantly higher risk of all-cause mortality (HR: 1.35; 95% CI: 1.31-1.39), breast cancer-related mortality was only higher in patients with diabetes who received chemotherapy (HR: 1.20; 95% CI: 1.07- 1.35), compared to their non-diabetes counterparts.[85] These results may not be generalizable to patients 65 years or younger nor to those who are not covered under Medicare, and may not reflect the current milieu of breast cancer screening and treatment.[85]

Meanwhile, Jiralerspong et al. found an increased risk of overall mortality for obese patients (HR: 1.24; 95% CI: 1.04-1.48) compared to the non-obese group, as well as for patients with any diabetes (HR: 1.39; 95% CI: 1.10-1.77) compared to non-diabetes.[86] There was also an association with higher BMI and risk of breast cancer mortality (HR: 1.23; 95% CI: 1.00-1.52), however not with diabetes status (HR: 1.04; 95% CI: 0.75-1.45) in this study of 6,342 patients with early-stage breast cancer.[86]

In 2012, Liu et al. used a Swedish cohort to assess the impact of type 2 diabetes on cancer-specific mortality outcomes, including breast cancer.[87] The population was restricted to those >39

years old who had a hospitalization for cancer between 1961 and 2008, totalling over 1 million patients, including 146,764 patients with breast cancer.[87] Type 2 diabetes was associated with a 45% increased risk of breast cancer death compared to non-diabetes (HR: 1.45; 95% CI: 1.32-1.59).[87] When stratified by obesity status, obese patients with type 2 diabetes had an even higher risk of breast cancer death (HR: 2.50; 95% CI: 1.22-5.13), though this was based on a limited number of patients.[87] Although this was a large, population-based study, there are several notable methodological concerns. First, both type 2 diabetes status and cancer data were based on hospitalization data, which may represent more severe disease and may not be externally valid.[87] Furthermore, because the exposure was defined based on having at least 1 previous hospitalization for type 2 diabetes, this may introduce misclassification of diabetes status.[87] Additionally, comorbidities and physical activity were not included as covariates.[87]

Chen et al. investigated this association among an Asian population of 4,390 patients with newly diagnosed early-stage breast cancer and found that patients with any diabetes had lower breast cancer survival (HR, 1.53; 95% CI: 1.14-2.05) and overall survival (HR: 1.71; 95% CI: 1.33- 2.19).[88] This association remained consistent among various subgroups including age, tumor stage, lymph node status, receptor status, and adjuvant chemotherapy and hormone treatment status, however data on BMI was not available.[88]

Wu et al. investigated the impact of several comorbidities on breast cancer mortality outcomes, including all diabetes, among 8,952 patients using data from California Breast Cancer Survivorship Consortium, which is comprised of questionnaire and cancer registry data.[89] Compared to their non-diabetic counterparts, patients with diabetes had a 75% increased risk of overall mortality (HR: 1.75; 95% CI: 1.50-2.05) and 48% increased risk of breast cancer-related mortality (HR: 1.48; 95% CI: 1.18-1.87), after adjusting for patient demographics, comorbidities,

tumor characteristics, and lifestyle factors.[89] However, there were inconsistencies in cohort entry (date of diagnosis vs date of interview) and data collection on covariates, including self-reported comorbidities, between the pooled studies.[89]

More recently, Lawrence et al. conducted a similar study among 9,222 nonelderly Medicaid-insured patients with breast cancer, with overall, cancer-specific and cardiovascular-specific mortality as study outcomes.[90] Patients with type 2 diabetes had an elevated risk of all-cause mortality (HR: 1.40; 95% CI: 1.21-1.63) and cancer-specific mortality (HR: 1.24; 95% CI: 1.04-1.47).[90] However, nonelderly Medicaid-insured women have been found to be at higher risk of death from breast cancer and type 2 diabetes-related complications compared to other insured groups, thus these results may not be generalizable to other populations.[90]

Within the literature there exists several limitations that should be noted. First, there is the inconsistent measurement and inclusion of key covariates across cohort studies, including age, BMI, and comorbidities, may leave confounding as a concern.[9 78 79 81 88 89 91-93] Furthermore, several studies measured comorbidities using self-reporting,[80 82-84 89 94] while others used medical records.[79 85 87 90 95] Inclusion of complete, accurate and valid comorbidity measurement is essential to adjust for confounding, as diabetes is associated with disease of multiple organ systems that may interact with mortality. Second, several studies had limited power to assess mortality outcomes, in particular breast cancer-related mortality, due to a small number of breast cancer deaths.[78 81 83 84 91] Lastly, inconsistent exposure and outcome ascertainment, as well as concerns related to data validity and completeness,[79] may limit the interpretability of the published studies.

To conclude, type 2 diabetes may increase the risk of breast cancer mortality, however previous study results have been inconsistent with important methodological limitations. Nevertheless, prevalence of type 2 diabetes is increasing simultaneously with that of breast

cancer,[7 11] thus further investigation is needed to address the limitations of the existing literature to improve concurrent clinical care of these two highly prevalent diseases.

Table 3. Summary of Main Studies Addressing the Association Between Type 2 Diabetes and Breast Cancer Mortality Outcomes

	Year	Median Follow-Up (yrs)	Main Outcomes	Measure of Effect
Systematic Review & Meta-Analysis				
Peairs et al.	2011	Not reported	All-cause mortality	HR: 1.49; 95% CI: 1.35-1.65
De Bruijn et al.	2013	Not reported	Breast cancer mortality	HR: 1.38; 95% CI: 1.20-1.58
Zhou et al.	2014	Not reported	All-cause mortality Breast cancer mortality	HR: 1.37; 95% CI: 1.34-1.41 HR: 1.17; 95% CI: 1.11-1.22
Zhao et al.	2016	Not reported	Overall survival Disease-free survival	HR: 1.51; 95% CI: 1.34-1.70 HR: 1.28; 95% CI: 1.09-1.50
Observational Studies				
Srokowski et al.	2009	Not reported	All-cause mortality Breast cancer mortality	HR: 1.35; 95% CI: 1.31-1.39 HR: 1.20; 95% CI: 1.07-1.35 among patients who received chemotherapy
Zhou et al.	2010	15.8	Total cancer mortality Breast cancer mortality	HR: 1.44; 95% CI 1.21-1.70 HR: 1.65; 95% CI 0.93-2.93
Lam et al.	2011	4.0	All-cause cancer mortality Breast cancer mortality	HR: 1.23; 95% CI: 1.12-1.35 HR: 0.75; 95% CI: 0.39-1.47
Liu et al.	2012	Not reported	Breast cancer mortality	HR: 1.45; 95% CI: 1.32-1.59
Chen at al.	2012	5.6	Overall survival Breast cancer survival	HR: 1.71; 95% CI: 1.33- 2.19 HR: 1.53 95% CI: 1.14-2.05
Nechuta et al.	2013	5.3	All-cause mortality Breast cancer mortality	HR: 1.40; 95% CI: 1.06-1.85 HR: 0.98; 95% CI: 0.68-1.41
Jiralerspong et al.	2013	5.4	Overall survival Breast cancer survival	HR: 1.39; 95% CI: 1.10-1.77 HR: 1.04; 95% CI 0.75-1.45
Luo et al.	2014	Not reported	All-cause mortality Breast cancer mortality	HR: 1.26; 95% CI: 1.06-1.48 HR: 0.74; 95% CI: 0.53-1.02
Luo et al.	2015	Not reported	All-cause mortality Breast cancer mortality	HR: 1.46; 95% CI: 1.12-1.86 HR: 1.13; 95% CI: 0.70-1.84
Wu et al.	2015	Not reported	Overall mortality Breast cancer mortality	HR: 1.75; 95% CI: 1.50-2.05 HR: 1.48; 95% CI: 1.18-1.87
Maskarinec et al.	2019	Not reported	All-cause mortality Breast cancer survival	HR: 1.23; 95% CI: 1.08-1.40 HR: 0.84; 95% CI: 0.65-1.09
Tao et al.	2020	13.0	All-cause mortality Breast cancer mortality	HR: 1.31; 95% CI: 1.10-1.57 HR: 0.98; 95% CI: 0.77-1.25
Lawrence et al.	2020	Not reported	All-cause mortality Cancer mortality	HR: 1.40; 95% CI: 1.21-1.63 HR: 1.24; 95% CI; 1.04-1.47

2.5.2 Association Between Type 2 Diabetes and Breast Cancer Mortality Outcomes Among Patients with Metastatic Breast Cancer

Patients with type 2 diabetes have been found to be more likely to be diagnosed with advanced-stage breast cancer, even after adjusting for covariates like mammography screening.[10] [96] Metastatic breast cancer may impact disease progression and treatment options, contributing to differences in outcomes, particularly among patients with type 2 diabetes.[10] However, the association between type 2 diabetes and breast cancer mortality outcomes among patients with metastatic disease has been rarely studied, with only 2 previous studies addressing this research question. Murto et al. conducted a cohort study analyzing the association between diabetes and breast cancer stage and survival among 73,170 patients with breast cancer in Finland.[97] Compared to non-diabetes, breast cancer patients with diabetes were more likely to be diagnosed with locally advanced (Odds Ratio (OR): 1.26; 95% CI: 1.18-1.35) or metastatic (OR: 1.59; 95% CI: 1.44-1.75) disease, and were at higher risk of breast cancer death (HR: 1.36; 95% CI: 1.27-1.46).[97] Several key variables were not available, including use of hormone replacement therapy, tumour characteristics, BMI, smoking status and socioeconomic status.[97] Conversely, Cheung et al. found no significant difference in 5-year overall survival between 244 patients with diabetes and 244 patients without diabetes (matched for age, sex, ethnicity, and receptor subtype) with metastatic breast cancer.[98] Moreover, poor glycemic control, as defined by a median RBG >180 mg/ dL or a HbA1c > 7%, was also not associated with worse 5-year overall survival when compared to good glycemic control (HbA1c ≤ 7%).[98] However, due to the small sample size of patients with a HbA1c >7%, this may have limited the statistical power.[98]

2.5.3 Biological Plausibility

Type 2 diabetes and breast cancer are two complex, heterogeneous diseases that share several risk factors, including obesity, older age, lifestyle behaviours and genetic predisposition.[5] [13] Type 2 diabetes has been associated with increased incidence and mortality of several cancers, including liver, endometrial, colorectal, pancreatic, bladder and breast cancer.[99] Indeed, a growing body of evidence suggests that there is an association between breast cancer incidence and mortality among women with type 2 diabetes.[69] Though not thoroughly understood, several possible biological mechanisms have been identified linking type 2 diabetes with breast cancer mortality.

Hyperinsulinemia

Hyperinsulinemia is a characteristic of type 2 diabetes that may promote tumour growth through several mechanisms.[100] First, the mitogenic effects of insulin may be enhanced for years or even decades from the progression of prediabetes to type 2 diabetes.[100] Insulin binds to insulin-like growth factor 1 (IGF-1) receptors and decreases production of other IGF-1 binding proteins, leading to higher concentrations of circulating IGF-1.[100] Higher IGF-1 may promote cancer cell proliferation as it activates cellular signaling pathways that favour cancer cell survival, growth and migration.[100] While this insulin-IGF axis has been observed in several types of cancer, IGF-1 expression is greater in mammary tissues, contributing to enhanced growth of malignant tumours via this mechanism.[69] Second, insulin receptors are often overexpressed in breast cancer cells, thus hyperinsulinemia may directly enable cancer growth via increased insulin receptor binding.[100] Third, hyperinsulinemia may also influence circulating levels bioactive hormones, particularly estrogen, which is related to breast cancer risk.[70] Sex hormone binding globulin is a

protein that binds to sex hormones to help regulate levels of circulating androgens and estrogens.[69] Elevated blood glucose and insulin has been associated to lower levels of sex hormone binding globulin, thereby increasing bioavailability of sex hormones.[69] Indeed, higher estrogen levels have been observed in women with type 2 diabetes compared to non-diabetes.[69] Consequently, with approximately 80% of breast cancers being HR-positive, increased estrogen levels may propel cancer growth.[58]

Hyperglycemia

Glucose is an energy source of the cell, fueling cell growth and proliferation.[69] In cancer cells, normal glucose metabolism is disrupted as cells shift to glycolysis for faster glucose uptake.[69] Thus, it is hypothesized that hyperglycemia may exacerbate this toxic mechanism and provide a rich energy source that favours tumour development.[69 101] On an intracellular level, hyperglycemia may help promote tumour protein and DNA synthesis, further favouring cancer cell survival.[69] Additionally, hyperglycemia leads to the formation of advanced glycation end products and reactive oxygen species, which are involved in the pathophysiology of both diabetes and cancer.[69] Advanced glycation end products trigger inflammatory pathways, genetic mutations, and neoplastic transformation of epithelial cells.[101] Similarly, reactive oxygen species can contribute to tumour creation through DNA damage and cancer signalling pathways related to metastasis.[69] Thus, chronic hyperglycemia may contribute to cancer cell proliferation and signalling pathways via increased production of oxidants and inflammation.[69] However, it is important to note that hyperglycemia and hyperinsulinemia are two interrelated characteristics of a complex metabolic condition, therefore there is currently no consensus on whether hyperglycemia is an independent factor in promoting tumour progression.[69]

Obesity

Obesity is a shared risk factor of cancer and diabetes, and increasing BMI has been shown to be associated with increased cancer mortality.[100] With most patients with type 2 diabetes classified as overweight or obese, central adiposity in particular is a contributor to the metabolic dysregulation that creates an ideal milieu for cancer cell proliferation.[101] Indeed, adipose tissue produces several pro-inflammatory cytokines, including interleukin-6 and tumour necrosis factor-alpha, which have been associated with cancer in addition to diabetes.[69] More specifically, interleukin-6 triggers cellular signaling pathways that promote breast cancer cell development and metastasis, while excessive tumour necrosis factor-alpha promotes tumour growth and reduces cancer cell apoptosis.[69] Additionally, higher levels of estrogens are associated with obesity due to increased aromatase activity in adipose tissue, which may promote growth of HR-positive breast cancers.[100]

Obesity is closely related to hyperinsulinemia and hyperglycemia, thus may exacerbate the respective biological mechanisms previously discussed.[70] Due this interrelatedness, it is still not yet fully understood the individual contribution of each mechanism.[70]

Systemic Inflammation and Oxidative Stress

Hyperinsulinemia, hyperglycemia and obesity each play a role in the metabolic dysregulation of type 2 diabetes that contributes to systemic inflammation and oxidative stress.[100] As previously discussed, all of these elements contribute to this microenvironment that is more prone to malignant mutations by direct DNA damage as well as impaired anti-oxidant capability, favouring tumour growth.[100] [101] Furthermore, inflammation related to increased cytokine production inhibits the immune response, favouring cancer cell survival and disease progression.[69]

2.5.4 Knowledge Gaps

In summary, the available evidence on the association between type 2 diabetes and breast cancer mortality is inconsistent. Across studies there is heterogeneity in terms of diabetes definition and ascertainment, ranging from self-reported status to recorded clinical measurements, which may lead to exposure misclassification. Furthermore, there is very limited published literature assessing the association between severity of diabetes and breast cancer outcomes. Additionally, inadequate adjustment for confounding is a concern as covariate inclusion and measurement were highly inconsistent across studies, with some key variables (such as age, BMI, and comorbidities) missing from some statistical models altogether. The sample sizes across studies also varied greatly, with many of the studies assessing the risk of breast cancer-related mortality with a small number of events. Finally, for breast cancer-related mortality in particular, outcome misclassification is a concern, and no studies have considered competing risks.

To date, there have been no large cohort studies using valid, high quality longitudinal data to assess the association between type 2 diabetes and breast cancer mortality outcomes for metastatic and non-metastatic disease, separately. Moreover, there are no studies that have assessed whether breast cancer outcomes vary across glycated HbA1c levels among women with type 2 diabetes compared with non-diabetic glycemic levels. Given the increasing number of patients with type 2 diabetes at breast cancer diagnosis, there is a need to understand how diabetes may impact breast cancer outcomes. To address this gap, this thesis assessed whether pre-existing type 2 diabetes is associated with breast cancer-related mortality and all-cause mortality among women with newly diagnosed breast cancer. The following chapters describe the objectives, methodology, and findings of this research work.

CHAPTER 3: OBJECTIVES AND HYPOTHESES

3.1 Primary Objectives

The primary objective of this thesis is to investigate whether pre-existing type 2 diabetes is associated with an increased risk of breast cancer-related mortality, compared with non-diabetes, among women newly diagnosed with non-metastatic and metastatic breast cancer, separately.

3.1.1 Secondary Objectives

This thesis has 3 secondary objectives:

1. To determine whether pre-existing type 2 diabetes is associated with an increased risk of all-cause mortality;
2. To determine whether the risk of the outcomes vary across HbA1c categories (<6.5%, 6.5-7.0%, 7.1-8.0%, >8.0%) among women with type 2 diabetes compared with normal glycemic levels;
3. To determine whether BMI (<25 kg/m², 25-29 kg/m², ≥30 kg/m², unknown) is an effect modifier of the association on the multiplicative scale;
4. To determine whether age (<55 years, ≥55 years) is an effect modifier of the association on the multiplicative scale.

3.2 Hypothesis

The primary hypothesis is that type 2 diabetes will be associated with an increased risk of breast cancer-related mortality, compared with non-diabetes, for both the non-metastatic and metastatic cohorts.

3.2.1 Secondary Hypotheses

1. Pre-existing type 2 diabetes will be associated with an increased risk of all-cause mortality, compared with non-diabetes, for both the non-metastatic and metastatic cohorts;
2. Risk of the outcomes will increase with increasing glycated HbA1c categories among women with type 2 diabetes compared with normal glycemic levels;
3. There is no effect measure modification by BMI;
4. There is no effect measure modification by age.

CHAPTER 4: METHODOLOGY

This chapter will provide greater details on the methodology described in the manuscript found in Chapter 5, as certain aspects were not covered because of word limitations. Specifically, it will provide additional information on the data source, study cohort, exposure and outcomes definitions, the follow-up period, and covariates.

4.1 Data Source

This study was conducted using the UK Clinical Practice Research Datalink (CPRD). In 1987, this database began as the Value Added Medical Products dataset, expanding into the General Practice Research Database in 1993, and finally becoming the CPRD in 2012.[102] In the UK, general practitioners are the first point of contact within the National Health Service for non-emergency health conditions.[102] General practitioners will manage patient care or refer to secondary care as needed, with routine data collection from both primary and secondary care.[102] Participating general practices contribute to the CPRD on a monthly basis, providing patient information from their first to final visit.[102] The CPRD is comprised of the Gp Online Data (GOLD) or Aurum datasets. Depending on the patient management software used, general practices contribute to either CPRD GOLD or Aurum.[103] Thus, with the GOLD and Aurum datasets combined, the CPRD is one of the largest longitudinal medical records from primary care, covering 2000 general practices comprising of approximately 60 million patients that are representative of the general population of the UK in relation to age, sex, and ethnicity.[102 104] This database is comprised of anonymized data on clinical diagnoses, symptoms, tests, specialist referrals and prescriptions as well as patient characteristics such as demographics, anthropometrics and lifestyle factors.[102] Data in the CPRD is largely captured by Read codes and Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT) classification system, which provide

clinicians a standardized system to record clinical care.[102] Prescription data is recorded using British National Formulary codes and numerical data is collected for clinical measurements.[102] Additionally, the GOLD and Aurum databases of the CPRD can be linked to secondary care databases.[102] This includes linkage to hospitalization data from the Hospital Episode Statistics Admitted Patient Care (HES APC), deprivation data from the Index of Multiple Deprivation and Townsend scores, mortality data from the Office for National Statistics (ONS) databases and cancer registration data from the National Cancer Intelligence Network.[102]

The CPRD offers valid, high quality longitudinal data that has been used in over 3000 peer-reviewed epidemiological publications.[104] Breast cancer is well recorded within the CPRD, with up to 97% concordance between the CPRD and UK cancer registries.[105 106] Furthermore, diabetes diagnosis in the CPRD has been found to have a sensitivity of over 90%.[107] Due to the overall validity of diagnoses within the CPRD, it is a dataset that has been used to conduct many observational studies, including those that assess the risk of cancer mortality among patients with diabetes compared with non-diabetes.[108-110] Thus, the CPRD is an appropriate data source to address our research question.[104]

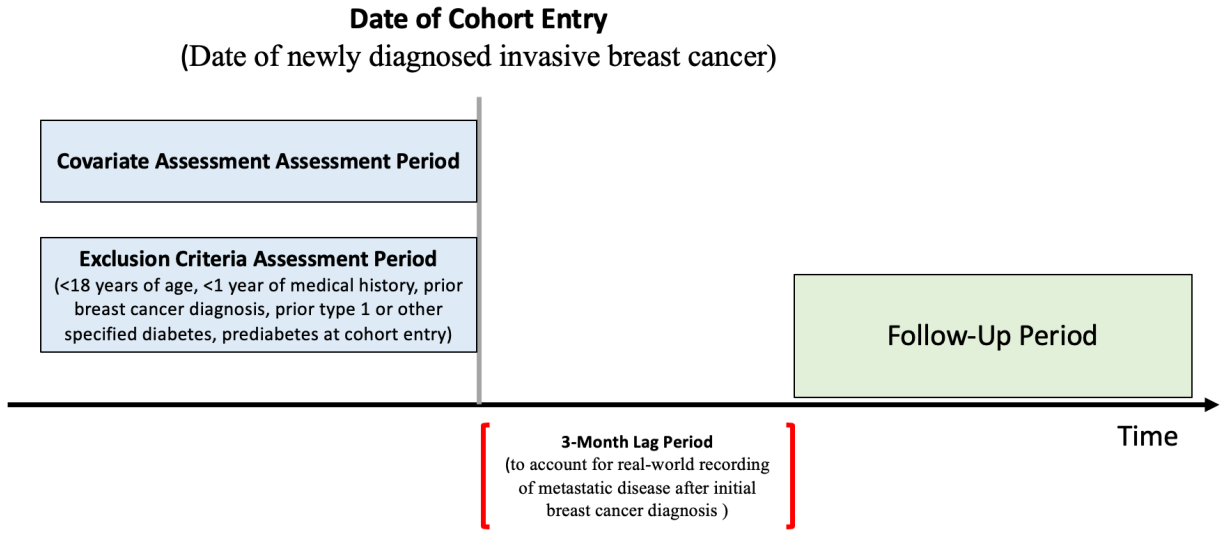
The study protocol was approved by the independent scientific advisory committee of the CPRD (protocol number 22_002073) and by the research ethics board of the Jewish General Hospital, Montreal, Canada.

4.2 Study Population and Follow-Up

The study included patients who were newly diagnosed with invasive breast cancer between April 1, 1998 and December 31, 2020 with eligible linkage to the HES APC and ONS databases. The Read and SNOMED-CT codes from the CPRD Aurum and GOLD databases that

were used to identify invasive breast cancer cases are summarized in **Supplementary Table 1** and **Supplementary Table 2**, respectively. The cohort was restricted to patients at least 18 years of age and those with at least one year of medical history in the CPRD. Patients with prediabetes or forms of diabetes other than type 2 were excluded. Prediabetes was identified using Read codes (prediabetes, impaired glucose tolerance, impaired fasting glucose, non-diabetic hyperglycemia), or glycemic lab values (HbA1c, FPG, 75g 2hr OGTT) within the prediabetes range. Other forms of diabetes were identified using Read codes. Cohort entry was defined by the first-ever diagnosis of breast cancer during the study period. Patients with metastatic and non-metastatic breast cancer were analyzed separately, and thus separate cohorts were constructed for each of these groups. All patients were followed from 3 months after their initial breast cancer diagnosis until one of the study outcomes, end of registration with the general practice, or end of study (March 29, 2021), whichever came first. This 3-month lag was used to account for real-world recording of metastatic disease after initial breast cancer diagnosis, thus ensuring that patients with metastases at diagnosis were captured. **Figure 1** summarizes the study follow-up period for the non-metastatic and metastatic cohorts.

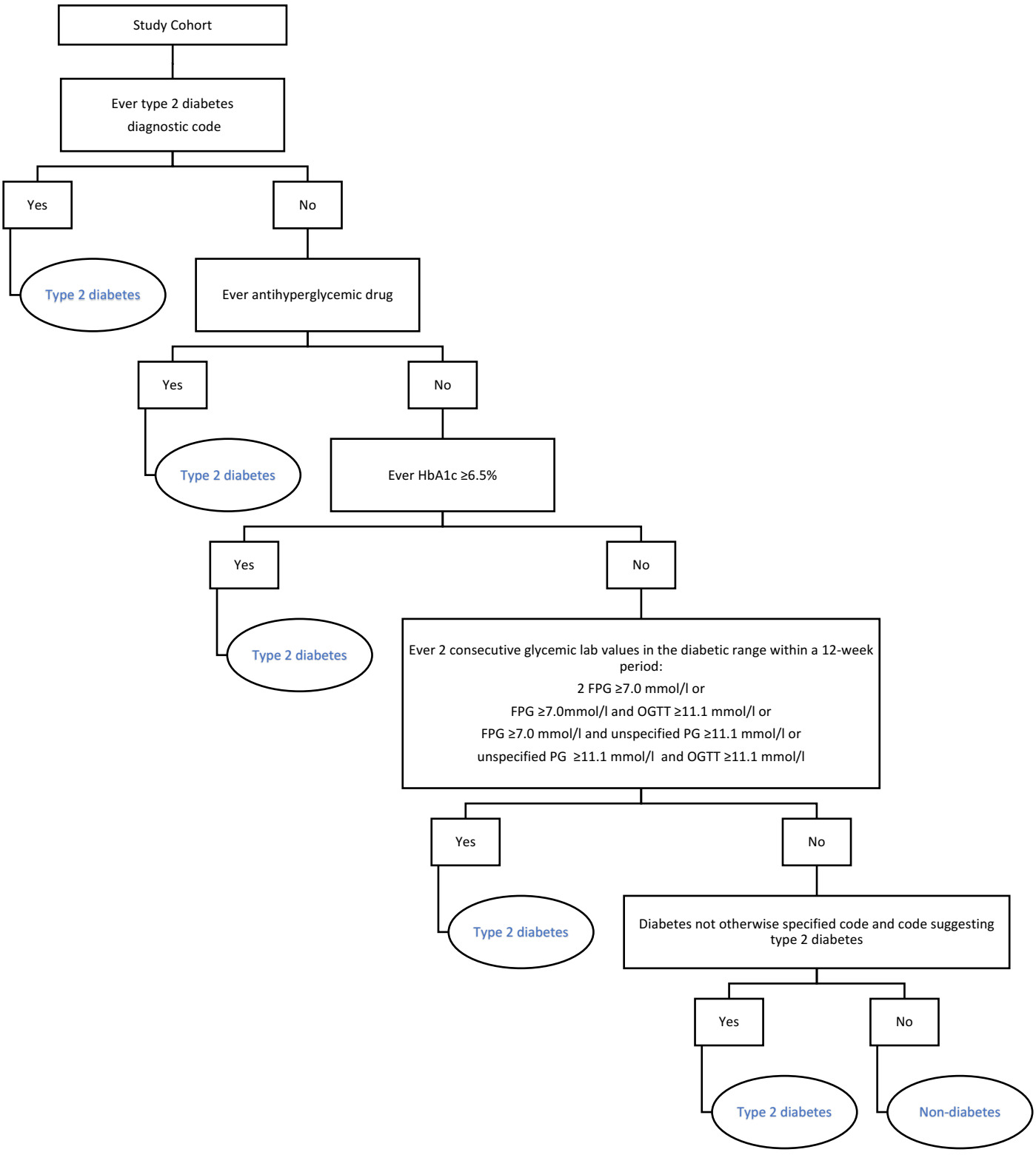
Figure 1. Study follow-up period for the metastatic & non-metastatic cohorts



4.3 Exposure Definition

Patient exposure was based on diabetes status prior to the first-ever breast cancer diagnosis. Patients were classified into the type 2 diabetes group if they had any of the following at any time before cohort entry: a type 2 diabetes diagnosis, a prescription for an antihyperglycemic drug, a HbA1c ≥6.5%, or 2 consecutive glycemic lab values (HbA1c, FPG, 75g 2hr OGTT, Plasma Glucose (PG)) in the diabetic range within a 12-week period. Requiring 2 consecutive lab values within a 12-week period was used to reflect real-world clinical practice of repeat glycemic testing to confirm type 2 diabetes diagnosis and to reduce exposure misclassification. Additionally, patients with both a recorded code for an unspecified type of diabetes and a clinical code suggestive of a type 2 diabetes diagnosis (ex: nephropathy due to type 2 diabetes) were also classified into the type 2 diabetes group. The remaining patients were placed in the non-diabetes group. Patients were considered continuously exposed based their diabetes status as determined before cohort entry. **Figure 2** provides a summary of the algorithm used to ascertain diabetes status.

Figure 2. Algorithm for classifying type 2 diabetes status among the study cohort



Abbreviations: HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, plasma glucose

4.4 Outcome Definition

As previously mentioned, patients were followed from 3 months after their first breast cancer diagnosis until one of the study outcomes, end of registration with the general practice, or end of the study period, whichever came first. The primary and secondary outcomes of interest were determined by pre-specified International Classification of Diseases, Tenth Revision (ICD-10) codes for malignant breast cancer (ICD-10 codes: C50.0-C50.9) and any cause of death, respectively. CPRD primary care data was linked to the ONS Death Registration Data, which is considered the gold standard for mortality data in the UK, to identify study outcomes.[103]

4.5 Confounders

The Cox proportional hazards models were adjusted for 33 confounders. All models were adjusted for the following demographic/lifestyle variables measured at or ever before cohort entry, as these are shared risk factors of type 2 diabetes and breast cancer and are thus associated with both the exposure and the outcome: age, BMI (<25 kg/m², 25-29 kg/m², ≥30 kg/m², unknown), smoking status (ever, never, unknown), alcohol-related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic flexure) and patient level index of multiple deprivation as a measure of socioeconomic status.

The models also included covariates related to diabetes severity, such as microvascular complications (neuropathy, renal disease, retinopathy), macrovascular complications (angina, myocardial infarction, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease), as well as respiratory disease (chronic obstructive pulmonary disease, asthma), dementia and PCOS.

Other health-related variables were included as well. Previous cancer diagnosis (other than non-melanoma skin cancer) was included as this may lead patients to screen for other cancers, including breast cancer. Additionally, variables potentially associated with breast cancer were considered, including previous oophorectomy,[111] as well as other commonly prescribed drugs such as anti-hypertensive drugs (angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics, other antihypertensive drugs),[48] statins,[48] non-steroidal anti-inflammatory drugs,[48] anticoagulants,[48 112] antiplatelet medications,[48 112] hormonal replacement therapy[48] and oral contraceptives.[111] **Table 4** provides a summary of the covariates and their corresponding definition, code classification system, and covariate assessment period.

Table 4. Summary of Covariates

Covariate	Variable Type	Definition	Covariate Assessment Period
Demographic/Lifestyle Variables			
Age	Continuous	Cohort entry year minus birth year	Cohort entry
BMI	Categorical	<25 kg/m², 25-29 kg/m², ≥30 kg/m², unknown	Cohort entry
Alcohol-related disorders	Binary	Present/absent (alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic flexure)	Ever before cohort entry
Smoking status	Categorical	ever, never, unknown	Cohort entry
Patient level index of multiple deprivation	Categorical	1st Quintile (least deprived), 2nd Quintile, 3rd Quintile, 4th Quintile, 5th Quintile (most deprived)	Cohort entry
Year of cohort entry	Categorical	1998-2002, 2003-2007, 2008-2012, 2013-2017, 2018-2021	Cohort entry
Diabetes-Related Variables			
Angina	Binary	Present/absent	Ever before cohort entry
Myocardial infarction	Binary	Present/absent	Ever before cohort entry
Stroke	Binary	Present/absent	Ever before cohort entry
Transient ischemic attack	Binary	Present/absent	Ever before cohort entry
Coronary artery disease	Binary	Present/absent	Ever before cohort entry
Heart failure	Binary	Present/absent	Ever before cohort entry
Peripheral vascular disease	Binary	Present/absent	Ever before cohort entry
Neuropathy	Binary	Present/absent	Ever before cohort entry
Renal disease	Binary	Present/absent	Ever before cohort entry
Retinopathy	Binary	Present/absent	Ever before cohort entry
Other Health-Related Variables			
Respiratory disease	Binary	Present/absent chronic obstructive pulmonary disease, asthma	Ever before cohort entry
Dementia	Binary	Present/absent	Ever before cohort entry
PCOS	Binary	Present/absent	Ever before cohort entry
Previous cancer	Binary	Present/absent	Ever before cohort entry
Previous oophorectomy	Binary	Present/absent	Ever before cohort entry
Anti-Hypertensive Drugs			
Angiotensin-converting-enzyme inhibitors	Binary	Present/absent	Ever before cohort entry
Angiotensin II receptor blockers	Binary	Present/absent	Ever before cohort entry
Beta blockers	Binary	Present/absent	Ever before cohort entry
Calcium channel blockers	Binary	Present/absent	Ever before cohort entry
Diuretics	Binary	Present/absent	Ever before cohort entry
Other antihypertensive drugs	Binary	Present/absent	Ever before cohort entry
Other Prescriptions Drugs			
Statins	Binary	Present/absent	Ever before cohort entry
Non-steroidal anti-inflammatory drugs	Binary	Present/absent	Ever before cohort entry
Anticoagulants	Binary	Present/absent	Ever before cohort entry
Antiplatelet medications	Binary	Present/absent	Ever before cohort entry
Hormonal replacement therapy	Binary	Present/absent	Ever before cohort entry
Oral contraceptives	Binary	Present/absent	Ever before cohort entry

CHAPTER 5: MANUSCRIPT: THE ASSOCIATION BETWEEN PRE-EXISTING TYPE 2 DIABETES ON BREAST CANCER-RELATED AND ALL-CAUSE MORTALITY AMONG WOMEN WITH BREAST CANCER

The following chapter presents the manuscript of the study on the association between pre-existing type 2 diabetes and breast cancer outcomes among women newly diagnosed with breast cancer. First, the Background provides background information on breast cancer and type 2 diabetes, as well as the study rationale. Second, the Methods section describes the data source, study population, follow-up, exposure definition, potential confounders, and statistical analyses. Then, the Results section is presented, including descriptive characteristics of the cohort and the primary, secondary and sensitivity analyses. Finally, the Discussion provides an interpretation of the findings, comparisons with previous literature and strengths and limitations of the study. This manuscript will be submitted to *Diabetes Care* and formatted accordingly.

The association between pre-existing type 2 diabetes on cancer-related and all-cause mortality among women with breast cancer

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5.1 Abstract

Background: As one of the most common cancers among women, breast cancer may be associated with poorer outcomes among patients with type 2 diabetes (T2D), however this relationship remains understudied.

Objectives: The objective of this study was to investigate whether pre-existing T2D is associated with an increased risk of breast cancer-related and all-cause mortality, compared with non-diabetes, among women newly diagnosed with non-metastatic and metastatic breast cancer, separately. Additionally, we investigated whether the risk of the study outcomes vary across glycated hemoglobin A1c (HbA1c) categories.

Methods: Using the Clinical Practice Research Datalink, we assembled a cohort of patients at least 18 years old, newly diagnosed with invasive breast cancer between 1998 and 2020, with follow-up until March 2021. Patients with T2D were identified by recorded diabetes diagnoses, antihyperglycemic drugs, and elevated glycemic levels. Multivariable Cox proportional hazards models were fit to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of the study outcomes. In a secondary analysis, we estimated the HRs for the outcomes across glycated HbA1c categories to determine how it is associated with mortality.

Results: We identified 157,298 patients with newly diagnosed breast cancer, including 13,908 (8.8%) with T2D. Among patients with non-metastatic breast cancer, T2D was associated with a 12% increased risk of breast cancer mortality (2.19 v 1.43 per 100 person years; HR: 1.12, 95% CI: 1.04-1.20) and a 21% increased risk of all-cause mortality (6.43 v 3.15 per 100 person years; HR: 1.21, 95% CI 1.16-1.26). Among patients with metastatic breast cancer, T2D was associated with a 22% increased risk of breast cancer mortality (5.76 v 3.68 per 100 person years; HR: 1.22, 95% CI 1.11-1.35) and a 24% increased risk of all-cause mortality (9.25 v 5.20 per 100 person

years; HR: 1.24, 95% CI: 1.15-1.33). The secondary analysis showed that higher HbA1c was associated with an increased risk of mortality outcomes among women with type 2 diabetes, compared to non-diabetes in both the non-metastatic and metastatic cohorts.

Conclusion: In this large population-based cohort study, T2D was associated with a greater risk of breast cancer-related and all-cause mortality, with an increased risk among patients with T2D in the highest HbA1c category, compared to non-diabetes. Our findings may be important to understand the prognostic differences of patients with T2D, which may indicate the need for more targeted clinical care guidelines to manage both diseases concurrently.

5.2 Background

Breast cancer is one of the most prevalent malignancies globally, with an increased incidence among women with type 2 diabetes.[1,2] Approximately 10 to 20% of patients with breast cancer have type 2 diabetes at diagnosis, and while overall survival has improved in recent decades, these patients may have poorer outcomes compared to their non-diabetic counterparts.[1-3]

It has been suggested that type 2 diabetes may create an ideal metabolic environment for cancer cells.[4-6] Hyperinsulinemia may promote breast cancer cell growth directly or indirectly by elevating insulin-like growth factor 1 (IGF-1) and bioactive sex hormones.[4-6] Moreover, hyperglycemia and low-grade inflammation are related to cell-signaling pathways that may enable malignant cell growth and impair antioxidant capability.[5-8] Finally, diabetes and cancer share several risk factors including age, obesity and lifestyle behaviours that may contribute to poorer outcomes.

Several studies have associated type 2 diabetes with increased all-cause mortality,[3,9-13] however the association with breast cancer-related mortality is inconsistent.[3,10,14,15] Moreover, hyperglycemia severity, diabetes duration and associated comorbidities have not been adequately addressed in the literature.[16,17] Finally, while type 2 diabetes has been associated with an increased risk of advanced-stage breast cancer at diagnosis, possibly due to differences in screening and treatment patterns, the impact type 2 diabetes on metastatic breast cancer is not well studied.[3,18]

The objective of this study was to investigate whether type 2 diabetes is associated with an increased risk of breast cancer-related and all-cause mortality among women newly diagnosed with non-metastatic and metastatic breast cancer, separately. Additionally, we investigated whether the risk of the outcomes vary across glycated HbA1c categories among women with type 2 diabetes compared to non-diabetes.

5.3 Methods

Data Source

This study was conducted using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD). The CPRD is one of the largest longitudinal medical records from primary care, covering 2000 general practices comprising of approximately 60 million patients that are representative of the general population of the UK in relation to age, sex, and ethnicity. [19 20] This database is comprised of anonymized data on clinical diagnoses, symptoms, tests, specialist referrals and prescriptions as well as patient characteristics such as demographics, anthropometrics, and lifestyle factors. [19] Clinical care, including medical diagnoses and procedures, is recorded using the Read code and SNOMED-CT classification system. [19] Prescription data is recorded using British National Formulary codes and clinical measurements are entered as numerical data. [19] The CPRD was linked to the Hospital Episode Statistics Admitted Patient Care (HES APC) for hospitalization data, recorded as International Classification of Diseases 10th Revision (ICD-10) codes, as well as to the Office for National Statistics (ONS) databases to identify mortality events during the follow-up period. [19] Additional linkage to deprivation data from the Index of Multiple Deprivation and Townsend scores provided a measure of socioeconomic status. [19] The CPRD and the linked secondary databases offer high quality longitudinal data that has been validated by several studies, with breast cancer diagnosis having high concordance (>90%) with the UK National Cancer Data Repository. [20 21]

The study protocol was approved by the independent scientific advisory committee of the CPRD (protocol number 22_002073) and by the research ethics board of the Jewish General Hospital, Montreal, Canada.

Study Population and Follow-Up

We assembled a cohort of women newly diagnosed with invasive breast cancer between April 1, 1998 and December 31, 2020, with follow-up until March 29, 2021. Patients with metastatic and non-metastatic breast cancer were analyzed separately, and thus separate cohorts were constructed. For both cohorts, cohort entry date was defined by the first-ever diagnosis of breast cancer during the study period. The Read and SNOMED-CT codes from the CPRD Aurum and GOLD databases that were used to identify invasive breast cancer cases are summarized in **Supplementary Table 1** and **Supplementary Table 2**, respectively. The cohorts included patients who were at least 18 years of age and had at least one year of medical history in the CPRD before cohort entry. Patients with prediabetes or forms of diabetes other than type 2 were excluded. All patients meeting the study inclusion criteria were followed starting 3 months after cohort entry to account for real-world recording of metastasis following the initial breast cancer diagnosis. Patients were followed until one of the study outcomes (primary outcome: breast cancer mortality (ICD-10 codes: C50.0-C50.9); secondary outcome: all-cause mortality), end of registration with the general practice, or end of study (March 29, 2021), whichever came first.

Exposure Definition

We developed an algorithm to identify patients with pre-existing type 2 diabetes in each cohort. Patients with type 2 diabetes were identified based on the presence of one of the following criteria at any time before cohort entry: a recorded type 2 diabetes diagnostic code, a antihyperglycemic drug prescription, a glycated HbA1c ≥6.5%, or 2 consecutive glycemic blood tests (Fasting Plasma Glucose, 75g Oral Glucose Tolerance Test or Random Blood Glucose) in the diabetic range within a 12-week period. Additionally, patients with both a diagnostic code for

an unspecified form of diabetes and a clinical code supporting type 2 diabetes (ex: nephropathy due to type 2 diabetes) were also classified into the type 2 diabetes group. The remaining patients were classified as non-diabetes.

Potential Confounders

All models were adjusted for the following covariates measured at cohort entry, as these are shared risk factors of type 2 diabetes and breast cancer and are thus associated with both the exposure and the outcome: age, body mass index (BMI) (<25 kg/m², 25-29 kg/m², ≥30 kg/m², unknown), smoking status (ever, never, unknown), and patient level index of multiple deprivation as a measure of socioeconomic status. Comorbidities were defined using ever look back, which included macrovascular (angina, myocardial infarction, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease) and microvascular (renal disease, retinopathy, and neuropathy) complications of diabetes. Additionally, we adjusted for alcohol-related disorders (alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis, and hepatic flexure), polycystic ovary syndrome, respiratory disease (asthma, chronic obstructive pulmonary disease), previous cancer, dementia, as well as previous oophorectomy. Finally, we adjusted for ever use of hormonal replacement therapy, oral contraceptives, statins, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, diuretics, other antihypertensive drugs, non-steroidal anti-inflammatory drugs, anticoagulants, antiplatelet medications, and year of cohort entry.

Statistical Analysis

Primary Analyses

We used descriptive statistics to describe the patient characteristics with and without diabetes. Crude incidence rates of breast cancer mortality and all-cause mortality with 95% confidence intervals (CI) were calculated for the non-metastatic and metastatic cohorts based on Poisson distribution. Kaplan-Meier curves were constructed to display the cumulative incidence of the outcomes during the study period. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% CIs for the association between type 2 diabetes and breast cancer-related and all-cause mortality for patients with non-metastatic and metastatic disease, separately. All models were adjusted for the potential confounders listed above. Models were also stratified by 5-year calendar bands (1998-2002, 2003-2007, 2008-2012, 2013-2017, 2018-2021) to account for changes in the incidence of breast cancer and its outcomes during the 23-year study period.

Secondary Analyses

We conducted two secondary analyses. First, among patients with a baseline HbA1c in the year before breast cancer diagnosis, we estimated the HRs for the study outcomes across HbA1c categories (<6.5%, 6.5-7.0%, 7.1-8.0%, >8.0%), comparing patients with type 2 diabetes to non-diabetes. Second, we assessed whether age and BMI were effect measure modifiers of the association on the multiplicative scale. Effect modification was assessed by including interaction terms between these variables and the exposure variable in the outcome model.

Sensitivity Analyses

To investigate the robustness of our results, we performed two sensitivity analyses. First, we used the Fine and Gray model to assess the impact of competing risks due to deaths from other causes using inverse probability of censoring weighting for breast cancer-related mortality. Second, to additionally account for patients who develop diabetes after breast cancer diagnosis, we calculated the HRs using a time-varying exposure definition, where patients could transition unidirectionally from non-diabetes to type 2 diabetes. We conducted all analyses with SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), and R, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

5.4 Results

Figure 1 depicts the study flow chart illustrating the process for assembling metastatic and non-metastatic breast cancer cohorts. The cohort included 157,298 women newly diagnosed with malignant breast cancer which included 13,908 (8.8%) with type 2 diabetes and a total of 32,030 (20.3%) patients with metastasis at diagnosis. Patients in the non-metastatic and metastatic groups were followed for a mean of 7.1 years (standard deviation (SD) 5.5) and 5.9 years (SD 5.0), respectively. In the non-metastatic group, there were 13,060 deaths due to breast cancer and 29,624 deaths due to all causes during 882,815 person-years of follow-up, generating a crude incidence of 1.48 (95% CI: 1.45-1.50) and 3.36 (95% CI: 3.32-3.39) per 100 person-years, respectively. In the metastatic group, there were 7,220 deaths due to breast cancer and 10,317 deaths due to all causes during 189,200 person-years of follow-up, generating a crude incidence of 3.82 (95% CI: 3.73-3.91) and 5.45 (95% CI: 5.35-5.56) per 100 person-years, respectively. **Figures 2-5** show a higher cumulative incidence of both outcomes among patients with type 2 diabetes, compared to non-diabetes, for both the non-metastatic and metastatic cohorts.

Table 1 presents baseline characteristics for the cohort by diabetes status for patients with non-metastatic and metastatic breast cancer, separately. For both the non-metastatic and metastatic cohorts, compared with non-diabetes, patients with type 2 diabetes were more likely to be older, to be obese, to have had alcohol-related disorders, to be ever smokers, to be situated in areas of higher deprivation, to have more comorbidities and to have used prescription drugs. Overall, patients with type 2 diabetes were less likely to have used hormone replacement therapy, but more likely to have had an oophorectomy, compared to patients without diabetes.

Primary & Secondary Analyses

Non-Metastatic Cohort

Breast Cancer Mortality

Table 2 summarizes the crude and adjusted HRs for type 2 diabetes and the study outcomes. Among the non-metastatic cohort, after adjusting for age, type 2 diabetes was associated with an increased risk of breast cancer mortality (age-adjusted HR: 1.13, 95% CI: 1.06-1.20), compared to non-diabetes. This risk was similar in the fully adjusted model, as patients with type 2 diabetes had a 12% increased risk of breast cancer mortality (2.19 v 1.43 per 100 person years; fully adjusted HR: 1.12, 95% CI: 1.04-1.20), compared to non-diabetes.

Interaction with Age and BMI for Breast Cancer Mortality

Table 3 presents the HRs for study outcomes comparing diabetes with non-diabetes, stratified by age (<55 years; ≥ 55 years) and BMI (<25kg/m², 25-29.9 kg/m², ≥30 kg/m², unknown). The effect of diabetes, compared with no diabetes, on breast cancer mortality was higher among patients <55 years of age (HR: 1.25, 95% CI: 1.01-1.55) compared with patients ≥ 55 years of age (HR: 1.09, 95% CI: 1.01-1.17). The effect of diabetes, compared with no diabetes, on breast cancer mortality was higher among patients with BMI <25kg/m² (HR: 1.27, 95% CI: 1.11-1.45) compared to the effect among patients with BMI 25-29.9kg/m² (HR: 1.06, 95% CI: 0.94-1.20), and patients with BMI ≥30kg/m² (HR: 1.13, 95% CI: 1.02-1.25).

All-Cause Mortality

Among the non-metastatic cohort, after adjusting for age, type 2 diabetes was associated with an increased risk of all-cause mortality (age-adjusted HR: 1.32, 95% CI: 1.27-1.37),

compared to non-diabetes. In the fully adjusted model, type 2 diabetes was associated with a 21% increased risk of all-cause mortality (6.43 v 3.15 per 100 person years; fully adjusted HR: 1.21, 95% CI: 1.16-1.26), compared with non-diabetes. The results are presented in **Table 2**.

Interaction with Age and BMI for All-Cause Mortality

The effect of diabetes, compared with no diabetes, on all-cause mortality was higher among patients <55 years of age (HR: 1.53, 95% CI: 1.29-1.83) compared with patients ≥ 55 years of age (HR: 1.18, 95% CI: 1.13-1.23). The effect of diabetes, compared with no diabetes, on all-cause mortality was higher among patients with BMI <25kg/m² (HR: 1.27, 95% CI: 1.18-1.37) compared to the effect among patients with BMI 25-29.9kg/m² (HR: 1.18, 95% CI: 1.10-1.27), and patients with BMI ≥30kg/m² (HR: 1.22, 95% CI: 1.14-1.30). The results are presented in **Table 3**.

Hazard Ratios for Breast Cancer Mortality and All-Cause Mortality Comparing Baseline Glycated Hemoglobin A1c Levels Among Patients Without Metastasis

Table 4 presents the HRs for breast cancer mortality and all-cause mortality comparing HbA1c levels among patients with breast cancer, restricted to patients with type 2 diabetes with a recorded HbA1c value in the year before cohort entry. Among patients with non-metastatic disease with a HbA1c <6.5%, type 2 diabetes was not associated with an increased risk of breast cancer-related mortality (2.16 vs 1.43 per 100 person years; fully adjusted HR: 1.08, 95% CI: 0.96-1.22) but was associated with all-cause mortality (6.39 vs 3.15 per 100 person years; fully adjusted HR: 1.14, 95% CI: 1.06-1.22). There was an increased risk of breast cancer mortality across the lowest three categories of HbA1c, though these did not reach statistical significance. Risk of all-cause mortality was significantly increased across all categories of HbA1c for patients with type 2 diabetes, compared to non-diabetes. There was a statistically significant increased risk of both

breast cancer mortality (2.27 vs 1.43 per 100 person years; fully adjusted HR: 1.29, 95% CI: 1.10-1.52) and all-cause mortality (6.56 vs 3.15 per 100 person years; fully adjusted HR: 1.43, 95% CI: 1.30-1.57) among patients with type 2 diabetes who had a baseline HbA1c >8.0%, compared to non-diabetes.

Metastatic Cohort

Breast Cancer Mortality

Among the metastatic cohort, compared with non-diabetes, type 2 diabetes was associated with an increased risk of breast cancer mortality after adjusting for age (age-adjusted HR: 1.21, 95% CI: 1.11-1.31). In the fully adjusted model, type 2 diabetes was associated with a 22% increase in risk of breast cancer mortality (5.76 v 3.68 per 100 person years; adjusted HR: 1.22, 95% CI: 1.11-1.35), compared to non-diabetes. The results are presented in **Table 2**.

Interaction with Age and BMI for Breast Cancer Mortality

The effect of diabetes, compared with no diabetes, on breast cancer mortality was higher among patients <55 years of age (HR: 1.32, 95% CI: 1.04-1.66) compared with patients ≥55 years of age (HR: 1.19, 95% CI: 1.08-1.32). The effect of diabetes, compared with no diabetes, on breast cancer mortality was higher among patients with BMI <25kg/m² (HR: 1.51, 95% CI: 1.24-1.84) compared to the effect among patients with BMI 25-29.9kg/m² (HR: 1.29, 95% CI: 1.11-1.51), and patients with BMI ≥30kg/m² (HR: 1.10, 95% CI: 0.97-1.26). The results are presented in **Table 3.**

All-Cause Mortality

Among the metastatic cohort, after adjusting for age, type 2 diabetes was associated with an increased risk of all-cause mortality (age-adjusted HR: 1.26, 95% CI: 1.19-1.35), compared to non-diabetes. In the fully adjusted model, type 2 diabetes was similarly associated with a 24% increased risk of all-cause mortality (9.25 v 5.20 per 100 person years; fully adjusted HR: 1.24, 95% CI: 1.15-1.33). The results are presented in **Table 2.**

Interaction with Age and BMI for All-Cause Mortality

The effect of diabetes, compared with no diabetes, on all-cause mortality was higher among patients <55 years of age (HR: 1.43, 95% CI: 1.16-1.77) compared with patients ≥55 years of age (HR: 1.19, 95% CI: 1.10-1.29). The effect of diabetes, compared with no diabetes, on all-cause mortality was higher among patients with BMI <25 kg/m² (HR: 1.51, 95% CI 1.30-1.76) compared to the effect among patients with BMI 25-29.9kg/m² (HR: 1.17, 95% CI: 1.03-1.33), and patients with BMI ≥30 kg/m² (HR: 1.15, 95% CI: 1.04-1.28). The results are presented in **Table 3.**

Hazard Ratios for Breast Cancer Mortality and All-Cause Mortality Comparing Baseline Glycated Hemoglobin A1c Levels Among Patients with Metastasis

Among patients with metastatic disease, type 2 diabetes was not associated with an increased risk of breast cancer-related (5.36 vs 3.68 per 100 person years; fully adjusted HR: 1.07, 95% CI: 0.90-1.27) or all-cause mortality (8.93 vs 5.20 per 100 person years; fully adjusted HR: 1.09, 95% CI: 0.95-1.24) for those with a HbA1c <6.5% (**Table 4**). There was a statistically significant increased risk for both mortality outcomes among patients with type 2 diabetes in all other HbA1c categories, with the highest risk associated with a baseline HbA1c >8.0% for breast cancer mortality (6.59 vs 3.68 per 100 person years; fully adjusted HR: 1.54, 95% CI: 1.27-1.87)

and all-cause mortality (10.64 vs 5.20 per 100 person years; fully adjusted HR: 1.63, 95% CI: 1.40-1.90), compared to non-diabetes.

Sensitivity Analyses

Results of the sensitivity analyses are summarized in **Tables 5-7**. Overall, nearly all sensitivity analyses generated findings that were consistent with those of the primary analysis. When comparing the risk of breast cancer mortality between type 2 diabetes and non-diabetes, with non-breast cancer deaths as competing events, there was a slight attenuation of the risk in both the non-metastatic (fully adjusted HR: 1.05, 95% CI: 0.98-1.13) and metastatic cohorts (fully adjusted HR: 1.18, 95% CI: 1.07-1.31). Using a time-dependent exposure definition, the risk of both breast cancer mortality and all-cause mortality remained increased in the type 2 diabetes groups for both the non-metastatic and metastatic cohorts. **Supplementary Figures 1-4** show the HRs of the study outcomes across 5-year calendar bands for the cohorts, separately. In the non-metastatic cohort, overlapping confidence intervals across the 5-year calendar bands show no trend with calendar time for both mortality outcomes. Similarly, confidence intervals overlap in the metastatic cohort, with a consistent trend among the 2003-2007, 2008-2012 and 2013-2017 categories for breast cancer mortality and across all categories for all-cause mortality.

5.5 Discussion

Our study found that pre-existing type 2 diabetes is associated with increased risk of breast cancer-related and all-cause mortality in breast cancer patients with non-metastatic and metastatic disease, after adjusting for potential confounders, with most of the confounding due to age. Our results also suggest that patients <55 years of age had a greater risk of these outcomes compared to those ≥55 years of age, which may be due to younger patients experiencing more aggressive breast cancer which progresses faster among patients with diabetes. Women with breast cancer with a BMI <25kg/m² had a greater risk of these outcomes, perhaps because lower BMI may be indicative of patients with more severe illness, particularly among those with diabetes. When treating non-breast cancer deaths as competing events, this association between type 2 diabetes and breast cancer mortality was attenuated in both cohorts. To account for the impact of a type 2 diabetes diagnosis before and after cancer diagnosis on the study outcomes, we performed a time varying analysis in which the risk remained increased for both breast cancer and all-cause mortality in both cohorts.

Comparison with Previous Studies

The existing literature on the relationship between type 2 diabetes and breast cancer mortality remains mixed, possibly due to inconsistencies across studies in terms of diabetes status ascertainment, sample size and adjustment for covariates, particularly for comorbidities. Previous studies have indicated that there is an increased risk of breast cancer mortality among diabetes groups, [22-28] however a systematic review by Zhou et al. found that this outcome did not remain robust after the sensitivity analysis. [11] Similarly, there are several observational studies that did not find a significant association between type 2 diabetes and breast cancer mortality, [9 29-31] while an

increased risk of all-cause mortality among breast cancer patients with type 2 diabetes has been well studied. [22-25 27-31]

We observed a greater risk of mortality outcomes associated with type 2 diabetes within the metastatic cohort, which may be explained by several factors. First, a systematic review and meta-analysis by Peairs et al. noted that several studies found that pre-existing diabetes was associated with later stage disease at breast cancer diagnosis. [3] This may be due to more rapid disease progression secondary to the metabolic environment of diabetes or differences in breast cancer screening. [5-7 32] However, Lipscombe et al. found that patients with diabetes were at higher risk of being diagnosed with breast cancer at a later stage, including lymph node metastasis and larger tumour size, even after accounting for mammogram screening and other variables.[18] Second, patients with diabetes have been found to receive different patterns of cancer treatment or less aggressive treatment due to a higher risk of complications, which may impact survival outcomes.[3]

For both the non-metastatic and metastatic breast cancer cohorts, a HbA1c of <6.5% among the type 2 diabetes group was not associated with an increased risk of breast cancer mortality, which may indicate that type 2 diabetes may not negatively impact breast cancer prognosis among patients with adequate glycemic control. Conversely, a HbA1c of <6.5% was associated with an increased risk of all-cause mortality in the non-metastatic cohort. Alternatively, poorer glycemic control was associated with worse breast cancer outcomes, as there was a statistically significant increased risk of both breast cancer-related and all-cause mortality among patients with type 2 diabetes who had a baseline HbA1c >8.0%, compared to non-diabetes. This finding is consistent with a study by Monzavi-Karbassi et al. where patients in the highest category of random blood glucose had the shortest overall survival for breast cancer, but this study had a small sample size

and did not include cancer-specific mortality data.[17] Similarly, a study by Erickson et al. (n=3,003) found that among the study population of patients with existing breast cancer, the risk of all-cause mortality was highest among those with HbA1c ≥7.0% (HR: 2.35, 95% CI: 1.56-3.54), but not significant for those with an HbA1c 6.5% to 6.9%.[33] Alternatively, Zhou et al. did not find an increased risk of breast cancer mortality for both undiagnosed and known diabetes, however the number of breast cancer-specific deaths was very small and several key cofounders were not available to include in the analysis.[34] Our findings may suggest that variation in glycemic control within the type 2 diabetes population may lead to differences in prognosis in mortality outcomes.

Biological Mechanism

Type 2 diabetes and breast cancer are two complex, heterogeneous diseases that share several risk factors, including obesity, older age, lifestyle behaviours and genetic predisposition.[8] Indeed, several possible biological mechanisms have been identified linking type 2 diabetes with breast cancer mortality.[7] First, hyperinsulinemia is a characteristic of type 2 diabetes that may promote tumour growth through several mitogenic mechanisms, including increased circulating IGF-1, increased insulin receptor binding in mammary tissues and increased bioactive sex hormones.[5 6 35] Second, hyperglycemia may contribute to cancer cell proliferation and signaling pathways via increased production of oxidants and inflammation.[6] Both hyperinsulinemia and hyperglycemia are closely related to obesity, which creates a pro-inflammatory state through production of cytokines, including interleukin-6 and tumour necrosis factor-alpha, that have been associated with both cancer and diabetes.[4 6] Thus, these interrelated elements may each play a role favouring tumour growth, cancer cell survival and metastasis.[5-7]

Strengths and Limitations

This study has several strengths. First, the large sample size of over 150,000 women with breast cancer, with over 1 million person-years of follow-up time, gives our study strong statistical power. Second, we constructed the cohorts using primary care data from the CPRD, which has been shown to contain high quality data for research purposes.[21 36 37] Finally, the models were adjusted for many potential confounders, including comorbidities, lifestyle factors and prescription drugs.

This study also has several limitations. First, though type 2 diabetes status was determined by diagnostic codes, glycemic blood values or antihyperglycemic drug prescriptions, diabetes is a largely asymptomatic disease that often goes undiagnosed for many years, thus misclassification of exposure is possible. Furthermore, the CPRD records test results and prescriptions written by general practitioners rather than specialists, although diabetes is almost exclusively managed by general practitioners in the UK. Secondly, we did not have any information on tumor characteristics, including cancer stage, grade, and hormone receptor status. There is also the possibility of outcome misclassification, although breast cancer has been shown to be well recorded in the ONS when compared with the UK National Cancer Data Repository.[21 38] Lastly, given the observational design of the study, residual confounding from unmeasured or unknown variables is possible.

Conclusion

In this population-based study, pre-existing type 2 diabetes was associated with an increased risk of breast cancer-related and all-cause mortality, for patients with non-metastatic and metastatic disease. Furthermore, poor glycemic control, as measured by HbA1c, was associated with worse mortality outcomes among women with type 2 diabetes, compared to non-diabetes.

The metabolic abnormalities that characterize type 2 diabetes may promote malignancy initiation and growth, while differences in screening and treatment in this population may lead to worse outcomes. Additional large cohort studies are warranted to better understand the prognostic differences in patients with pre-existing type 2 diabetes compared to non-diabetes, which may indicate the need for more targeted clinical care guidelines to manage diabetes and breast cancer concurrently.

5.6 References

1. Eketunde AO. Diabetes as a Risk Factor for Breast Cancer. *Cureus* 2020;12(5):e8010. doi: 10.7759/cureus.8010 [published Online First: 20200507]
2. World Health Organization. Breast Cancer: World Health Organization; 2021 [updated 26 March 2021]. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer (accessed 28 November 2022).
3. Peairs KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol* 2011;29(1):40-6. doi: 10.1200/JCO.2009.27.3011 [published Online First: 20101129]
4. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33(7):1674-85. doi: 10.2337/dc10-0666
5. Vigneri P, Frasca F, Sciacca L, et al. Diabetes and cancer. *Endocr Relat Cancer* 2009;16(4):1103-23. doi: 10.1677/ERC-09-0087 [published Online First: 20090720]
6. Wang M, Yang Y, Liao Z. Diabetes and cancer: Epidemiological and biological links. *World J Diabetes* 2020;11(6):227-38. doi: 10.4239/wjd.v11.i6.227
7. Zhu B, Qu S. The Relationship Between Diabetes Mellitus and Cancers and Its Underlying Mechanisms. *Front Endocrinol (Lausanne)* 2022;13:800995. doi: 10.3389/fendo.2022.800995 [published Online First: 20220211]
8. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018;14(2):88-98. doi: 10.1038/nrendo.2017.151 [published Online First: 20171208]
9. Tao H, O'Neil A, Choi Y, et al. Pre- and Post-diagnosis Diabetes as a Risk Factor for All-Cause and Cancer-Specific Mortality in Breast, Prostate, and Colorectal Cancer Survivors: a Prospective Cohort Study. *Front Endocrinol (Lausanne)* 2020;11:60. doi: 10.3389/fendo.2020.00060 [published Online First: 20200218]
10. Zhao XB, Ren GS. Diabetes mellitus and prognosis in women with breast cancer: A systematic review and meta-analysis. *Medicine (Baltimore)* 2016;95(49):e5602. doi: 10.1097/md.0000000000005602
11. Zhou Y, Zhang X, Gu C, et al. Influence of diabetes mellitus on mortality in breast cancer patients. *ANZ J Surg* 2015;85(12):972-8. doi: 10.1111/ans.12877 [published Online First: 20141013]

12. Mu L, Zhu N, Zhang J, et al. Type 2 diabetes, insulin treatment and prognosis of breast cancer. *Diabetes Metab Res Rev* 2017;33(1) doi: 10.1002/dmrr.2823 [published Online First: 20160620]
13. Redaniel MT, Jeffreys M, May MT, et al. Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. *Cancer Causes Control* 2012;23(11):1785-95. doi: 10.1007/s10552-012-0057-0 [published Online First: 20120913]
14. Luo J, Hendryx M, Virnig B, et al. Pre-existing diabetes and breast cancer prognosis among elderly women. *British Journal of Cancer* 2015;113(5):827-32. doi: 10.1038/bjc.2015.249
15. De Bruijn KM, Arends LR, Hansen BE, et al. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. *Br J Surg* 2013;100(11):1421-9. doi: 10.1002/bjs.9229
16. Diabetes Canada. Diabetes in Canada Backgrounder Ottawa: Diabetes Canada; 2022. Available from: https://www.diabetes.ca/DiabetesCanadaWebsite/media/Advocacy-and-Policy/Backgrounder/2022_Backgrounder_Canada_English_1.pdf (accessed 28 November 2022).
17. Monzavi-Karbassi B, Gentry R, Kaur V, et al. Pre-diagnosis blood glucose and prognosis in women with breast cancer. *Cancer Metab* 2016;4:7. doi: 10.1186/s40170-016-0147-7 [published Online First: 20160406]
18. Lipscombe LL, Fischer HD, Austin PC, et al. The association between diabetes and breast cancer stage at diagnosis: a population-based study. *Breast Cancer Res Treat* 2015;150(3):613-20. doi: 10.1007/s10549-015-3323-5 [published Online First: 20150317]
19. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44(3):827-36. doi: 10.1093/ije/dyv098 [published Online First: 20150606]
20. CPRD. Data: CPRD; 2022 [updated 11 October 2022]. Available from: https://cprd.com/data#:~:text=CPRD%20data%20are%20sourced%20from,for%2025%25%20of%20the%20patients (accessed 9 August 2023).
21. Boggon R, van Staa TP, Chapman M, et al. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiol Drug Saf* 2013;22(2):168-75. doi: 10.1002/pds.3374 [published Online First: 20121213]

22. Chen WW, Shao YY, Shau WY, et al. The impact of diabetes mellitus on prognosis of early breast cancer in Asia. *Oncologist* 2012;17(4):485-91. doi: 10.1634/theoncologist.2011-0412 [published Online First: 20120330]
23. Fernández-Arce L, Robles-Rodríguez N, Fernández-Feito A, et al. Type 2 Diabetes and all-cause mortality among Spanish women with breast cancer. *Cancer Causes & Control* 2022;33(2):271-78. doi: 10.1007/s10552-021-01526-x
24. Lawrence WR, Hosler AS, Gates Kuliszewski M, et al. Impact of preexisting type 2 diabetes mellitus and antidiabetic drugs on all-cause and cause-specific mortality among Medicaid-insured women diagnosed with breast cancer. *Cancer Epidemiol* 2020;66:101710. doi: 10.1016/j.canep.2020.101710 [published Online First: 20200401]
25. Lee KN, Torres MA, Troeschel AN, et al. Type 2 diabetes, breast cancer specific and overall mortality: Associations by metformin use and modification by race, body mass, and estrogen receptor status. *PLoS One* 2020;15(5):e0232581. doi: 10.1371/journal.pone.0232581 [published Online First: 20200505]
26. Liu X, Ji J, Sundquist K, et al. The impact of type 2 diabetes mellitus on cancer-specific survival: a follow-up study in Sweden. *Cancer* 2012;118(5):1353-61. doi: 10.1002/cncr.26420 [published Online First: 20110728]
27. Srokowski TP, Fang S, Hortobagyi GN, et al. Impact of Diabetes Mellitus on Complications and Outcomes of Adjuvant Chemotherapy in Older Patients With Breast Cancer. *Journal of Clinical Oncology* 2009;27(13):2170-76. doi: 10.1200/jco.2008.17.5935
28. Wu AH, Kurian AW, Kwan ML, et al. Diabetes and other comorbidities in breast cancer survival by race/ethnicity: the California Breast Cancer Survivorship Consortium (CBCSC). *Cancer Epidemiol Biomarkers Prev* 2015;24(2):361-8. doi: 10.1158/1055-9965.Epi-14-1140 [published Online First: 20141125]
29. Jiralerspong S, Kim ES, Dong W, et al. Obesity, diabetes, and survival outcomes in a large cohort of early-stage breast cancer patients. *Ann Oncol* 2013;24(10):2506-14. doi: 10.1093/annonc/mdt224 [published Online First: 20130621]
30. Lega IC, Austin PC, Fischer HD, et al. The Impact of Diabetes on Breast Cancer Treatments and Outcomes: A Population-Based Study. *Diabetes Care* 2018;41(4):755-61. doi: 10.2337/dc17-2012

31. Maskarinec G, Shvetsov YB, Conroy SM, et al. Type 2 diabetes as a predictor of survival among breast cancer patients: the multiethnic cohort. *Breast Cancer Res Treat* 2019;173(3):637-45. doi: 10.1007/s10549-018-5025-2 [published Online First: 20181026]
32. Lipscombe LL, Hux JE, Booth GL. Reduced screening mammography among women with diabetes. *Arch Intern Med* 2005;165(18):2090-5. doi: 10.1001/archinte.165.18.2090
33. Erickson K, Patterson RE, Flatt SW, et al. Clinically defined type 2 diabetes mellitus and prognosis in early-stage breast cancer. *J Clin Oncol* 2011;29(1):54-60. doi: 10.1200/JCO.2010.29.3183 [published Online First: 20101129]
34. Zhou XH, Qiao Q, Zethelius B, et al. Diabetes, prediabetes and cancer mortality. *Diabetologia* 2010;53(9):1867-76. doi: 10.1007/s00125-010-1796-7
35. Lumachi F, Santeufemia DA, Basso SM. Current medical treatment of estrogen receptor-positive breast cancer. *World J Biol Chem* 2015;6(3):231-9. doi: 10.4331/wjbc.v6.i3.231
36. Margulis AV, Fortuny J, Kaye JA, et al. Validation of Cancer Cases Using Primary Care, Cancer Registry, and Hospitalization Data in the United Kingdom. *Epidemiology* 2018;29(2):308-13. doi: 10.1097/ede.0000000000000786
37. Williams R, van Staa TP, Gallagher AM, et al. Cancer recording in patients with and without type 2 diabetes in the Clinical Practice Research Datalink primary care data and linked hospital admission data: a cohort study. *BMJ Open* 2018;8(5):e020827. doi: 10.1136/bmjopen-2017-020827 [published Online First: 20180526]
38. Arhi CS, Bottle A, Burns EM, et al. Comparison of cancer diagnosis recording between the Clinical Practice Research Datalink, Cancer Registry and Hospital Episodes Statistics. *Cancer Epidemiol* 2018;57:148-57. doi: 10.1016/j.canep.2018.08.009 [published Online First: 20181002]

5.7 Figures and Tables

Figure 1. Study flow chart illustrating the process for assembling metastatic and non-metastatic breast cancer cohorts in the UK CPRD between 1998 and 2020

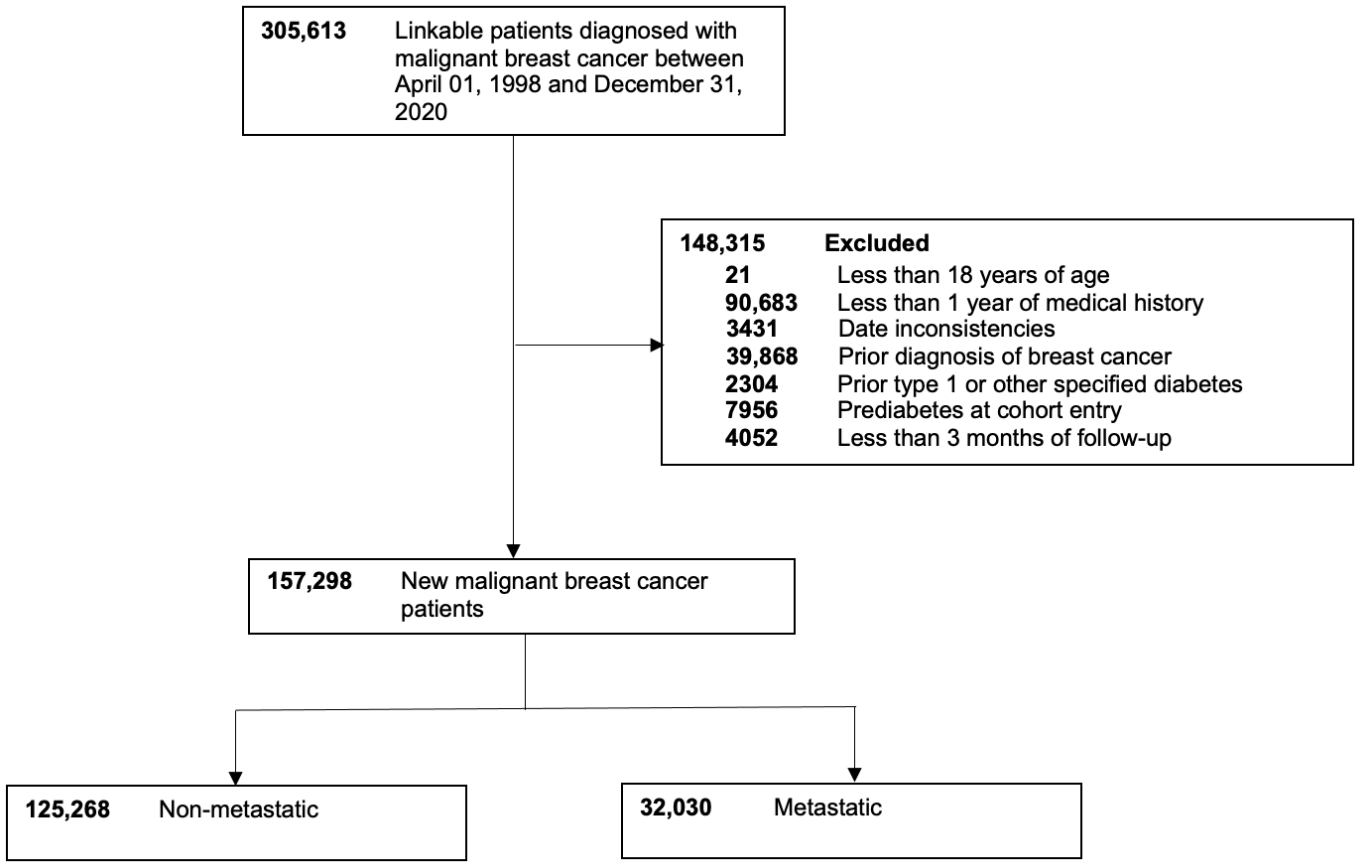


Figure 2. Cumulative incidence curves of breast cancer mortality for type 2 diabetes vs. non-diabetes among patients with non-metastatic breast cancer

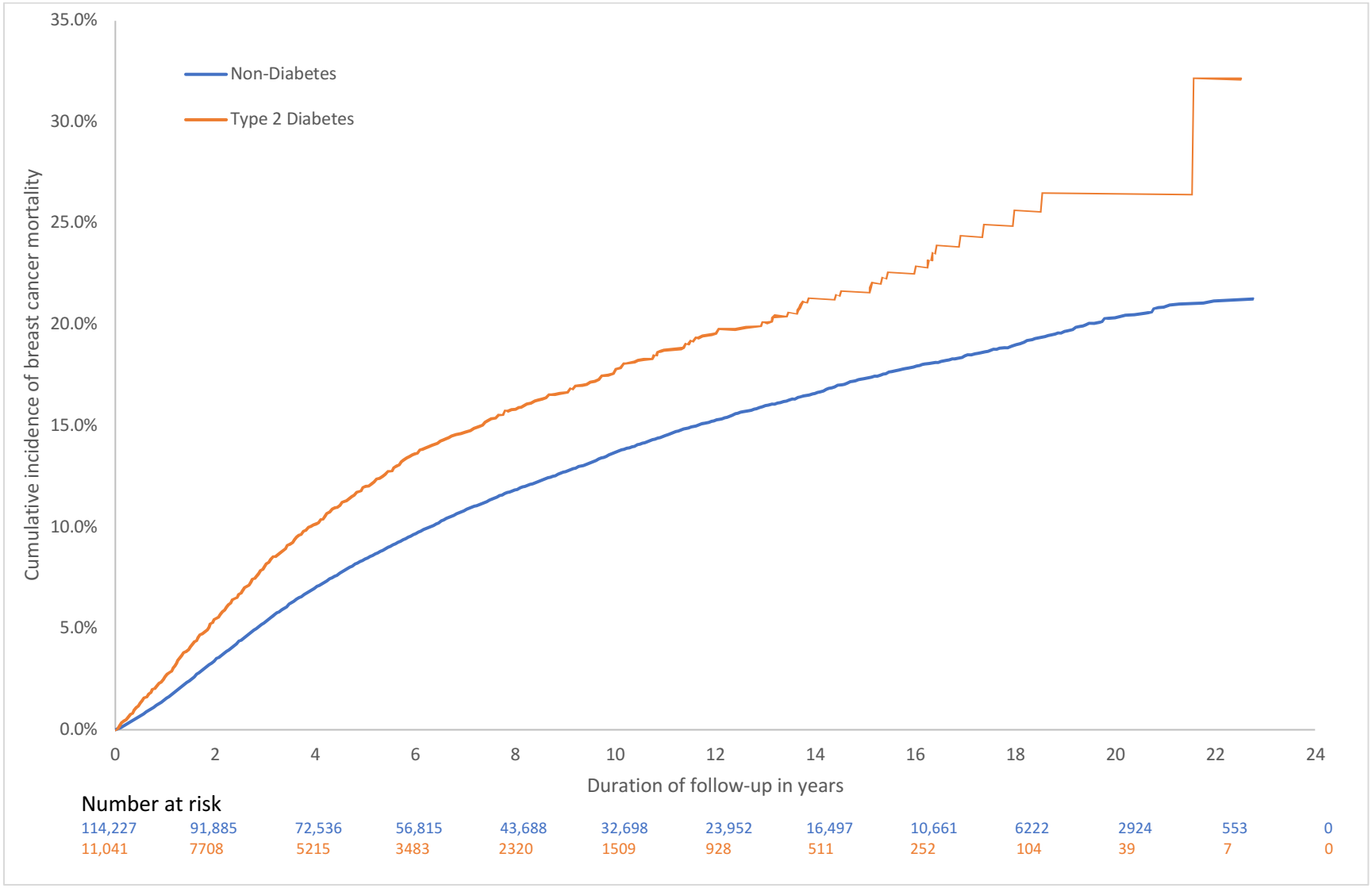


Figure 3. Cumulative incidence curves of all-cause mortality for type 2 diabetes vs. non-diabetes among patients with non-metastatic breast cancer

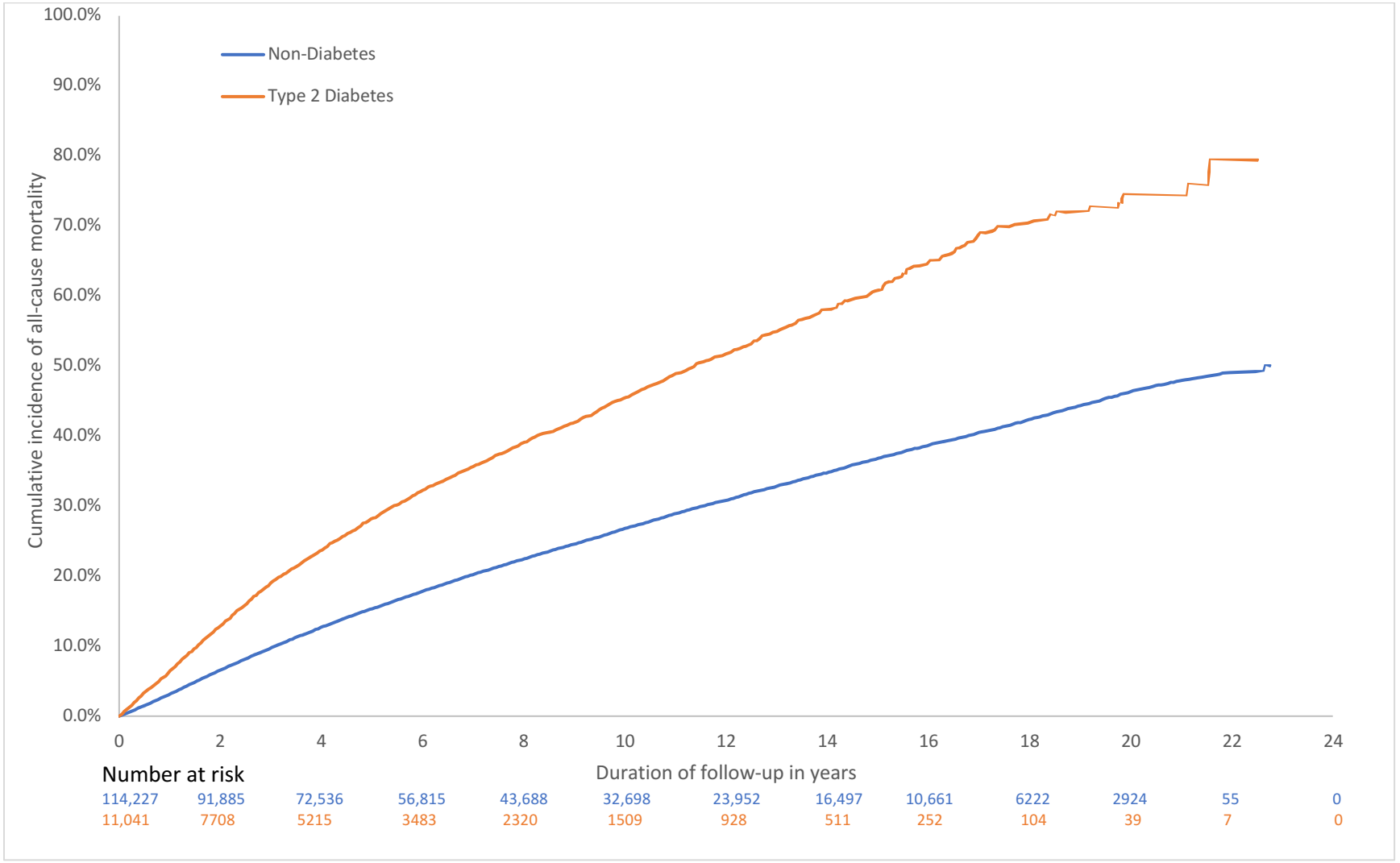


Figure 4. Cumulative incidence curves of breast cancer mortality for type 2 diabetes vs. non-diabetes among patients with metastatic breast cancer

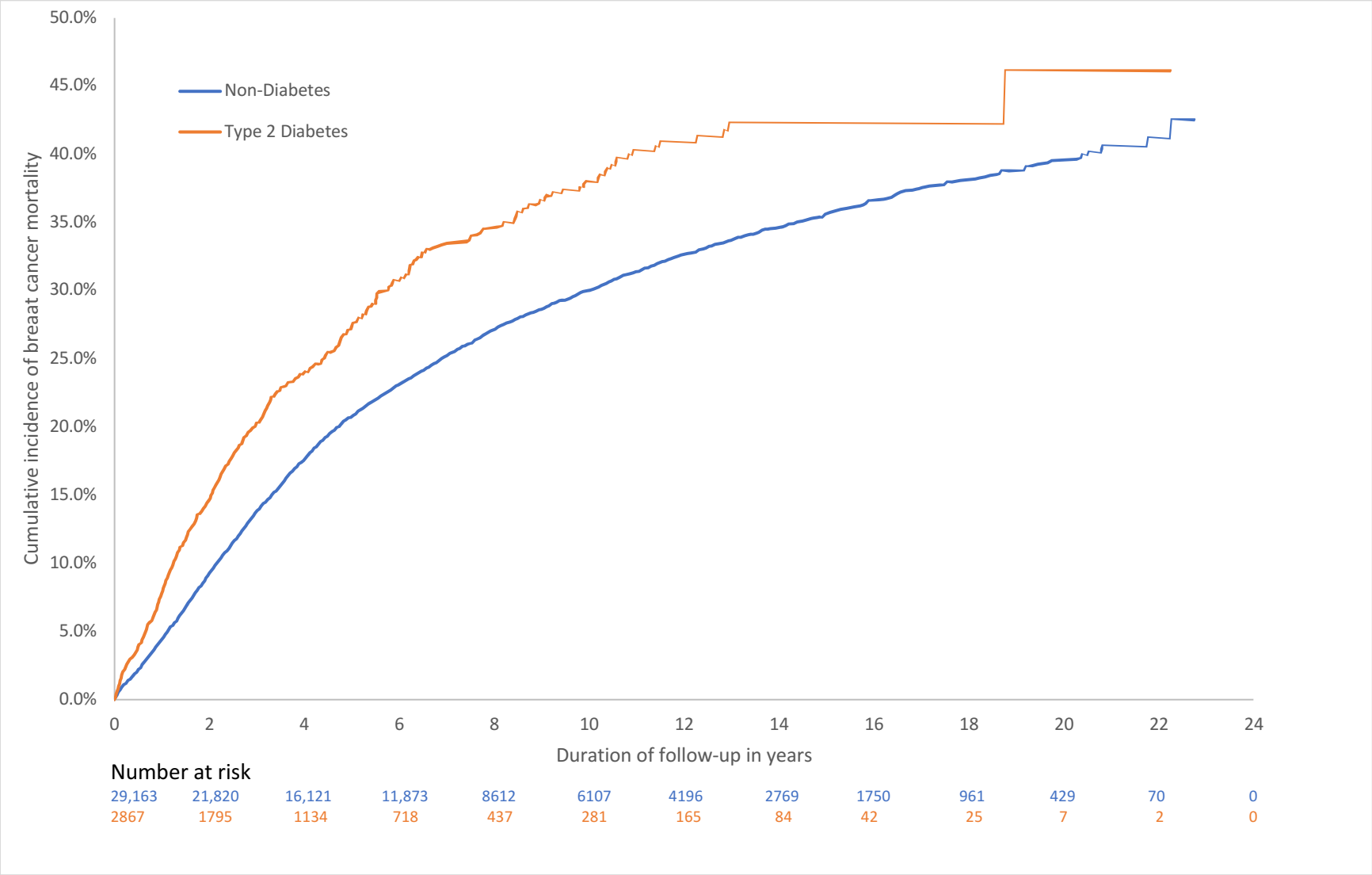


Figure 5. Cumulative incidence curves of all-cause mortality for type 2 diabetes vs. non-diabetes among patients with metastatic breast cancer

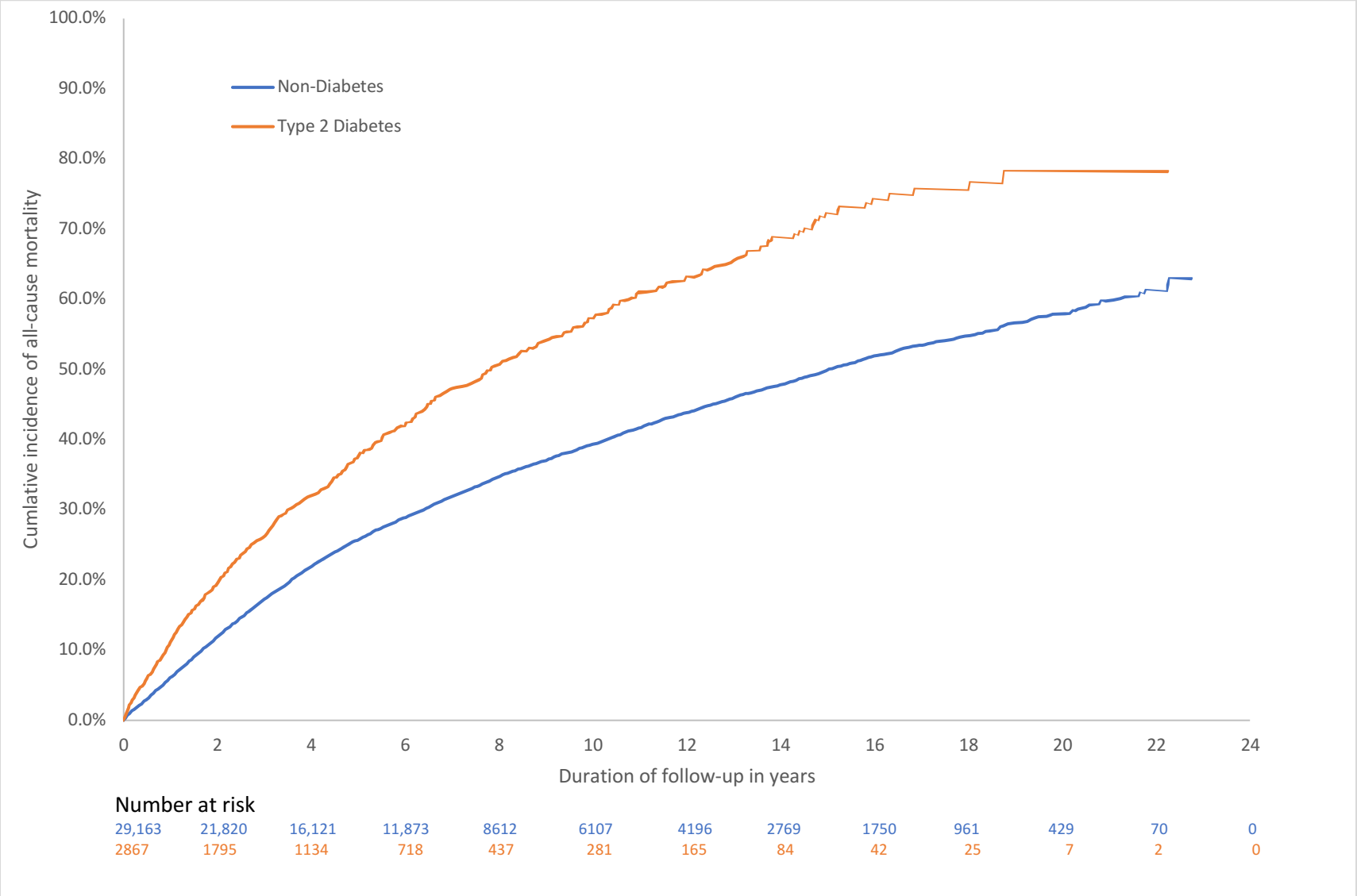


Table 1. Baseline Demographic and Clinical Characteristics of Study Cohort and Stratified by Type 2 Diabetes Status at Cohort Entry

	Non-Metastatic		Metastatic	
Characteristic	**Type 2 Diabetes (n=11 041)**	**Non-Diabetes (n=114 227)**	**Type 2 Diabetes (n=2 867)**	**Non-Diabetes (n=29 163)**
Age, years, mean (SD)	71.7 (12.1)	62.1 (14.2)	69.0 (11.8)	59.2 (13.7)
Body mass index, n (%)				
<25 kg/m²	2 023 (18.3)	43 351 (38.0)	415 (14.5)	10 399 (35.7)
25-29.9 kg/m²	3 207 (29.0)	31 707 (27.8)	816 (28.5)	8 489 (29.1)
≥30 kg/m²	5 317 (48.2)	21 673 (19.0)	1 547 (54.0)	6 347 (21.8)
Unknown	494 (4.5)	17 496 (15.3)	89 (3.1)	3,928 (13.5)
Smoking status, n (%)				
Ever	7 563 (68.5)	64 883 (56.8)	2 058 (71.8)	17 217 (59.0)
Never	3 295 (29.8)	42 413 (37.1)	779 (27.2)	10 641 (36.5)
Unknown	183 (1.7)	6 931 (6.1)	30 (1.0)	1 305 (4.5)
Alcohol-related disorders, n (%)	490 (4.4)	3 278 (2.9)	116 (4.0)	942 (3.2)
Patient Level Index of Multiple Deprivation, n (%)				
1st Quintile - least deprived	2 095 (19.0)	30 000 (26.3)	466 (16.3)	7 003 (24.0)
2nd Quintile	2 222 (20.1)	26 907 (23.6)	561 (19.6)	6 699 (23.0)
3rd Quintile	2 170 (19.7)	22 689 (19.9)	581 (20.3)	5 769 (19.8)
4th Quintile	2 315 (21.0)	19 202 (16.8)	614 (21.4)	5 366 (18.4)
5th Quintile - most deprived	2 229 (20.2)	15 344 (13.4)	640 (22.3)	4 307 (14.8)
Unknown quintile	10 (0.1)	85 (0.1)	5 (0.2)	19 (0.1)
Angina, n (%)	1 553 (14.1)	4 511 (3.9)	311 (10.8)	878 (3.0)
Myocardial infarction, n (%)	704 (6.4)	1 842 (1.6)	138 (4.8)	335 (1.1)
Stroke, n (%)	1 062 (9.6)	4 084 (3.6)	215 (7.5)	750 (2.6)
Transient ischemic attack, n (%)	695 (6.3)	2 717 (2.4)	144 (5.0)	492 (1.7)
Coronary artery disease, n (%)	1 882 (17.0)	4 687 (4.1)	389 (13.6)	937 (3.2)
Coronary heart failure, n (%)	1 016 (9.2)	2 748 (2.4)	180 (6.3)	394 (1.4)
Peripheral vascular disease, n (%)	927 (8.4)	2 084 (1.8)	186 (6.5)	436 (1.5)
Renal disease, n (%)	2 646 (24.0)	6 749 (5.9)	632 (22.0)	1 557 (5.3)
Retinopathy, n (%)	2 682 (24.3)	2 003 (1.8)	735 (25.6)	452 (1.5)
Neuropathy, n (%)	2 078 (18.8)	771 (0.7)	517 (18.0)	203 (0.7)
Polycystic ovary syndrome, n (%)	270 (2.4)	1 280 (1.1)	83 (2.9)	357 (1.2)
Chronic obstructive pulmonary disease, n (%)	1 558 (14.1)	8 127 (7.1)	392 (13.7)	1 863 (6.4)
Asthma, n (%)	2 252 (20.4)	16 021 (14.0)	605 (21.1)	4 169 (14.3)
Previous cancer, n (%)	5 252 (47.6)	41 719 (36.5)	1 808 (63.1)	15 440 (52.9)
Dementia, n (%)	620 (5.6)	2 320 (2.0)	69 (2.4)	226 (0.8)
Oophorectomy, n (%)	843 (7.6)	5 902 (5.2)	233 (8.1)	1 561 (5.4)
Hormonal replacement therapy, n (%)	2 970 (26.9)	32 290 (28.3)	731 (25.5)	7 802 (26.8)
Oral contraceptives, n (%)	850 (7.7)	22 175 (19.4)	293 (10.2)	7 322 (25.1)
Statins, n (%)	7 906 (71.6)	17 464 (15.3)	2 065 (72.)	4 115 (14.1)
Angiotensin-converting-enzyme inhibitors, n (%)	6 555 (59.4)	18 796 (16.5)	1 743 (60.8)	4 359 (14.9)
Angiotensin II receptor blockers, n (%)	2 757 (25.0)	7 421 (6.5)	691 (24.1)	1 755 (6.0)
Beta blockers, n (%)	4 911 (44.5)	26 526 (23.2)	1 259 (43.9)	6 611 (22.7)

Calcium channel blockers, n (%)	5 289 (47.9)	19 598 (17.2)	1 357 (47.3)	4 600 (15.8)
Diuretics, n (%)	4 462 (40.4)	16 409 (14.4)	1 005 (35.1)	3 438 (11.8)
Other antihypertensive drugs, n (%)	696 (6.3)	4 285 (3.8)	176 (6.1)	1 071 (3.7)
Non-steroidal anti-inflammatory drugs, n (%)	8 320 (75.4)	71 013 (62.2)	2 213 (77.2)	18 497 (63.4)
Anticoagulants, n (%)	1 227 (11.1)	4 307 (3.8)	254 (8.9)	890 (3.1)
Antiplatelet medications, n (%)	1 085 (9.8)	3 027 (2.6)	230 (8.0)	613 (2.1)
Year, n (%)				
1998-2002	967 (8.8)	20 900 (18.3)	185 (6.5)	4 170 (14.3)
2003-2007	1 966 (17.8)	27 718 (24.3)	421 (14.7)	6 146 (21.1)
2008-2012	2 654 (24.0)	27 395 (24.0)	688 (24.0)	7 522 (25.8)
2013-2017	3 416 (30.9)	25 180 (22.0)	962 (33.6)	7 431 (25.5)
2018-2021	2 038 (18.5)	13 034 (11.4)	611 (21.3)	3 894 (13.4)

Abbreviations: SD, standard deviation.

Table 2. Crude and Adjusted Hazard Ratios for the Association Between Type 2 Diabetes and Breast Cancer Mortality Outcomes

	Exposure	No. of patients	Events	Person-years	Incidence rate (95% CI) *	Crude HR (95% CI)	Age-adjusted HR (95% CI)	Adjusted HR (95% CI) †
Breast Cancer Mortality	**Non-metastatic**							
	Non-diabetes	114,227	11,863	828,109	1.43 (1.41-1.46)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes	11,041	1197	54,706	2.19 (2.07-2.32)	1.41 (1.33-1.50)	1.13 (1.06-1.20)	1.12 (1.04-1.20)
	Metastatic							
	Non-diabetes	29,163	6529	177,207	3.68 (3.60-3.77)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes	2867	691	11,994	5.76 (5.34-6.21)	1.42 (1.31-1.54)	1.21 (1.11-1.31)	1.22 (1.11-1.35)
All-Cause Mortality	**Non-metastatic**							
	Non-diabetes	114,227	26,104	828,109	3.15 (3.11-3.19)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes	11,041	3520	54,706	6.43 (6.22-6.65)	2.01 (1.94-2.08)	1.32 (1.27-1.37)	1.21 (1.16-1.26)
	Metastatic							
	Non-diabetes	29,163	9207	177,207	5.20 (5.09-5.30)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes	2867	1110	11,994	9.25 (8.72-9.82)	1.68 (1.58-1.79)	1.26 (1.19-1.35)	1.24 (1.15-1.33)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100 person-years.

† The models were adjusted for age, body mass index (BMI), smoking status, alcohol-related disorders, patient level index of multiple deprivation, angina, myocardial infarction, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease, renal disease, retinopathy, neuropathy, polycystic ovary syndrome (PCOS), respiratory disease, previous cancer, dementia, previous oophorectomy, use of hormonal replacement therapy, oral contraceptives, statins, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, diuretics, other antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, anticoagulants, and antiplatelet medications. The models were also stratified by 5-year calendar bands.

Table 3. Hazard Ratios for Breast Cancer Mortality Comparing Type 2 Diabetes with Non-Diabetes Among Patients with Malignant Breast Cancer (Interaction with Age & BMI)

	Exposure	< 55 years of age	≥ 55 years of age	BMI <25	BMI 25-29.9	BMI ≥30
Breast Cancer Mortality	**Non-metastatic**					
	Non-diabetes	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes	1.25 (1.01-1.55)	1.09 (1.01-1.17)	1.27 (1.11-1.45)	1.06 (0.94-1.20)	1.13 (1.02-1.25)
			p-interaction=0.22			*p-interaction=0.07*
	Metastatic					
	Non-diabetes	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes	1.32 (1.04-1.66)	1.19 (1.08-1.32)	1.51 (1.24-1.84)	1.29 (1.11-1.51)	1.10 (0.97-1.26)
			p-interaction=0.43			*p-interaction=0.04*
All-Cause Mortality	**Non-metastatic**					
	Non-diabetes	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes	1.53 (1.29-1.83)	1.18 (1.13-1.23)	1.27 (1.18-1.37)	1.18 (1.10-1.27)	1.22 (1.14-1.30)
			p-interaction=0.04			*p-interaction=0.44*
	Metastatic					
	Non-diabetes	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes	1.43 (1.16-1.77)	1.19 (1.10-1.29)	1.51 (1.30-1.76)	1.17 (1.03-1.33)	1.15 (1.04-1.28)
			p-interaction=0.10			*p-interaction=0.007*

The models were adjusted for age, body mass index (BMI), smoking status, alcohol-related disorders, patient level index of multiple deprivation, angina, myocardial infarction, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease, renal disease, retinopathy, neuropathy, polycystic ovary syndrome (PCOS), respiratory disease, previous cancer, dementia, previous oophorectomy, use of hormonal replacement therapy, oral contraceptives, statins, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, diuretics, other antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, anticoagulants, and antiplatelet medications. The models were also stratified by 5-year calendar bands.

Table 4. Hazard Ratios for Breast Cancer Mortality and All-Cause Mortality Comparing HbA1c levels Among Patients with Malignant Breast Cancer (Restricted to Patients with Diabetes with Known HbA1c in the Year Prior to Cohort)

	Exposure	No. of patients	Events	Person-years	Incidence rate * (95% CI) *	Crude HR (95% CI)	Age-adjusted HR (95% CI)	Adjusted HR (95% CI) †
Breast Cancer Mortality	**Non-metastatic**							
	Non-diabetes	114,227	11,863	828,109	1.43 (1.41-1.46)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes§							
	HbA1c <6.5%	2982	302	13,989	2.16 (1.92-2.42)	1.38 (1.23-1.55)	1.05 (0.93-1.18)	1.08 (0.96-1.22)
	HbA1c 6.5-7.0%	2532	250	11,944	2.09 (1.84-2.37)	1.32 (1.17-1.50)	1.01 (0.89-1.15)	1.07 (0.93-1.22)
	HbA1c 7.1-8.0%	2008	210	10,744	1.95 (1.70-2.24)	1.26 (1.10-1.45)	1.06 (0.92-1.21)	1.08 (0.93-1.25)
	HbA1c >8.0%	1465	168	7393	2.27 (1.94-2.64)	1.47 (1.26-1.71)	1.32 (1.14-1.54)	1.29 (1.10-1.52)
	Metastatic							
	Non-diabetes	29,163	6529	177,207	3.68 (3.60-3.77)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes‡							
	HbA1c <6.5%	703	152	2834	5.36 (4.54-6.29)	1.30 (1.11-1.53)	1.02 (0.87-1.20)	1.07 (0.90-1.27)
	HbA1c 6.5-7.0%	727	172	2995	5.74 (4.92-6.67)	1.41 (1.21-1.64)	1.18 (1.01-1.37)	1.24 (1.05-1.45)
	HbA1c 7.1-8.0%	521	129	2324	5.55 (4.63-6.59)	1.38 (1.16-1.65)	1.17 (0.99-1.40)	1.22 (1.01-1.47)
	HbA1c >8.0%	451	117	1777	6.59 (5.45-7.89)	1.60 (1.33-1.92)	1.50 (1.25-1.80)	1.54 (1.27-1.87)
All-Cause Mortality	**Non-metastatic**							
	Non-diabetes	114,227	26,104	828,109	3.15 (3.11-3.19)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes§							
	HbA1c <6.5%	2982	894	13,989	6.39 (5.98-6.82)	1.99 (1.86-2.13)	1.22 (1.14-1.31)	1.14 (1.06-1.22)
	HbA1c 6.5-7.0%	2532	705	11,944	5.90 (5.48-6.36)	1.84 (1.70-1.98)	1.12 (1.04-1.21)	1.08 (1.00-1.17)
	HbA1c 7.1-8.0%	2008	617	10,744	5.74 (5.30-6.21)	1.80 (1.66-1.95)	1.24 (1.15-1.34)	1.18 (1.09-1.29)
	HbA1c >8.0%	1465	485	7393	6.56 (5.99-7.17)	2.05 (1.88-2.24)	1.57 (1.44-1.72)	1.43 (1.30-1.57)
	Metastatic							
	Non-diabetes	29,163	9207	177,207	5.20 (5.09-5.30)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
	Diabetes‡							

	HbA1c <6.5%	703	253	2834	8.93 (7.86-10.10)	1.61 (1.42-1.82)	1.08 (0.95-1.22)	1.09 (0.95-1.24)
	HbA1c 6.5-7.0%	727	265	2995	8.85 (7.81-9.98)	1.60 (1.42-1.81)	1.17 (1.03-1.32)	1.18 (1.03-1.34)
	HbA1c 7.1-8.0%	521	202	2324	8.69 (7.53-9.97)	1.59 (1.39-1.83)	1.19 (1.03-1.37)	1.22 (1.05-1.41)
	HbA1c >8.0%	451	189	1777	10.64 (9.18-12.27)	1.92 (1.66-2.22)	1.65 (1.43-1.91)	1.63 (1.40-1.90)

Abbreviations: HR, hazard ratio; CI, confidence interval.

***** Per 100 person-years.

† The models were adjusted for age, body mass index (BMI), smoking status, alcohol-related disorders, patient level index of multiple deprivation, angina, myocardial infarction, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease, renal disease, retinopathy, neuropathy, polycystic ovary syndrome (PCOS), respiratory disease, previous cancer, dementia, previous oophorectomy, use of hormonal replacement therapy, oral contraceptives, statins, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, diuretics, other antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, anticoagulants, and antiplatelet medications. The models were also stratified by 5-year calendar bands.

§2054 patients were excluded due to missing HbA1c.

Table 5. Hazard Ratios for Breast Cancer Mortality Comparing Type 2 Diabetes with Non-Diabetes Among Patients with Malignant Breast Cancer (Non-Breast Cancer Deaths as Competing Events)

Exposure	No. of patients	Events	Person-years	Incidence rate * (95% CI) *	Crude HR (95% CI)	Age-adjusted HR (95% CI)	Adjusted HR (95% CI) †
Non-metastatic							
Non-diabetes	114,227	11,863	828,109	1.43 (1.41-1.46)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Diabetes	11,041	1197	54,706	2.19 (2.07-2.32)	1.24 (1.17-1.32)	1.03 (0.97-1.10)	1.05 (0.98-1.13)
Metastatic							
Non-diabetes	29,163	6529	177,207	3.68 (3.60-3.77)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Diabetes	2867	691	11,994	5.76 (5.34-6.21)	1.31 (1.21-1.42)	1.16 (1.07-1.26)	1.18 (1.07-1.31)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100 person-years.

† The models were adjusted for age, body mass index (BMI), smoking status, alcohol-related disorders, patient level index of multiple deprivation, angina, myocardial infarction, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease, renal disease, retinopathy, neuropathy, polycystic ovary syndrome (PCOS), respiratory disease, previous cancer, dementia, previous oophorectomy, use of hormonal replacement therapy, oral contraceptives, statins, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, diuretics, other antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, anticoagulants, and antiplatelet medications. The models were also stratified by 5-year calendar bands.

Table 6. Hazard Ratios for Breast Cancer Mortality Comparing Type 2 Diabetes with Non-Diabetes Among Malignant Breast Cancer Patients (Time-Dependent Exposure)

Exposure	Events	Person-years	Incidence rate * (95% CI) *	Crude HR (95% CI)	Age-adjusted HR (95% CI)	Adjusted HR (95% CI) †
Non-metastatic						
Non-diabetes	10,987	784,352	1.40 (1.37-1.43)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Diabetes	2073	98,463	2.11 (2.02-2.20)	1.58 (1.51-1.66)	1.36 (1.30-1.43)	1.38 (1.31-1.46)
Metastatic						
Non-diabetes	6088	167,908	3.63 (3.54-3.72)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Diabetes	1132	21,292	5.32 (5.01-5.64)	1.57 (1.48-1.68)	1.40 (1.32-1.50)	1.45 (1.35-1.56)

Abbreviations: HR, hazard ratio; CI, confidence interval.

* Per 100 person-years.

† The models were adjusted for age, body mass index (BMI), smoking status, alcohol-related disorders, patient level index of multiple deprivation, angina, myocardial infarction, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease, renal disease, retinopathy, neuropathy, polycystic ovary syndrome (PCOS), respiratory disease, previous cancer, dementia, previous oophorectomy, use of hormonal replacement therapy, oral contraceptives, statins, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, diuretics, other antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, anticoagulants, and antiplatelet medications. The models were also stratified by 5-year calendar bands

Table 7. Hazard Ratios for All-Cause Mortality Comparing Type 2 Diabetes with Non-Diabetes Among Patients with Malignant Breast Cancer (Time-Dependent Exposure)

Exposure	Events	Person-years	Incidence rate * (95% CI) *	Crude HR (95% CI)	Age-adjusted HR (95% CI)	Adjusted HR (95% CI) †
Non-metastatic						
Non-diabetes	23,684	784,352	3.02 (2.98-3.06)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Diabetes	5940	98,463	6.03 (5.88-6.19)	2.03 (1.97-2.09)	1.48 (1.44-1.52)	1.40 (1.36-1.45)
Metastatic						
Non-diabetes	8501	167,908	5.06 (4.96-5.17)	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Diabetes	1816	21,292	8.53 (8.14-8.93)	1.76 (1.67-1.85)	1.42 (1.35-1.50)	1.42 (1.34-1.51)

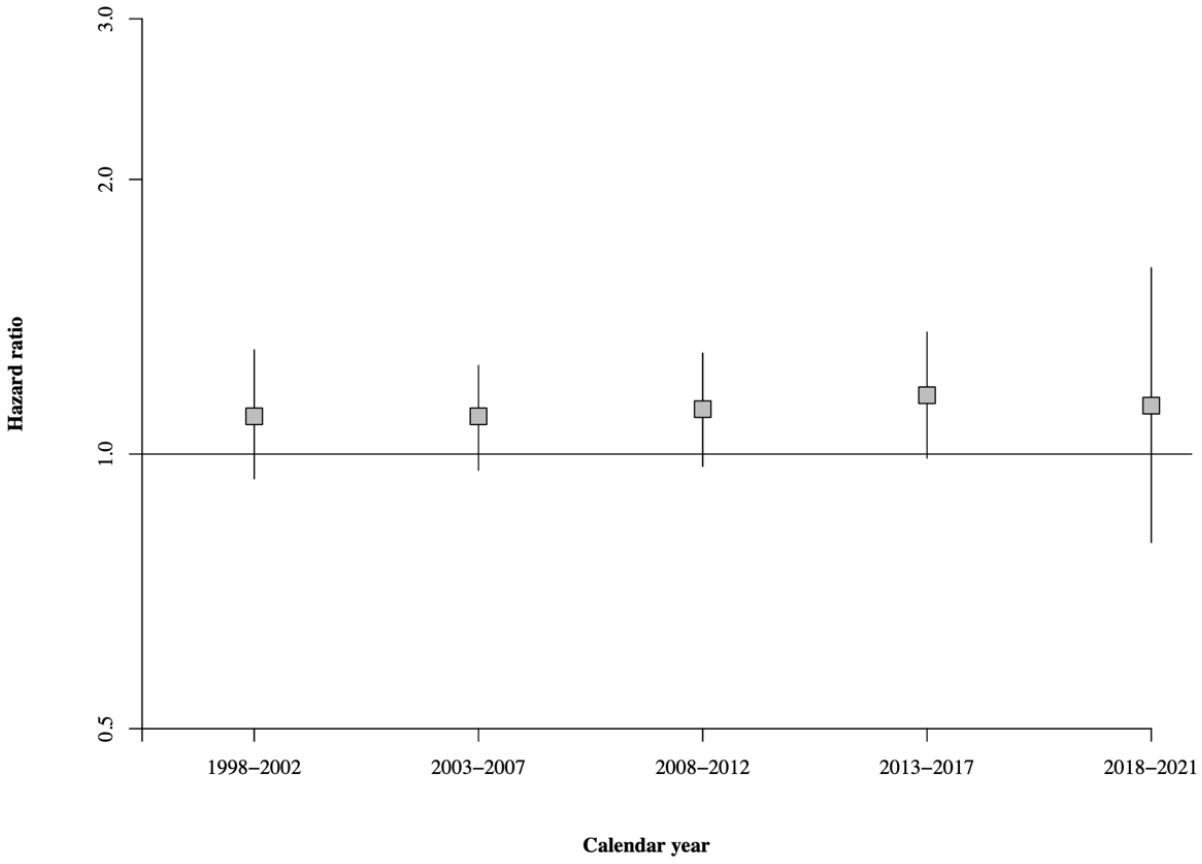
Abbreviations: HR, hazard ratio; CI, confidence interval.

***** Per 100 person-years.

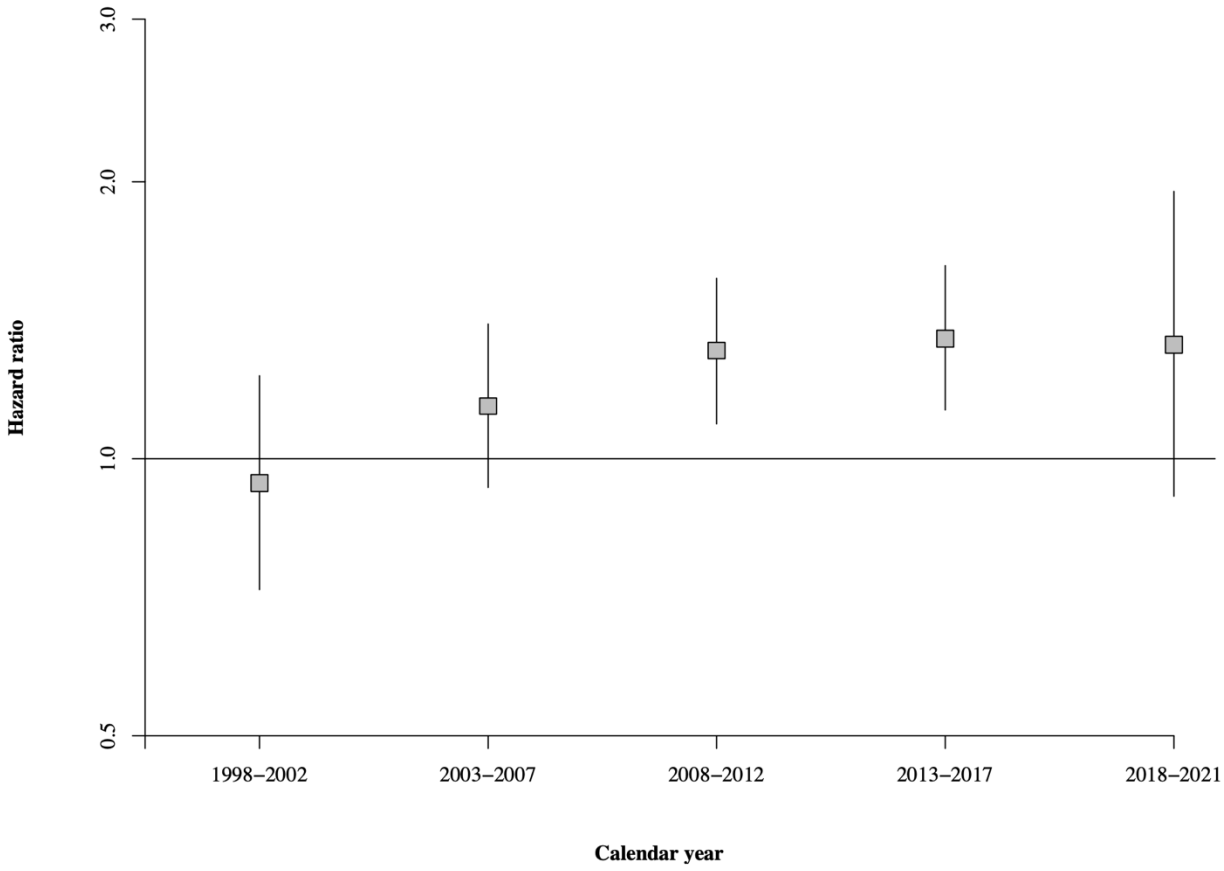
† The models were adjusted for age, body mass index (BMI), smoking status, alcohol-related disorders, patient level index of multiple deprivation, angina, myocardial infarction, stroke, transient ischemic attack, coronary artery disease, heart failure, peripheral vascular disease, renal disease, retinopathy, neuropathy, polycystic ovary syndrome (PCOS), respiratory disease, previous cancer, dementia, previous oophorectomy, use of hormonal replacement therapy, oral contraceptives, statins, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers, diuretics, other antihypertensive drugs, non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, anticoagulants, and antiplatelet medications. The models were also stratified by 5-year calendar bands.

5.8 Supplemental Material

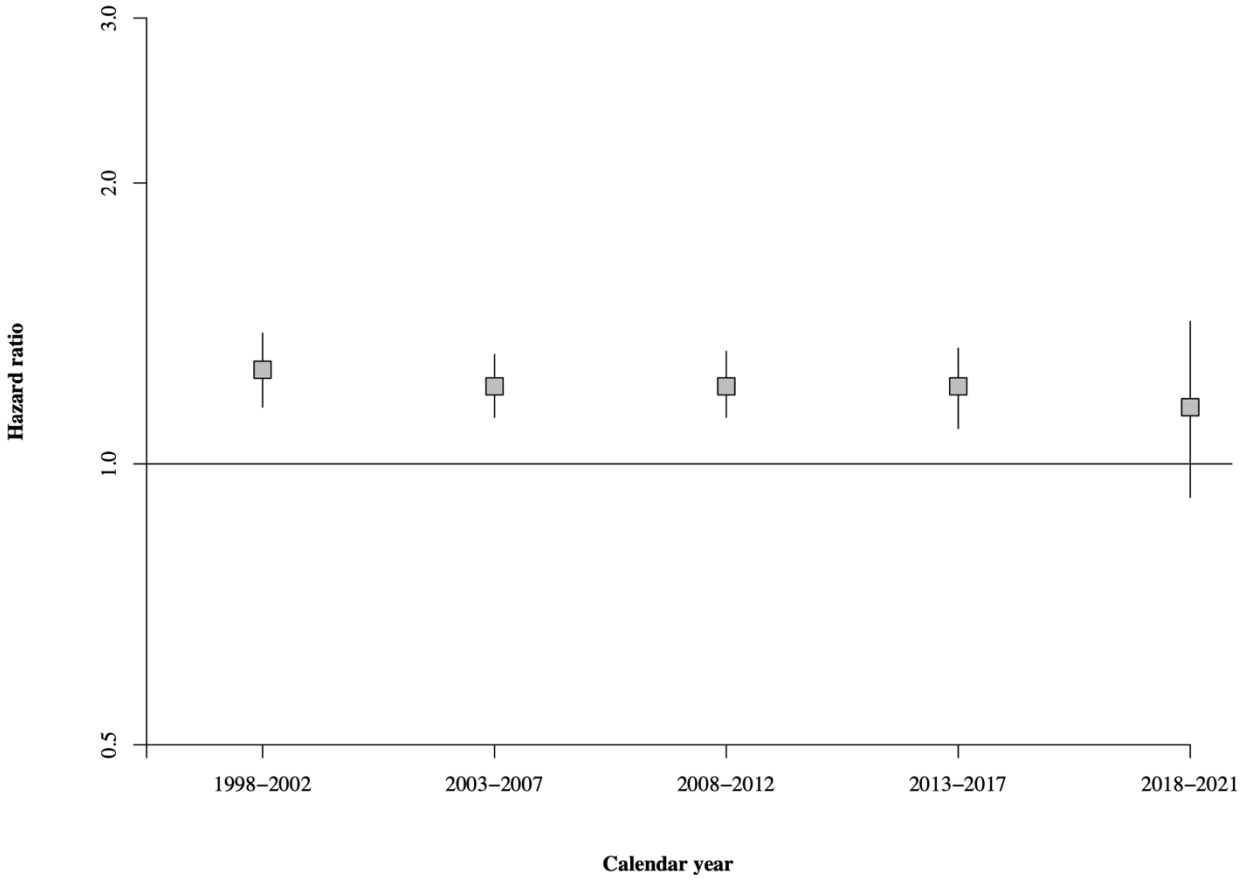
Supplementary Figure 1. Hazard ratio of breast cancer mortality across 5-year calendar bands for the non-metastatic cohort



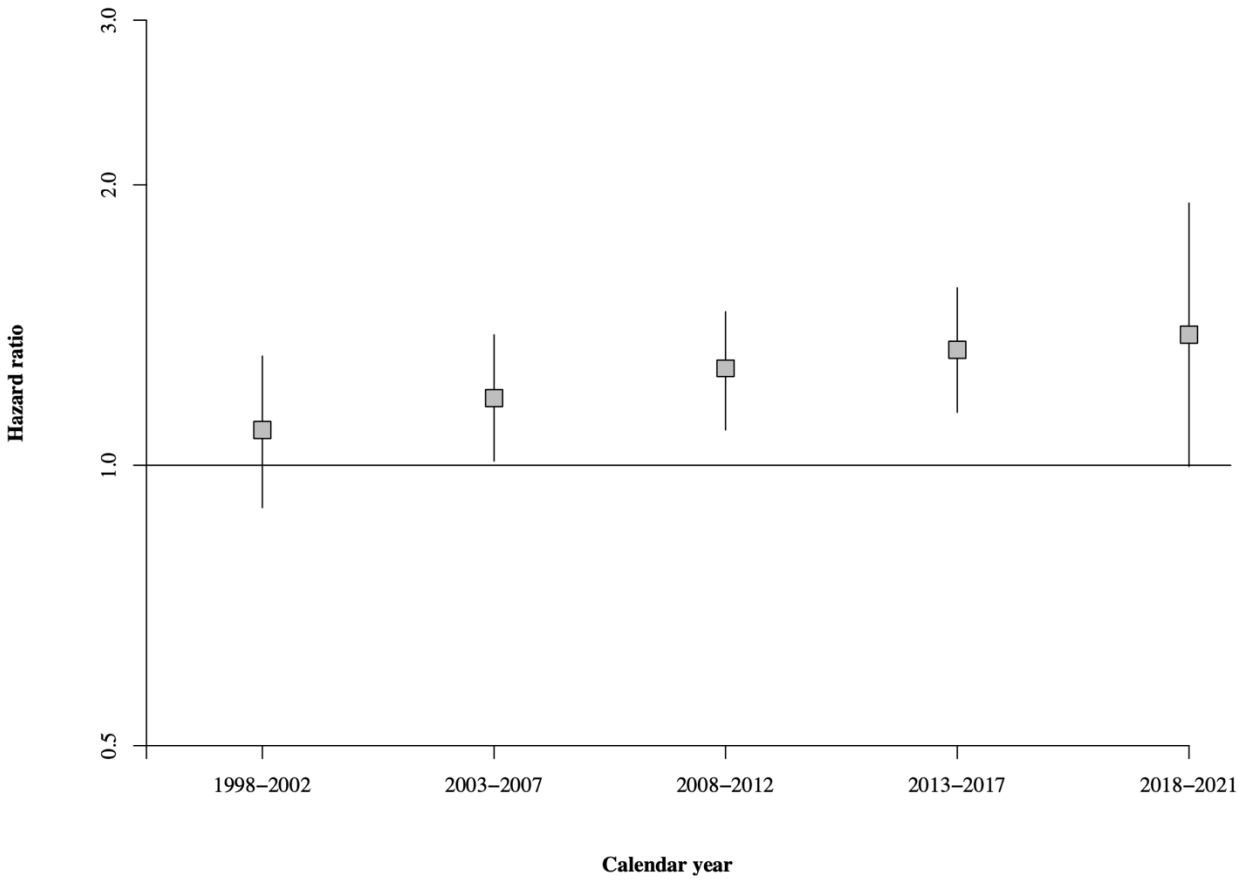
Supplementary Figure 2. Hazard ratio of breast cancer mortality across 5-year calendar bands for the metastatic cohort



Supplementary Figure 3. Hazard ratio of all-cause mortality across 5-year calendar bands for the non-metastatic cohort



Supplementary Figure 4. Hazard ratio of all-cause mortality across 5-year calendar bands for the metastatic cohort



Supplementary Table 1. Aurum Read & SNOMED-CT Codes for Primary Invasive Breast Cancer

Medical Code	Original Read Code	Cleansed Read Code	Read Term	SNOMED-CT Code	SNOMED-CT Description
1228259019	BB911	BB91100	[M]Infiltrating duct and lobular carcinoma	35232005	1228260012
1232564019	BB910	BB91000	[M]Intraductal papillary adenocarcinoma with invasion	64524002	1232565018
880321000006118	B346-99	B346.99	Ca breast - axillary tail	188156001	8.80321E+14
880271000006114	B340-99	B340.99	Ca breast - nipple/central	188147009	8.80271E+14
990571000006118	B34-98	B34..98	Ca breast - NOS	372064008	9.90571E+14
880331000006115	B34z-99	B34z.99	Ca breast - NOS	5.49521E+14	8.80331E+14
880291000006110	B343-99	B343.99	Ca breast-lower,inner quadrant	188153009	8.80291E+14
880311000006114	B345-99	B345.99	Ca breast-lower,outer quadrant	188155002	8.80311E+14
880281000006112	B342-99	B342.99	Ca breast-upper,inner quadrant	188152004	8.80281E+14
880301000006111	B344-99	B344.99	Ca breast-upper,outer quadrant	188154003	8.80301E+14
531851000006119	B34-1	B34..11	Ca female breast	372064008	1210642019
880261000006119	B34-99	B34..99	Carcinoma breast	372064008	8.80261E+14
3845571000006116	^ESCTDU384557		Duct adenocarcinoma	82711006	137209013
307631000006111	BB91-1	BB91.11	Duct carcinoma	82711006	137210015
38455510000006114	^ESCTDU384555		Duct cell carcinoma	82711006	137207010

3845561000006111	^ESCTDU384556		Ductal carcinoma	82711006	137208017
3067781000006111	^ESCTIN306778		Infiltrating duct and lobular carcinoma	35232005	58790014
310311000006110	BB91	BB91.00	Infiltrating duct carcinoma	82711006	137203014
310321000006119	BB9G	BB9G.00	Infiltrating ductular carcinoma	58477004	97180015
3958791000006112	^ESCTIN395879		Infiltrating lobular carcinoma	89740008	148781013
3067811000006113	^ESCTIN306781		Intraductal and lobular carcinoma	35232005	58793011
3549251000006113	^ESCTIN354925		Intraductal papillary adenocarcinoma with invasion	64524002	107241015
3958781000006114	^ESCTLO395878		Lobular adenocarcinoma	89740008	148780014
3067801000006110	^ESCTLO306780		Lobular and ductal carcinoma	35232005	58792018
291540014	BB9F	BB9F.00	Lobular carcinoma	89740008	148778015
155089014	B3401	B340100	Malignant neoplasm of areola of female breast	93680004	155089014
289146012	B346	B346.00	Malignant neoplasm of axillary tail of female breast	188156001	289146012
5351531000006113	^ESCTMA535153		Malignant neoplasm of breast	254837009	3446624010
289141019	B341	B341.00	Malignant neoplasm of central part of female breast	188151006	289141019
289149017	B34y0	B34y000	Malignant neoplasm of	188159008	289149017

			ectopic site of female breast		
1210642019	B34	B34..00	Malignant neoplasm of female breast	372064008	1210642019
289151018	B34z	B34z.00	Malignant neoplasm of female breast NOS	372064008	1210642019
289143016	B343	B343.00	Malignant neoplasm of lower-inner quadrant of female breast	188153009	289143016
289145011	B345	B345.00	Malignant neoplasm of lower-outer quadrant of female breast	188155002	289145011
289137018	B340	B340.00	Malignant neoplasm of nipple and areola of female breast	188147009	289137018
155417012	B3400	B340000	Malignant neoplasm of nipple of female breast	93924008	155417012
289140018	B340z	B340z00	Malignant neoplasm of nipple or areola of female breast NOS	188147009	289137018
289148013	B34y	B34y.00	Malignant neoplasm of other site of female breast	372064008	1210642019
289150017	B34yz	B34yz00	Malignant neoplasm of other site of female breast NOS	372064008	1210642019
289142014	B342	B342.00	Malignant neoplasm of upper-inner	188152004	289142014

			quadrant of female breast		
289144010	B344	B344.00	Malignant neoplasm of upper-outer quadrant of female breast	188154003	289144010
289147015	B347	B347.00	Malignant neoplasm, overlapping lesion of breast	188157005	289147015
5351501000006117	^ESCTMA535150		Malignant tumor of breast	254837009	379661016
292137017	Byu6	Byu6.00	Malignant tumour of breast	254837009	379664012
8017201000006114	^ESCTPR801720		Primary invasive malignant neoplasm of female breast	4.5221E+13	3287797013
4024671000006119	^ESCTPR402467		Primary malignant neoplasm of areola of female breast	93680004	510448014
4025821000006115	^ESCTPR402582		Primary malignant neoplasm of female breast	93796005	510640013
4027021000006119	^ESCTPR402702		Primary malignant neoplasm of nipple of female breast	93924008	510852015
4028011000006114	^ESCTPR402801		Primary malignant neoplasm of skin of breast	94012007	510995017

Supplementary Table 2. GOLD Read Codes for Primary Invasive Breast Cancer

Medical Code	Read Code	Read Term
348	B34..11	Ca female breast
3968	B34..00	Malignant neoplasm of female breast
9470	B34z.00	Malignant neoplasm of female breast NOS
12499	Byu6.00	[X]Malignant neoplasm of breast
20685	B346.00	Malignant neoplasm of axillary tail of female breast
23380	B340000	Malignant neoplasm of nipple of female breast
23399	B344.00	Malignant neoplasm of upper-outer quadrant of female
26853	B340.00	Malignant neoplasm of nipple and areola of female br
29826	B342.00	Malignant neoplasm of upper-inner quadrant of female
31546	B341.00	Malignant neoplasm of central part of female breast
38475	B34yz00	Malignant neoplasm of other site of female breast NO
39760	BB91100	[M]Infiltrating duct and lobular carcinoma
42070	B345.00	Malignant neoplasm of lower-outer quadrant of female
45222	B343.00	Malignant neoplasm of lower-inner quadrant of female
49148	B347.00	Malignant neoplasm, overlapping lesion of breast
56715	B34y.00	Malignant neoplasm of other site of female breast
59831	B340z00	Malignant neoplasm of nipple or areola of female bre
64686	B340100	Malignant neoplasm of areola of female breast
95057	B34y000	Malignant neoplasm of ectopic site of female breast
8351	BB91.00	[M]Infiltrating duct carcinoma
21833	BB91.11	[M]Duct carcinoma NOS
12427	BB9F.00	[M]Lobular carcinoma NOS
7319	BB9G.00	[M]Infiltrating ductular carcinoma
30189	BB91000	[M]Intraductal papillary adenocarcinoma with invasion

CHAPTER 6: DISCUSSION

6.1 Summary of Findings

The aim of this study was to investigate whether pre-existing type 2 diabetes is associated with an increased risk of breast cancer-related and all-cause mortality among women newly diagnosed with non-metastatic and metastatic breast cancer, separately. This thesis study was conducted in response to evidence in the scientific literature that indicated patients with type 2 diabetes may experience worse breast cancer outcomes compared to their non-diabetic counterparts. This large, population-based cohort study that was conducted using the UK CPRD found that type 2 diabetes was associated with an increased risk of breast cancer-related and all-cause mortality in patients with non-metastatic and metastatic disease, separately, compared to patients without diabetes. In the secondary analyses, among patients with metastases, HbA1c ≥6.5% was associated with an increased risk of both breast cancer-related and all-cause mortality among patients with type 2 diabetes, compared to non-diabetes. Among patients with non-metastatic breast cancer, a similar trend was seen for all-cause mortality, however only the HbA1c >8% category was significantly associated with an increased risk of breast cancer mortality. Moreover, in both cohorts, the effect of diabetes, compared with no diabetes, on both mortality outcomes was higher among patients <55 years of age compared with patients ≥55 years of age, as well as higher among patients with a BMI <25 kg/m² compared with patients in the BMI categories ≥25kg/m². Finally, the results from the primary analysis remained consistent across both sensitivity analyses that examined various sources of bias.

6.2 Clinical Implications

The co-occurrence of type 2 diabetes and cancer is increasing,[70] with up to 20% of patients with breast cancer also having diabetes,[6] thus presenting a significant public health concern with clinical implications. As such, epidemiological and biological evidence provide the basis for investigating whether type 2 diabetes may have clinically relevant effects in the prognosis of breast cancer.[69 100] Type 2 diabetes may directly influence disease progression through metabolic pathways mediated by hyperglycemia, hyperinsulinemia, inflammatory cytokines, and sex hormones.[69] Moreover, cancer and diabetes share several risk factors, including age, obesity and lifestyle factors, which may also promote disease progression.[69 70 100] Concurrently, type 2 diabetes may have indirect effects on prognosis by influencing cancer screening,[113] diagnosis,[10 114] and treatment patterns among this population.[85 115] Specifically, women with diabetes have been found to be less likely to undergo mammography,[113] even though this screening test may be important to reduce breast cancer mortality.[113 116] Lipscombe et al. found that women with diabetes were 32% less likely to have had a mammogram over a 2-year period despite having more contact with primary care and specialists compared to their non-diabetic counterparts.[117] As such, type 2 diabetes has been found to be associated with more advanced disease at breast cancer diagnosis, including metastasis, compared to patients without diabetes.[10 114] Moreover, there is evidence that breast cancer patients with type 2 diabetes may receive less aggressive treatment compared to patients without diabetes,[118] possibly due to the increase risk of treatment-related complications, such as chemotherapy toxicity.[85] Given that type 2 diabetes has been associated with increased breast cancer incidence and mortality,[76] screening and treatment regimens tailored to this population may be important for clinical outcomes.

With this complex relationship between diabetes and cancer, there has been recent interest in the effects of glycemic control on cancer outcomes. Indeed, hyperglycemia has been associated with poorer overall survival among breast cancer patients,[119 120] however these concerns have not been sufficiently corroborated in subsequent large epidemiologic studies. This thesis study suggests that poorer glycemic control may be associated with an increased risk of breast-cancer related and all-cause mortality, particularly for patients with a HbA1c >8.0%. Thus, assessing glycemic control at breast cancer diagnosis may have prognostic implications for clinicians to consider. Furthermore, glycemic screening at cancer diagnosis may also be important because type 2 diabetes may go undiagnosed for many years, with an estimated 174.8 million undiagnosed cases worldwide,[121] including approximately 2.3 million undiagnosed cases in Canada alone.[4] As the number of patients with both breast cancer and type 2 diabetes increases, the topic of this thesis study may be relevant for the clinical management of breast cancer in tandem with type 2 diabetes.

There is biological evidence in the scientific literature for a potential effect of type 2 diabetes on breast cancer mortality, though the existing literature on this research question is inconsistent.[3 8 76 77] This information prompted this thesis study, and the results provide real-world evidence for a potential association between type 2 diabetes and breast cancer mortality outcomes. Epidemiologic studies such as the one described in this thesis are important for investigating unintended clinically relevant effects of co-occurring diseases in real-world populations. Randomized controlled trials are often not feasible for rare outcomes like cancer due to the need for large sample sizes and extended follow-up periods, in addition to the high financial cost of conducting such studies. Given that breast cancer is one of the most common cancers among women worldwide,[1] the results of this and future studies on the topic may have important

implications for informing more targeted clinical care for women with breast cancer who have pre-existing type 2 diabetes.

6.3 Strengths and Limitations

This thesis has several strengths. First, the cohorts were built using primary care data from the CPRD, which has been shown to be representative of the UK population and contains high quality data for research purposes.[106 122 123] Second, the large sample size of over 150,000 patients with breast cancer, with over 1 million person-years of follow-up time, provides strong statistical power to answer this research question. Third, the models were adjusted for over 30 potential confounders, including comorbidities, lifestyle factors and prescription drugs. Lastly, results were consistent across different sensitivity analyses, which assessed the robustness of the study results. Although the inverse-probability of censoring weighting analysis attenuated the point estimates for breast cancer mortality in both the non-metastatic and metastatic cohorts, the 95% CIs generated by this sensitivity analysis overlap with those from the primary analysis.

This thesis also has several limitations. First, given the observational design of this study, residual confounding by unknown or unmeasured variables, such as family history of breast cancer and race/ethnicity, is possible. However, it is unlikely that these unknown variables were distributed differentially between the exposure groups. Second, time-dependent confounding is also a possibility given that covariates were measured at baseline and follow-up extended up to 22 years for some patients. Third, though diabetes status was determined by recorded diagnostic codes, glycemic blood values or anti-hyperglycemic drug prescriptions, type 2 diabetes is a largely asymptomatic disease that often goes undiagnosed for many years, thus misclassification of exposure is possible. However, exposure misclassification is expected to be non-differential between the different exposure groups. Fourth, the CPRD records test results and prescriptions

written by general practitioners rather than specialists, although long-term diabetes care is almost exclusively managed by general practitioners in the UK.[124 125] There is also the possibility of outcome misclassification, although breast cancer has been shown to be well recorded in the CPRD when compared with the UK National Cancer Data Repository.[105 106] Lastly, the CPRD does not have any information on tumor characteristics, including cancer stage, grade, and hormone receptor status, however these are likely on the causal pathway. Future studies should investigate whether type 2 diabetes has impact on these prognostic characteristics of breast cancer.

6.4 Future Directions

While the study findings suggest that type 2 diabetes is associated with a higher risk of breast cancer-related and all-cause mortality among patients with breast cancer, it would be premature to make recommendations for more targeted clinical practice guidelines for this patient population. Breast cancer mortality has decreased in recent decades,[1] thus there is a need for future well-designed studies to reassess this association that may evolve over time, while allowing for the accumulation of more follow-up time and breast cancer cases, in order to confirm our findings.

Additional studies should quantify the relationship between the severity of diabetes-related hyperglycemia and breast cancer outcomes. There is significant heterogeneity in glycemic control within diabetic populations due to various factors including lifestyle behaviours, drug interventions, and comorbidities.[11] To date, however, glycemic control and its association with breast cancer outcomes has not been thoroughly investigated. Future studies that assess the risk of these outcomes as a function of glycemic control at cancer diagnosis are needed to account for the heterogeneity of disease severity within the type 2 diabetes population.

Another important direction of research should be to investigate whether pre-existing prediabetes, a prevalent precursor to type 2 diabetes that is characterized by chronic hyperglycemia below the diabetes threshold,[17] is associated with an increased risk of poorer breast cancer outcomes. Prediabetes has emerged as a distinct pathophysiological state that is becoming recognized as a significant global health issue.[17 20] As of 2017, an estimated 352 million adults aged 20 to 79 were living with prediabetes worldwide.[20] This number is expected to rise to approximately 587 million people by 2045, representing 8.3% of the global adult population.[20] Diabetes Canada estimates that there are 5.9 million Canadians living with prediabetes, with an increasing incidence trend that is expected to continue.[4] There is some evidence that hyperglycemia that is below the diabetic range (i.e. prediabetes) is associated with a higher risk of mortality and recurrence, [108 114-116] however the published literature is very limited.[120 126-128] Moreover, existing observational studies have important methodological limitations, including small sample size, lack of cancer-specific mortality data, and potential residual confounding due to missing data on key confounders (comorbidities, demographics, drugs). There is also inconsistency across the published studies in terms of the blood glucose measures used to define prediabetes, contributing further to the lack of clarity surrounding this research question. Despite these methodological limitations, these studies seem to point towards a potential association between prediabetes and breast cancer that warrants further investigation.

Finally, possible associations between type 2 diabetes and other cancers cannot be ruled out. Indeed, there is evidence that type 2 diabetes is associated with increased risk of mortality for other cancers, including the liver, pancreas, endometrium and colorectum.[9 76 129 130] As such, findings from past systematic reviews suggest that diabetes is associated with an increased risk of all-cause mortality[129] and cancer-specific mortality[76] across various cancer sites, however both

type 1 and type 2 diabetes were included. Given the existing evidence that type 2 diabetes may be an independent risk factor associated with cancer mortality outcomes,[69] further study is warranted to investigate if clinical management of diabetes can influence cancer prognosis.

To conclude, this thesis showed an association between type 2 diabetes and breast cancer mortality outcomes, which is concerning given the increasing incidence of both diseases globally.[70] Thus, clinicians should continue to monitor diabetes over the course of breast cancer treatment, as there is a biologically plausible mechanism for the involvement of diabetes in promoting breast cancer. Indeed, adequate glycemic control, as measured by glycated HbA1c, among patients with both breast cancer and type 2 diabetes may not be associated with worse outcomes compared to their non-diabetes counterparts, further suggesting the importance of diabetes management among this population.

CHAPTER 7: CONCLUSION

As the incidence of type 2 diabetes continues to rise in Canada and around the world,[4 11] understanding its relationship with breast cancer outcomes is of increasing clinical significance. Type 2 diabetes may impact breast cancer outcomes not only through its complex pathophysiology,[69] but also by influencing screening patterns and treatment options.[3 10] While type 2 diabetes has been associated with increased incidence of breast cancer,[99] its association with mortality outcomes is less understood. Furthermore, there is limited published literature that assesses the impact of glycemic control on breast cancer mortality outcomes among patients with type 2 diabetes.

The study detailed in this thesis is a large observational study that addresses several gaps in the literature regarding the association between type 2 diabetes and breast cancer mortality and all-cause mortality. The results indicate that pre-existing type 2 diabetes may be associated with an increased the risk of breast cancer-related and all-cause mortality among both non-metastatic and metastatic breast cancer, separately. Furthermore, poorer glycemic control may be associated with an increased risk of these outcomes. To further clarify this relationship, additional studies should quantify the relationship between type 2 diabetes-related hyperglycemia and breast cancer outcomes. First, future studies evaluating glycemia as a continuous variable to assess mortality risk as a function of glycemic control are needed to account for the heterogeneity of disease severity within the type 2 diabetes population. Second, future research should be directed towards investigating whether pre-existing prediabetes, a prevalent precursor to type 2 diabetes, is associated with an increased risk of poorer breast cancer outcomes, compared to non-diabetes and diabetes. Finally, given the clinical significance of this research question, the association between

type 2 diabetes and mortality risk of other malignancies, such as liver, pancreatic, endometrial, and colorectal cancers, should also be investigated.

CHAPTER 8: REFERENCES

1. World Health Organization. Breast Cancer: World Health Organization,; 2021 [updated 12 July 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/breast-cancer accessed 28 November 2022.
2. Government of Canada. Breast Cancer: Government of Canada,; 2019 [updated 9 December 2019. Available from: https://www.canada.ca/en/public-health/services/chronic-diseases/cancer/breast-cancer.html accessed 28 November 2022.
3. Peairs KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. *J Clin Oncol* 2011;29(1):40-6. doi: 10.1200/jco.2009.27.3011 [published Online First: 20101129]
4. Diabetes Canada. Diabetes in Canada Backgrounder Ottawa: Diabetes Canada; 2022 [Available from: https://www.diabetes.ca/DiabetesCanadaWebsite/media/Advocacy-and-Policy/Backgrounder/2022_Backgrounder_Canada_English_1.pdf accessed 28 November 2022.
5. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018;14(2):88-98. doi: 10.1038/nrendo.2017.151 [published Online First: 20171208]
6. Eketunde AO. Diabetes as a Risk Factor for Breast Cancer. *Cureus* 2020;12(5):e8010. doi: 10.7759/cureus.8010 [published Online First: 20200507]
7. Ahmadieh H, Azar ST. Type 2 diabetes mellitus, oral diabetic medications, insulin therapy, and overall breast cancer risk. *ISRN Endocrinol* 2013;2013:181240. doi: 10.1155/2013/181240 [published Online First: 20130117]
8. Zhou Y, Zhang X, Gu C, et al. Influence of diabetes mellitus on mortality in breast cancer patients. *ANZ J Surg* 2015;85(12):972-8. doi: 10.1111/ans.12877 [published Online First: 20141013]
9. Tao H, O'Neil A, Choi Y, et al. Pre- and Post-diagnosis Diabetes as a Risk Factor for All-Cause and Cancer-Specific Mortality in Breast, Prostate, and Colorectal Cancer Survivors: a Prospective Cohort Study. *Front Endocrinol (Lausanne)* 2020;11:60. doi: 10.3389/fendo.2020.00060 [published Online First: 20200218]

10. Lipscombe LL, Fischer HD, Austin PC, et al. The association between diabetes and breast cancer stage at diagnosis: a population-based study. *Breast Cancer Res Treat* 2015;150(3):613-20. doi: 10.1007/s10549-015-3323-5 [published Online First: 20150317]
11. Goyal R, Jialal I. Diabetes Mellitus Type 2. StatPearls. Treasure Island (FL)2022.
12. International Diabetes Federation. Diabetes facts & figures: International Diabetes Federation,; 2021 [updated 9 December 2021. Available from: https://idf.org/aboutdiabetes/what-is-diabetes/facts-figures.html accessed 29 November 2022.
13. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of Type 2 Diabetes Mellitus. *Int J Mol Sci* 2020;21(17) doi: 10.3390/ijms21176275 [published Online First: 20200830]
14. Alvarez S, Coffey R, Algotar AM. Prediabetes. StatPearls. Treasure Island (FL)2022.
15. Public Health Agency of Canada. Diabetes in Canada: Facts and figures from a public health perspective Ottawa: Public Health Agency of Canada,; 2011 [updated 15 December 2011. Available from: https://www.canada.ca/en/public-health/services/chronic-diseases/reports-publications/diabetes/diabetes-canada-facts-figures-a-public-health-perspective/chapter-4.html accessed 9 August 2023.
16. Wilcox G. Insulin and insulin resistance. *Clin Biochem Rev* 2005;26(2):19-39.
17. Bansal N. Prediabetes diagnosis and treatment: A review. *World J Diabetes* 2015;6(2):296-303. doi: 10.4239/wjd.v6.i2.296
18. Bhansali A, Dutta P. Pathophysiology of prediabetes. *J Indian Med Assoc* 2005;103(11):594-5, 99.
19. Brannick B, Wynn A, Dagogo-Jack S. Prediabetes as a toxic environment for the initiation of microvascular and macrovascular complications. *Exp Biol Med (Maywood)* 2016;241(12):1323-31. doi: 10.1177/1535370216654227
20. Hostalek U. Global epidemiology of prediabetes - present and future perspectives. *Clin Diabetes Endocrinol* 2019;5:5. doi: 10.1186/s40842-019-0080-0 [published Online First: 20190509]

21. Punthakee Z, Goldenberg R, Katz P. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. *Can J Diabetes* 2018;42 Suppl 1:S10-s15. doi: 10.1016/j.jcjd.2017.10.003

22. Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: An overview. *Avicenna J Med* 2020;10(4):174-88. doi: 10.4103/ajm.ajm_53_20 [published Online First: 20201013]

23. Ramachandran A. Know the signs and symptoms of diabetes. *Indian J Med Res* 2014;140(5):579-81.

24. World Health Organization. Classification of diabetes mellitus. Geneva: World Health Organization 2019.

25. Little RR, Rohlfing CL, Sacks DB. Status of hemoglobin A1c measurement and goals for improvement: from chaos to order for improving diabetes care. *Clin Chem* 2011;57(2):205-14. doi: 10.1373/clinchem.2010.148841 [published Online First: 20101209]

26. Eyth E, Naik R. Hemoglobin A1C. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC. 2022.

27. Ekoe JM, Goldenberg R, Katz P. Screening for Diabetes in Adults. *Can J Diabetes* 2018;42 Suppl 1:S16-s19. doi: 10.1016/j.jcjd.2017.10.004

28. Imran SA, Agarwal G, Bajaj HS, et al. Targets for Glycemic Control. *Can J Diabetes* 2018;42 Suppl 1:S42-s46. doi: 10.1016/j.jcjd.2017.10.030

29. Sievenpiper JL, Chan CB, Dworatzek PD, et al. Nutrition Therapy. *Can J Diabetes* 2018;42 Suppl 1:S64-s79. doi: 10.1016/j.jcjd.2017.10.009

30. Sigal RJ, Armstrong MJ, Bacon SL, et al. Physical Activity and Diabetes. *Can J Diabetes* 2018;42 Suppl 1:S54-s63. doi: 10.1016/j.jcjd.2017.10.008

31. Wharton S, Sharma AM, Lau DC. Weight management in diabetes. *Can J Diabetes* 2013;37 Suppl 1:S82-6. doi: 10.1016/j.jcjd.2013.01.025 [published Online First: 20130326]

32. Lipscombe L, Booth G, Butalia S, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. *Can J Diabetes* 2018;42 Suppl 1:S88-s103. doi: 10.1016/j.jcjd.2017.10.034

33. Chaudhury A, Duvoor C, Reddy Dendi VS, et al. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. *Frontiers in Endocrinology* 2017;8 doi: 10.3389/fendo.2017.00006
34. Bailey CJ. Metformin: historical overview. *Diabetologia* 2017;60(9):1566-76. doi: 10.1007/s00125-017-4318-z
35. Corcoran C, Jacobs TF. Metformin. StatPearls. Treasure Island (FL)2022.
36. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. *Diabetologia* 2017;60(9):1577-85. doi: 10.1007/s00125-017-4342-z
37. American Diabetes Association Professional Practice C. 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022;45(Suppl 1):S39-S45. doi: 10.2337/dc22-S003
38. Group UPDSU. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352(9131):854-65.
39. Han Y, Xie H, Liu Y, et al. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. *Cardiovascular Diabetology* 2019;18(1):96. doi: 10.1186/s12933-019-0900-7
40. Tahrani AA, Varughese GI, Scarpello JH, et al. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? *Bmj* 2007;335(7618):508-12. doi: 10.1136/bmj.39255.669444.AE
41. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. *Oman Med J* 2012;27(4):269-73. doi: 10.5001/omj.2012.68
42. Eggleton JS, Jialal I. Thiazolidinediones. StatPearls. Treasure Island (FL)2022.
43. Collins L, Costello RA. Glucagon-like Peptide-1 Receptor Agonists. StatPearls. Treasure Island (FL)2022.
44. Hsia DS, Grove O, Cefalu WT. An update on sodium-glucose co-transporter-2 inhibitors for the treatment of diabetes mellitus. *Curr Opin Endocrinol Diabetes Obes* 2017;24(1):73-79. doi: 10.1097/med.0000000000000311
45. Meece J. Basal Insulin Intensification in Patients with Type 2 Diabetes: A Review. *Diabetes Ther* 2018;9(3):877-90. doi: 10.1007/s13300-018-0395-3 [published Online First: 20180324]

46. Swinnen SG, Hoekstra JB, DeVries JH. Insulin therapy for type 2 diabetes. *Diabetes Care* 2009;32 Suppl 2(Suppl 2):S253-9. doi: 10.2337/dc09-S318
47. Canadian Cancer Society. Breast cancer statistics: Canadian Cancer Society,; 2022 [updated May 2022. Available from: https://cancer.ca/en/cancer-information/cancer-types/breast/statistics accessed 30 November 2022.
48. Lukasiewicz S, Czeczelewski M, Forma A, et al. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. *Cancers (Basel)* 2021;13(17) doi: 10.3390/cancers13174287 [published Online First: 20210825]
49. Alkabban FM, Ferguson T. Breast Cancer. StatPearls. Treasure Island (FL)2022.
50. American Society of Clinical Oncology (ASCO). Breast Cancer - Metastatic: Introduction: ASCO; 2021 [updated November 2022. Available from: https://www.cancer.net/cancer-types/breast-cancer-metastatic/introduction accessed 30 November 2022.
51. Fuller MS, Lee CI, Elmore JG. Breast cancer screening: an evidence-based update. *Med Clin North Am* 2015;99(3):451-68. doi: 10.1016/j.mcna.2015.01.002 [published Online First: 20150305]
52. Budh DP, Sapra A. Breast Cancer Screening. StatPearls. Treasure Island (FL)2022.
53. Shah TA, Guraya SS. Breast cancer screening programs: Review of merits, demerits, and recent recommendations practiced across the world. *J Microsc Ultrastruct* 2017;5(2):59-69. doi: 10.1016/j.jmau.2016.10.002 [published Online First: 20161128]
54. Nounou MI, ElAmrawy F, Ahmed N, et al. Breast Cancer: Conventional Diagnosis and Treatment Modalities and Recent Patents and Technologies. *Breast Cancer (Auckl)* 2015;9(Suppl 2):17-34. doi: 10.4137/bcbcr.S29420 [published Online First: 20150927]
55. Cancer Reseach UK. About breast cancer staging and grades: Cancer Research UK,; 2020 [updated 16 May 2023. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/about-breast-cancer-staging-grades accessed 1 December 2022.
56. American Society of Clinical Oncology (ASCO). Breast Cancer: Statistics: American Society of Clinical Oncology (ASCO),; 2022 [updated February 2023. Available from: https://www.cancer.net/cancer-types/breast-cancer/statistics accessed 1 December 2022.

57. American Cancer Society. Breast Cancer Hormone Receptor Status: American Cancer Society; 2021 [updated 8 November 2021. Available from: https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-hormone-receptor-status.html accessed 1 December 2021.
58. Lumachi F, Santeufemia DA, Basso SM. Current medical treatment of estrogen receptor-positive breast cancer. *World J Biol Chem* 2015;6(3):231-9. doi: 10.4331/wjbc.v6.i3.231
59. Cao SS, Lu CT. Recent perspectives of breast cancer prognosis and predictive factors. *Oncol Lett* 2016;12(5):3674-78. doi: 10.3892/ol.2016.5149 [published Online First: 20160919]
60. Moo TA, Sanford R, Dang C, et al. Overview of Breast Cancer Therapy. *PET Clin* 2018;13(3):339-54. doi: 10.1016/j.cpet.2018.02.006
61. Jordan RM, Oxenberg J. Breast Cancer Conservation Therapy. StatPearls. Treasure Island (FL)2022.
62. Goethals A, Rose J. Mastectomy. StatPearls. Treasure Island (FL)2022.
63. Masoud V, Pagès G. Targeted therapies in breast cancer: New challenges to fight against resistance. *World J Clin Oncol* 2017;8(2):120-34. doi: 10.5306/wjco.v8.i2.120
64. Miller E, Lee HJ, Lulla A, et al. Current treatment of early breast cancer: adjuvant and neoadjuvant therapy. *F1000Res* 2014;3:198. doi: 10.12688/f1000research.4340.1 [published Online First: 20140819]
65. Nabieva N, Fasching PA. Endocrine Treatment for Breast Cancer Patients Revisited-History, Standard of Care, and Possibilities of Improvement. *Cancers (Basel)* 2021;13(22) doi: 10.3390/cancers13225643 [published Online First: 20211111]
66. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. *J Clin Oncol* 2014;32(21):2255-69. doi: 10.1200/jco.2013.54.2258 [published Online First: 20140527]
67. Awan A, Esfahani K. Endocrine therapy for breast cancer in the primary care setting. *Curr Oncol* 2018;25(4):285-91. doi: 10.3747/co.25.4139 [published Online First: 20180814]
68. Scharl A, Salterberg A. Significance of Ovarian Function Suppression in Endocrine Therapy for Breast Cancer in Pre-Menopausal Women. *Geburtshilfe Frauenheilkd* 2016;76(5):516-24. doi: 10.1055/s-0042-106389

69. Wang M, Yang Y, Liao Z. Diabetes and cancer: Epidemiological and biological links. *World J Diabetes* 2020;11(6):227-38. doi: 10.4239/wjd.v11.i6.227

70. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33(7):1674-85. doi: 10.2337/dc10-0666

71. Tsilidis KK, Kasimis JC, Lopez DS, et al. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *Bmj* 2015;350:g7607. doi: 10.1136/bmj.g7607 [published Online First: 20150102]

72. Chen Y, Wu F, Saito E, et al. Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium. *Diabetologia* 2017;60(6):1022-32. doi: 10.1007/s00125-017-4229-z [published Online First: 20170307]

73. Ling S, Brown K, Miksza JK, et al. Association of Type 2 Diabetes With Cancer: A Meta-analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People. *Diabetes Care* 2020;43(9):2313-22. doi: 10.2337/dc20-0204

74. Noto H, Tsujimoto T, Noda M, et al. Significantly increased risk of cancer in patients with diabetes mellitus: A systematic review and meta-analysis. *Endocrine Practice* 2011;17(4):616-28. doi: 10.4158/EP10357.RA

75. The Emerging Risk Factors Collaboration. Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death. *New England Journal of Medicine* 2011;364(9):829-41. doi: 10.1056/NEJMoa1008862

76. De Bruijn KM, Arends LR, Hansen BE, et al. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. *Br J Surg* 2013;100(11):1421-9. doi: 10.1002/bjs.9229

77. Zhao XB, Ren GS. Diabetes mellitus and prognosis in women with breast cancer: A systematic review and meta-analysis. *Medicine (Baltimore)* 2016;95(49):e5602. doi: 10.1097/md.0000000000005602

78. Lam EKK, Batty GD, Huxley RR, et al. Associations of diabetes mellitus with site-specific cancer mortality in the Asia-Pacific region. *Ann Oncol* 2011;22(3):730-38. doi: 10.1093/annonc/mdq405 [published Online First: 20100812]

79. Strele I, Pildava S, Repsa I, et al. Pre-existing diabetes mellitus and all-cause mortality in cancer patients: a register-based study in Latvia. *Acta Oncologica* 2018;57(7):973-82. doi: 10.1080/0284186X.2017.1420909

80. Yeh H-C, Platz EA, Wang N-Y, et al. A Prospective Study of the Associations Between Treated Diabetes and Cancer Outcomes. *Diabetes Care* 2011;35(1):113-18. doi: 10.2337/dc11-0255

81. Zhou XH, Qiao Q, Zethelius B, et al. Diabetes, prediabetes and cancer mortality. *Diabetologia* 2010;53(9):1867-76. doi: 10.1007/s00125-010-1796-7

82. Nechuta S, Lu W, Zheng Y, et al. Comorbidities and breast cancer survival: a report from the Shanghai Breast Cancer Survival Study. *Breast Cancer Res Treat* 2013;139(1):227-35. doi: 10.1007/s10549-013-2521-2 [published Online First: 20130419]

83. Luo J, Virnig B, Hendryx M, et al. Diabetes, diabetes treatment and breast cancer prognosis. *Breast Cancer Res Treat* 2014;148(1):153-62. doi: 10.1007/s10549-014-3146-9 [published Online First: 20140927]

84. Luo J, Hendryx M, Virnig B, et al. Pre-existing diabetes and breast cancer prognosis among elderly women. *British Journal of Cancer* 2015;113(5):827-32. doi: 10.1038/bjc.2015.249

85. Srokowski TP, Fang S, Hortobagyi GN, et al. Impact of Diabetes Mellitus on Complications and Outcomes of Adjuvant Chemotherapy in Older Patients With Breast Cancer. *Journal of Clinical Oncology* 2009;27(13):2170-76. doi: 10.1200/jco.2008.17.5935

86. Jiralerspong S, Kim ES, Dong W, et al. Obesity, diabetes, and survival outcomes in a large cohort of early-stage breast cancer patients. *Ann Oncol* 2013;24(10):2506-14. doi: 10.1093/annonc/mdt224 [published Online First: 20130621]

87. Liu X, Ji J, Sundquist K, et al. The impact of type 2 diabetes mellitus on cancer-specific survival: a follow-up study in Sweden. *Cancer* 2012;118(5):1353-61. doi: 10.1002/cncr.26420 [published Online First: 20110728]

88. Chen WW, Shao YY, Shau WY, et al. The impact of diabetes mellitus on prognosis of early breast cancer in Asia. *Oncologist* 2012;17(4):485-91. doi: 10.1634/theoncologist.2011-0412 [published Online First: 20120330]

89. Wu AH, Kurian AW, Kwan ML, et al. Diabetes and other comorbidities in breast cancer survival by race/ethnicity: the California Breast Cancer Survivorship Consortium

(CBCSC). *Cancer Epidemiol Biomarkers Prev* 2015;24(2):361-8. doi: 10.1158/1055-9965.Epi-14-1140 [published Online First: 20141125]

90. Lawrence WR, Hosler AS, Gates Kuliszewski M, et al. Impact of preexisting type 2 diabetes mellitus and antidiabetic drugs on all-cause and cause-specific mortality among Medicaid-insured women diagnosed with breast cancer. *Cancer Epidemiol* 2020;66:101710. doi: 10.1016/j.canep.2020.101710 [published Online First: 20200401]
91. Mu L, Zhu N, Zhang J, et al. Type 2 diabetes, insulin treatment and prognosis of breast cancer. *Diabetes Metab Res Rev* 2017;33(1) doi: 10.1002/dmrr.2823 [published Online First: 20160620]
92. Lee KN, Torres MA, Troeschel AN, et al. Type 2 diabetes, breast cancer specific and overall mortality: Associations by metformin use and modification by race, body mass, and estrogen receptor status. *PLoS One* 2020;15(5):e0232581. doi: 10.1371/journal.pone.0232581 [published Online First: 20200505]
93. Fernández-Arce L, Robles-Rodríguez N, Fernández-Feito A, et al. Type 2 Diabetes and all-cause mortality among Spanish women with breast cancer. *Cancer Causes & Control* 2022;33(2):271-78. doi: 10.1007/s10552-021-01526-x
94. Maskarinec G, Shvetsov YB, Conroy SM, et al. Type 2 diabetes as a predictor of survival among breast cancer patients: the multiethnic cohort. *Breast Cancer Res Treat* 2019;173(3):637-45. doi: 10.1007/s10549-018-5025-2 [published Online First: 20181026]
95. Redaniel MT, Jeffreys M, May MT, et al. Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. *Cancer Causes Control* 2012;23(11):1785-95. doi: 10.1007/s10552-012-0057-0 [published Online First: 20120913]
96. Zhang F, de Haan-Du J, Sidorenkov G, et al. Type 2 Diabetes Mellitus and Clinicopathological Tumor Characteristics in Women Diagnosed with Breast Cancer: A Systematic Review and Meta-Analysis. *Cancers (Basel)* 2021;13(19) doi: 10.3390/cancers13194992 [published Online First: 20211005]
97. Murto MO, Artama M, Pukkala E, et al. Breast cancer extent and survival among diabetic women in a Finnish nationwide cohort study. *Int J Cancer* 2018;142(11):2227-33. doi: 10.1002/ijc.31250 [published Online First: 20180123]

98. Cheung YM, Hughes M, Harrod J, et al. The Effects of Diabetes and Glycemic Control on Cancer Outcomes in Individuals With Metastatic Breast Cancer. *J Clin Endocrinol Metab* 2022;107(9):2511-21. doi: 10.1210/clinem/dgac375

99. Bonagiri PR, Shubrook JH. Review of Associations Between Type 2 Diabetes and Cancer. *Clin Diabetes* 2020;38(3):256-65. doi: 10.2337/cd19-0077

100. Vigneri P, Frasca F, Sciacca L, et al. Diabetes and cancer. *Endocr Relat Cancer* 2009;16(4):1103-23. doi: 10.1677/ERC-09-0087 [published Online First: 20090720]

101. Zhu B, Qu S. The Relationship Between Diabetes Mellitus and Cancers and Its Underlying Mechanisms. *Front Endocrinol (Lausanne)* 2022;13:800995. doi: 10.3389/fendo.2022.800995 [published Online First: 20220211]

102. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44(3):827-36. doi: 10.1093/ije/dyv098 [published Online First: 20150606]

103. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. *Int J Epidemiol* 2019;48(6):1740-40g. doi: 10.1093/ije/dyz034

104. CPRD. Data: CPRD; 2022 [updated 11 October 2022; cited 2023. Available from: https://cprd.com/data#:~:text=CPRD%20data%20are%20sourced%20from,for%2025%25%20of%20the%20patients. accessed 9 August 2023.

105. Arhi CS, Bottle A, Burns EM, et al. Comparison of cancer diagnosis recording between the Clinical Practice Research Datalink, Cancer Registry and Hospital Episodes Statistics. *Cancer Epidemiol* 2018;57:148-57. doi: 10.1016/j.canep.2018.08.009 [published Online First: 20181002]

106. Boggon R, van Staa TP, Chapman M, et al. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiol Drug Saf* 2013;22(2):168-75. doi: 10.1002/pds.3374 [published Online First: 20121213]

107. Lawrenson R, Williams T, Farmer R. Clinical information for research; the use of general practice databases. *J Public Health Med* 1999;21(3):299-304. doi: 10.1093/pubmed/21.3.299

108. Alam NN, Wright AK, Rutter MK, et al. Body mass index and cancer mortality in patients with incident type 2 diabetes: A population-based study of adults in England. *Diabetes, Obesity and Metabolism* 2022;24(4):620-30. doi: 10.1111/dom.14614

109. Pearson-Stuttard J, Bennett J, Cheng YJ, et al. Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. *The lancet Diabetes & endocrinology* 2021;9(3):165-73. doi: 10.1016/S2213-8587(20)30431-9

110. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69(1):4-14. doi: 10.1111/j.1365-2125.2009.03537.x

111. Sun YS, Zhao Z, Yang ZN, et al. Risk Factors and Preventions of Breast Cancer. *Int J Biol Sci* 2017;13(11):1387-97. doi: 10.7150/ijbs.21635 [published Online First: 20171101]

112. Kinnunen PT, Murto MO, Artama M, et al. Anticoagulants and Breast Cancer Survival: A Nationwide Cohort Study. *Cancer Epidemiol Biomarkers Prev* 2020;29(1):208-15. doi: 10.1158/1055-9965.Epi-19-0147 [published Online First: 20191025]

113. Lipscombe LL, Hux JE, Booth GL. Reduced screening mammography among women with diabetes. *Arch Intern Med* 2005;165(18):2090-5. doi: 10.1001/archinte.165.18.2090

114. Lao C, Gurney J, Stanley J, et al. Association of diabetes and breast cancer characteristics at diagnosis. *Cancer Causes & Control* 2023;34(2):103-11. doi: 10.1007/s10552-022-01654-y

115. Lega IC, Austin PC, Fischer HD, et al. The Impact of Diabetes on Breast Cancer Treatments and Outcomes: A Population-Based Study. *Diabetes Care* 2018;41(4):755-61. doi: 10.2337/dc17-2012

116. Duffy SW, Tabár L, Yen AM, et al. Mammography screening reduces rates of advanced and fatal breast cancers: Results in 549,091 women. *Cancer* 2020;126(13):2971-79. doi: 10.1002/cncr.32859 [published Online First: 20200511]

117. Lipscombe LL, Hux JE, Booth GL. Reduced screening mammography among women with diabetes. *Archives of internal medicine* 2005;165(18):2090-5.

118. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, et al. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *Int J Cancer* 2007;120(9):1986-92. doi: 10.1002/ijc.22532

119. Erickson K, Patterson RE, Flatt SW, et al. Clinically Defined Type 2 Diabetes Mellitus and Prognosis in Early-Stage Breast Cancer. *Journal of Clinical Oncology* 2011;29(1):54-60. doi: 10.1200/jco.2010.29.3183

120. Monzavi-Karbassi B, Gentry R, Kaur V, et al. Pre-diagnosis blood glucose and prognosis in women with breast cancer. *Cancer Metab* 2016;4:7. doi: 10.1186/s40170-016-0147-7 [published Online First: 20160406]
121. Beagley J, Guariguata L, Weil C, et al. Global estimates of undiagnosed diabetes in adults. *Diabetes Res Clin Pract* 2014;103(2):150-60. doi: 10.1016/j.diabres.2013.11.001 [published Online First: 20131201]
122. Margulis AV, Fortuny J, Kaye JA, et al. Validation of Cancer Cases Using Primary Care, Cancer Registry, and Hospitalization Data in the United Kingdom. *Epidemiology* 2018;29(2):308-13. doi: 10.1097/ede.0000000000000786
123. Williams R, van Staa TP, Gallagher AM, et al. Cancer recording in patients with and without type 2 diabetes in the Clinical Practice Research Datalink primary care data and linked hospital admission data: a cohort study. *BMJ Open* 2018;8(5):e020827. doi: 10.1136/bmjopen-2017-020827 [published Online First: 20180526]
124. Hawthorne G, Hrisos S, Stamp E, et al. Diabetes care provision in UK primary care practices. *PLoS One* 2012;7(7):e41562. doi: 10.1371/journal.pone.0041562 [published Online First: 20120730]
125. Pierce M, Agarwal G, Ridout D. A survey of diabetes care in general practice in England and Wales. *Br J Gen Pract* 2000;50(456):542-5.
126. Contiero P, Berrino F, Tagliabue G, et al. Fasting blood glucose and long-term prognosis of non-metastatic breast cancer: a cohort study. *Breast Cancer Research and Treatment* 2013;138(3):951-59. doi: 10.1007/s10549-013-2519-9
127. Minicozzi P, Berrino F, Sebastiani F, et al. c. *European Journal of Cancer* 2013;49(18):3881-88. doi: 10.1016/j.ejca.2013.08.004
128. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364(9):829-41. doi: 10.1056/NEJMoa1008862
129. Barone BB, Yeh HC, Snyder CF, et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *Jama* 2008;300(23):2754-64. doi: 10.1001/jama.2008.824

130. Ling S, Zaccardi F, Issa E, et al. Inequalities in cancer mortality trends in people with type 2 diabetes: 20 year population-based study in England. *Diabetologia* 2023;66(4):657-73. doi: 10.1007/s00125-022-05854-8 [published Online First: 20230124]