Incretin-Based Drugs and the Incidence of Skin Cancer Among Patients with Type 2 Diabetes

Richeek Pradhan

Department of Epidemiology, Biostatistics, and Occupational Health
McGill University, Montreal
December 2022

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy in Epidemiology

Abstract

The prevalence of type 2 diabetes is rising worldwide. While several studies have investigated whether the incidence of cancer is higher among patients with type 2 diabetes, the existing literature has methodological shortcomings. In particular, whether skin cancer, the most common form of human cancer, occurs more frequently among patients with type 2 diabetes than the general population, is unclear. This is an important lacuna because some novel antihyperglycemic drugs, such as the incretin-based drugs, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), affect cellular pathways that influence carcinogenesis in the skin. Importantly, whether incretin-based drugs is affect the incidence of different types of skin cancer has also not been investigated. The overall purpose of this manuscript-based doctoral thesis was to address existing knowledge gaps regarding the burden of cancer overall and skin cancer in patients with type 2 diabetes, as well as the use of incretin-based drugs and the risk of skin cancer.

The objective of the first manuscript was to assess the association between type 2 diabetes and cancer. Using the United Kingdom Clinical Practice Research Datalink (CPRD), patients with type 2 diabetes were matched to patients without diabetes between 1988 to 2019. Poisson regression models were fit to estimate incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for cancer. Overall, 890,214 patients with type 2 diabetes were matched to an equal number of patients without type 2 diabetes. Patients with type 2 diabetes had a higher cancer incidence than patients without type 2 diabetes (IRR 1.19, 95% CI 1.18-1.21), but a null association with melanoma (IRR 0.96, 95% CI 0.92-1.01), and negative association with nonmelanoma skin cancer (IRR 0.90, 95% 0.88-0.91).

The objective of the second manuscript was to determine whether the use of DPP-4 inhibitors was associated with the incidence of melanoma and nonmelanoma skin cancer, separately, in patients with type 2 diabetes. Two new-user active comparator cohorts based on the CPRD were assembled: the first, with 96,739 new users of DPP-4 inhibitors and 209,341 new users of sulfonylurea had melanoma as the outcome, while the second, with 96,411 new users of DPP-4 inhibitors and 2,08,626 new users sulfonylurea had nonmelanoma skin cancer as the outcome. These cohorts were independently analyzed by fitting propensity score fine stratification weighted Cox proportional hazards models to estimate hazard ratios (HRs) with 95% CIs of melanoma and nonmelanoma skin cancer, separately. In the melanoma outcome cohort, DPP-4 inhibitor use was associated with a 23% reduction in the risk of melanoma compared with sulfonylurea use (HR 0.77, 95% CI 0.61-0.96). In contrast, in the nonmelanoma skin cancer cohort, DPP-4 inhibitor use was not associated with the incidence of nonmelanoma skin cancer compared with sulfonylureas (HR 1.06, 95% CI 0.98-1.15).

The objective of the third manuscript was to determine whether in patients with type 2 diabetes the use of GLP-1 RAs was associated with an increased risk of melanoma and nonmelanoma skin cancer, separately, compared with sulfonylurea use. Using the CPRD, two cohorts with melanoma and nonmelanoma skin cancer as outcomes, respectively, were constructed. The first cohort, with melanoma as the outcome, consisted of 11,786 patients initiating GLP-1 RAs and 208,519 patients initiating sulfonylureas, while the second cohort, with nonmelanoma skin cancer as the outcome, consisted of 11,778 patients initiating GLP-1 RAs and 207,305 patients initiating sulfonylureas. Independent Cox proportional hazards models weighted using propensity score fine stratification were fit to estimate HRs and 95% CIs of melanoma and nonmelanoma skin cancer, respectively. The use of GLP-1 RAs was not

associated with an increased risk of either melanoma (HR 0.96, 95% CI 0.53-1.75) or nonmelanoma skin cancer (HR 0.96, 95% CI 0.75-1.23).

Résumé

La prévalence du diabète de type 2 est en augmentation dans le monde entier. Bien que plusieurs études aient cherché à savoir si l'incidence du cancer est plus élevée chez les patients atteints de diabète de type 2, la littérature existante présente des lacunes méthodologiques. En particulier, on ne sait pas si le cancer de la peau, la forme la plus courante de cancer chez l'homme, est plus fréquent chez les patients atteints de diabète de type 2 que dans la population générale. Il s'agit d'une lacune importante car certains nouveaux médicaments antihyperglycémiques, tels que les médicaments à base d'incrétine, les inhibiteurs de la dipeptidyl peptidase-4 (DPP-4) et les agonistes du récepteur du glucagon-like peptide-1 (GLP-1 RAs), affectent les voies cellulaires qui sont très actives dans la pathogenèse du cancer de la peau. Il est important de noter que la question de savoir si l'utilisation de médicaments à base d'incrétine est associée à l'incidence de différents types de cancer de la peau n'a pas non plus été étudiée. L'objectif général de cette thèse de doctorat était de combler les lacunes existantes en matière de connaissances concernant le fardeau du cancer en général et du cancer de la peau chez les patients atteints de diabète de type 2, ainsi que l'utilisation de médicaments à base d'incrétine et le risque de cancer de la peau.

L'objectif du premier manuscrit était d'évaluer l'association entre le diabète de type 2 et le cancer. En utilisant le United Kingdom Clinical Practice Research Datalink (CPRD), les patients atteints de diabète de type 2 ont été appariés à des patients non diabétiques entre 1988 et 2019. Des modèles de régression de Poisson ont été ajustés pour estimer les ratios de taux d'incidence (IRR) avec des intervalles de confiance (IC) à 95 % pour le cancer. Au total, 890 214 patients atteints de diabète de type 2 ont été appariés à un nombre égal de patients sans diabète de type 2. Les patients atteints de diabète de type 2 avaient une incidence de cancer plus élevée que les

patients non diabétiques (IRR 1,19, IC à 95 % 1,18-1,21), mais une association nulle avec le mélanome (IRR 0,96, IC à 95 % 0,92-1,01), et une association négative avec le cancer de la peau autre que le mélanome (IRR 0,90, IC à 95 % 0,88-0,91).

L'objectif du second manuscrit était de déterminer si l'utilisation des inhibiteurs de la DPP-4 était associée à l'incidence du mélanome et du cancer de la peau non mélanique, séparément, chez les patients atteints de diabète de type 2. Deux cohortes de comparateurs actifs de nouveaux utilisateurs basées sur le CPRD ont été assemblées : la première, avec 96 739 nouveaux utilisateurs d'inhibiteurs de la DPP-4 et 209 341 nouveaux utilisateurs de sulfonylurée, ayant pour résultat le mélanome, tandis que la seconde, avec 96 411 nouveaux utilisateurs d'inhibiteurs de la DPP-4 et 2 08 626 nouveaux utilisateurs de sulfonylurée, ayant pour résultat le cancer de la peau sans mélanome. Ces cohortes ont été analysées indépendamment en ajustant des modèles de risques proportionnels de Cox pondérés par stratification fine du score de propension afin d'estimer les rapports de risque instantané (RRI pondéré) avec IC à 95 % du mélanome et du cancer de la peau sans mélanome, séparément. Dans la cohorte de résultats sur le mélanome, l'utilisation d'un inhibiteur de la DPP-4 a été associée à une réduction de 23 % du risque de mélanome par rapport à l'utilisation d'une sulfonylurée (RRI pondéré 0,77, IC à 95 % 0,61- 0,96). En revanche, dans la cohorte de cancer de la peau sans mélanome, l'utilisation d'un inhibiteur de la DPP-4 n'a pas été associée à l'incidence du cancer de la peau sans mélanome par rapport aux sulfonylurées (RRI pondéré 1,06, IC 95 % 0,98-1,15).

L'objectif du troisième manuscrit était de déterminer si, chez les patients atteints de diabète de type 2, l'utilisation des AR GLP-1 était associée à un risque accru de mélanome et de cancer cutané non mélanique, séparément, par rapport à l'utilisation des sulfonylurées. À l'aide

du CPRD, deux cohortes dont les résultats sont respectivement le mélanome et le cancer de la peau sans mélanome ont été construites. La première cohorte, avec le mélanome comme résultat, comprenait 11 786 patients ayant commencé à prendre des GLP-1 RAs et 208 519 patients ayant commencé à prendre des sulfonylurées, tandis que la seconde cohorte, avec le cancer de la peau sans mélanome comme résultat, comprenait 11 778 patients ayant commencé à prendre des GLP-1 RAs et 207 305 patients ayant commencé à prendre des sulfonylurées. Des modèles indépendants de risques proportionnels de Cox pondérés par une stratification fine du score de propension ont été ajustés pour estimer les RRI et les IC à 95 % du mélanome et du cancer de la peau sans mélanome, respectivement. L'utilisation de GLP-1 RAs n'a pas été associée à un risque accru de mélanome (RRI pondéré 0,96, 95% CI 0,53-1,75) ou de cancer de la peau non mélanique (RRI pondéré 0,96, 95% CI 0,75-1,23).

Acknowledgements

As a friend says, 'While thanking, err on the side of being lengthy.' So, here goes:

First and foremost, I am immensely thankful to my doctoral supervisor, Dr. Laurent Azoulay. I have benefitted beyond measure from his deep understanding of Epidemiology, Pharmacoepidemiology, and Causal Inference. His research approach combines confidence and optimism with a healthy mix of critical outlook and skepticism, a balance that I believe is key to scientific innovation. Discussing science with him has been just as fulfilling in person as on zoom. I am grateful that he has always encouraged me to come up with my own research ideas, be an independent thinker, and identify and address the critical questions in the field as a way to contribute to the existing literature. Besides providing me with countless opportunities to publish, collaborate, and lead, he has also been a compassionate mentor, allowing me to work remotely from India during much of the pandemic years, a time when staying away from my aging parents would have been a difficult and anxiety-provoking experience. In short, as an aspiring academic, if I am looking to model myself after a mentor, I need not search beyond my own doctoral supervisor.

I also want to thank my committee members, Dr. Robert Platt and Dr. Oriana Yu. I have not only been lucky to learn from Dr. Platt's profound knowledge of Epidemiological methods but have also been greatly enriched by his advice on career, academia, and work-life balance. I am thankful to Dr. Oriana Yu, whose insights as a physician have strengthened my study design and whose thorough feedback has allowed me to enhance the clinical relevance of my projects. And, my heartfelt gratitude goes to statistician and analyst Ms. Hui Yin, who, has taught me as much about the field as any Epidemiology professor. This thesis could not have been completed without her patient guidance on data analysis and advice on study designs.

I am also grateful for the world-class Pharmacoepidemiology training infrastructure I got access to at the Lady Davis Institute. Scientists such as Professors Kristian Fillion, Christel Renoux, James Brophy, Pierre Ernst, Jacques Le Lorier, and Antonios Douros have taught me how to work at the cutting-edge of the discipline while still being rooted in strong foundations. Interacting with my fellow trainees, Farzin, Julie, Devin, Alvi, Vanessa, and Samantha, in the lab, at journal clubs, in the corridors, has been the bedrock of my graduate education. And, all importantly, it has been an absolute privilege to learn Pharmacoepidemiology from Prof. Samy Suissa. The diverse and highly academic setting he has created at the Lady Davis Institute by assembling practitioners from all over the world will continue to benefit the field for years to come

I am also very grateful for having been given the opportunity to study Epidemiology at McGill. To learn how to think deeply about data and design from the likes of Professors James Hanley, Jay Kaufman, Claire Infante-Rivard, and my favorite, Olga Basso, has been an honor. I also feel incredibly fortunate for being able to train alongside cohort mates turned friends Nick, Jill, Susannah, Martha, Joseph, Samia, and Ivan: the egoless and fun environment in class we created for each other allowed us all to be better thinkers. Thanks also to my cohort mate and collaborator Professor Giorgia Sulis, whose work ethic is as inspiring as it is sometimes nerve racking, but I also know her sincerity as a friend is something I can always count on. I am much thankful to the administrative officers at McGill Epidemiology, Katherine Hayden and André Yves Gagnon, and at the Lady Davis Institute, Emily Schrider and Marisa Mancini, who have worked tirelessly to smoothen the administrative aspects of my training.

Onto the personal front now. The word “scientist” has always possessed an intimidating ring for me. That I could ever aspire to become one has largely been due to my friendships with

Dr. Sambuddha Chaudhuri and Dr. Supriyo Choudhury. My conversations with Sambuddha intensified at a time when, being unable to relate to the research in a basic science PhD program I had just enrolled in, I was facing a career crisis. Chats with him enabled me to articulate to myself why I, a queer, brown man, needed to pursue more socially contextualized research than to delve into the decontextualized (albeit fundamentally important) workings of cellular mechanisms. With Supriyo da, on the other hand, my education has been more hands-on: together we have worked on surveys, hospital-based studies, medical pedagogy, and research ethics. Seeing his enthusiasm transcend substantive areas and methodologies has helped me develop an apathy for scientific compartmentalization, which I think is an asset in today's interdisciplinary research landscape. Over the years, besides being fellow physician-researchers and collaborators, they have become existential allies. I also want to thank two of my oldest friends, Dr. Rena Guha and Dr. Pritikanta Paul for their generous encouragement, push, and glee that has always sustained me through thick and thin.

Lastly, I want to split the dedication of this thesis four ways. First, Ma, you make the world worthy of living for me just by existing. Thank you for everything. Secondly, Baba, you are my first teacher and the reason I love academics. A lot of what I am doing is just trying to make you proud. Third, Aveek, you have blurred the lines between scientific enquiry and artistic endeavors that were etched deep into my mind by years of conventional schooling. Being your friend was a thoroughly invigorating education. And finally, Mimmi, you are one of the most determined individuals I know. I find parallels between your traveling to the deepest interiors of Bengal to teach as a young woman and my travelling to the opposite side of the world to learn. I only hope I can lead my life with the same sense of duty and gratitude that you practiced throughout yours.

Statement of original contribution

This thesis attempts making several novel contributions to the literature on the diabetes-cancer association and the risk-benefit profile of a novel group of antihyperglycemic drug called incretin-based drugs. Despite several previous studies on the topic, there remain several unknowns in the diabetes-cancer association literature. Indeed, many of these studies have relatively short follow-up and are dated, the latter being an important lacuna given recent introductions of several novel antihyperglycemic drugs, updated cancer surveillance policies, and changes to prevalence of several cancer risk factors. In addition, questions such as whether the association between diabetes-cancer has changed over time, and whether patients with diabetes have a higher incidence of multiple cancers, have received little attention. In manuscript 1, we examined the burden of cancer overall and 22 site-specific cancers in patients with diabetes, compared with patients without diabetes. This included the association of diabetes with skin cancers, an area where the literature has several methodological shortcomings. We found that diabetes is associated with a 19% higher count of first cancer overall, and a 5% higher count of multiple cancers. Among patients with diabetes, the incidence of melanoma was similar to that of patients without diabetes, but the incidence of non-melanoma skin cancer was lower. Finally, we found that the magnitude of the diabetes-cancer association has increased in the last decade compared with previous decades. The fact that patients with diabetes have a poorer prognosis for skin cancer motivated us to examine the association of skin cancers with incretin-based drugs (dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon like peptide-1 receptor agonists (GLP-1 RAs)), drugs that affect cellular pathways involved in skin cancer pathogenesis. In manuscript 2, we investigated the association of DPP-4 inhibitors with skin cancer, finding that DPP-4 inhibitor new users had a 23% lower risk of melanoma, with risk reduction pronounced after two

years of use. In contrast, DPP-4 inhibitor use was not associated with the incidence of non-melanoma skin cancer. Given that this was the first study on these associations, out findings should be validated in other settings and incite further preclinical and clinical research into the potential role of DPP-4 inhibitors for chemoprevention of melanoma. In manuscript 3, we explored whether GLP-1 RAs are associated with a higher risk of skin cancer. Again, this was the first ever study on the topic, and we found that GLP-1 RA use was not associated with an increased risk of either melanoma or non-melanoma skin cancer. These findings should reassure regulators, physicians, and patients about the concerns raised regarding this association due to signals generated in clinical trials.

I have received guidance from my supervisor for my thesis objectives and clinical and methodological guidance from thesis committee members. The conception, execution, and drafting of the manuscripts were my own.

Contributions of Authors

Manuscript 1: Long-Term Patterns of Cancer Incidence Among Patients With and Without Type 2 Diabetes in the United Kingdom. *Diabetes Res Clin Pract.2022;185:109229*.

With the guidance of Dr. Azoulay, I developed the research question and conceptualized this study. I drafted the protocol and obtained ethics approval from the CPRD and Jewish General Hospital. I conducted the data analyses, was responsible for data management, interpreted the findings and drafted the manuscript. Dr. Yu provided clinical guidance, and Dr. Platt provided statistical guidance. All authors contributed to study design, data interpretation and critical revision of the manuscript. Dr. Azoulay acquired the data and is the guarantor for this study.

Manuscript 2: Dipeptidyl Peptidase-4 Inhibitors and the Risk of Skin Cancer Among Patients with Type 2 Diabetes: Population-Based Cohort Study. *Submitted to Diabetes Care*.

With the guidance of Dr. Azoulay, I developed the research question and conceptualized this study. I drafted the protocol and obtained ethics approval from the CPRD and Jewish General Hospital. I conducted the data analyses, was responsible for data management, interpreted the findings and drafted the manuscript. Dr. Yu provided clinical guidance, and Dr. Platt provided statistical guidance. All authors contributed to study design, data interpretation and critical revision of the manuscript. Dr. Azoulay acquired the data and is the guarantor for this study.

Manuscript 3: Glucagon Like Peptide-1 Receptor Agonists and the Risk of Skin Cancer Among Patients with Type 2 Diabetes: Population-Based Cohort Study. *Submitted to Diabetes Obesity and Metabolism*.

With the guidance of Dr. Azoulay, I developed the research question and conceptualized this study. I drafted the protocol and obtained ethics approval from the CPRD and Jewish General Hospital. I conducted the data analyses, was responsible for data management, interpreted the findings and drafted the manuscript. Dr. Yu provided clinical guidance, and Dr. Platt provided statistical guidance. All authors contributed to study design, data interpretation and critical revision of the manuscript. Dr. Azoulay acquired the data and is the guarantor for this study.

Statement of financial support

I would like to acknowledge the different sources of personal funding received that made possible the undertaking of the projects constituting this thesis. This includes stipendiary support from McGill Department of Epidemiology, Biostatistics and Occupational Health, a training grant from Canadian Institutes for Health Research Drug Safety and Effectiveness Safety Program, a travel award from the International Society for Pharmacoepidemiology, and a doctoral award from Fonds de Recherche du Québec Santé. The projects were funded by support by a foundation grant from Canadian Institutes for Health Research (FDN-143328).

Table of contents

List of tables

List of figures

List of acronyms and abbreviations

AMPK	AMP-activated protein kinase
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
CPRD	Clinical practice research datalink
DPP-4	Dipeptidyl peptidase-4
FDA	Food and Drug Administration
GEF	Guanine nucleotide exchange factors
GIP	Glucose-dependent insulinotropic polypeptide
GLP	Glucagon-like peptide
GLP-1 RA	Glucagon-like peptide 1 receptor agonist
GOLD	Gp online Data
HbA1c	Glycosylated hemoglobin a1c
HR	Hazard ratio
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	Major adverse cardiovascular events
NHS	National health service
PI3K	Phosphoinositol-3-kinase
PKA	Protein kinase A
PKC	Protein kinase C
RCT	Randomized controlled trial
SAVOR-TIMI	Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction
SGLT-2	Sodium-glucose cotransporter-2
SNOMED-CT	Systematized Nomenclature of Medicine – Clinical Terms
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects With Type 2 Diabetes
TZD	Thiazolidinedione
UK	United Kingdom
US	United States

Chapter 1. Introduction

1.1 Overview

Type 2 diabetes is a highly prevalent disease accounting in 2019 alone for more than 90% of the 463 million patients living with diabetes,[1] and 1.5 million excess deaths.[2] In Canada, it is one of the fastest-growing diseases, with 2.3 million individuals living with this condition.[3] Type 2 diabetes results in increased mortality, morbidity, and healthcare costs compared with the general population.[4] It is characterized by the increasing resistance of body tissues to the effects of the hormone insulin and eventual pancreatic dysfunction. [5] This leads to a state of persistent hyperglycemia,[6] which increases the risk of micro- and macro-vascular complications involving various body organs.[7] However, with better control of vascular complications, cancer has become a leading cause of death among patients with diabetes.[8 9]

Type 2 diabetes has been associated with an increased risk of several cancers, including those of the pancreas, biliary tract, breast, colon, and endometrium.[10] Proposed biological mechanisms explaining these associations include persistent disruption of the insulin/insulin-like growth factor (IGF) axis,[11 12] hyperglycemia,[13] and a chronic pro-inflammatory state due to increased levels of mitogenic cytokines.[14] Yet, a number of studies examining this association had significant, conclusion altering biases.[15 16] Moreover, many of these studies are old.[16] Consequently, whether the strength of association between diabetes and cancer has changed in recent years, with advent of new drug classes and altering levels of cancer risk factors in the population, is unclear. In particular, the association between diabetes and skin cancers is understudied, despite skin cancer related safety signals associated with novel antihyperglycemic agents such as incretin-based drugs.[17]

Incretin-based drugs (GLP-1 RAs and DPP-4 inhibitors) are together the most commonly used second-to-third line antihyperglycemic drugs in the treatment of type 2 diabetes mellitus.[18] These drugs have been shown to lower blood glucose levels without causing hypoglycemia while having either weight neutral (DPP-4 inhibitors) or weight-lowering effects (GLP-1 RAs).[19] GLP-1 RAs have also been shown to provide cardiorenal benefits in patients with diabetes.[19] However, with accumulating evidence from pre- and post-approval randomized controlled trials and increasing real-world use, previously unanticipated benefits and safety concerns regarding these drugs have emerged, including their association with melanoma and nonmelanoma skin cancer.[20]

For GLP-1 RAs, concerns about an association with skin cancer began when in a cardiovascular outcome trial of liraglutide, a GLP-1 RA,[17 21] the liraglutide group had a 159% higher risk of melanoma (hazard ratio [HR] 2.59, 95% confidence interval [CI] 0.92-7.27) and 25% higher risk of nonmelanoma skin cancer (HR 1.25, 95% CI 0.90-1.75), compared with placebo.[17 21] Notably, in lagged analysis excluding early events in the first year of follow-up, the risk of melanoma with liraglutide became 10-fold (HR 10.95, 95% CI 1.41-84.82). With respect to the DPP-4 inhibitor randomized controlled trials,[12] the only trial to report on skin cancer events revealed no imbalance with saxagliptin in the incidence of melanoma (HR 1.33, 95% CI 0.62-2.98), or of nonmelanoma skin cancer (HR 1.03, 95% CI 0.75-1.40), compared with placebo.[13] On the other hand, in a meta-analysis of 115 DPP-4 inhibitor trials found a 15% reduced odds of skin neoplasms (HR 0.85, 95% CI 0.72-0.99) with DPP-4 inhibitor use.[22] However, none of these studies were individually designed or powered to assess skin cancer as a safety endpoint. Indeed, even the largest incretin-based drug trials lacked generalizability to the diabetes population at large given the selective recruitment of patients at high risk of

cardiovascular diseases,[14] had relatively small sample sizes, and had short median durations of follow-up.[23] Furthermore, the reporting of skin cancer events was inconsistent across randomized controlled trials, with only three of the 12 long-term randomized controlled trials of incretin-based drugs reporting on skin cancer events. However, given the role of the GLP-1 hormone and the DPP-4 enzyme in regulating mitogenic pathways within skin cells,[24-27] the imbalances in skin cancer events observed in the incretin-based drug trials merit focused investigation.

On a population level, the high prevalence of diabetes and the increasing levels of mortality and morbidity from cancer that patients with diabetes suffer have become a public health emergency and need methodologically sound investigations. In particular, the association of skin cancer, the most common form of human cancer,[28] with diabetes itself, as well as commonly used antihyperglycemic agents such as incretin-based drugs, remains understudied. Thus, there is a need for well-designed real-world studies with long-term follow-up to investigate existing gaps in the understanding of the diabetes-cancer association, and the association between incretin-based drugs and skin cancer among patients with type 2 diabetes.

1.2 Research Objectives

The primary goal of this doctoral thesis was to address the gaps in knowledge regarding the diabetes-cancer association and the risk of skin cancer among users of incretin-based drugs. The specific objectives were:

1. To examine the incidence of cancer overall and site-specific cancers among patients with type 2 diabetes compared with individuals in the non-diabetic population.

2. To determine whether use of DPP-4 inhibitors, compared with use of sulfonylureas, is associated with the incidence of melanoma and nonmelanoma skin cancer among patients with type 2 diabetes.

3. To determine whether use of GLP-1-RAs, compared with use of sulfonylureas, is associated with an increased risk of melanoma and nonmelanoma skin cancer among patients with type 2 diabetes.

1.3 Thesis organization

This manuscript-based thesis contains seven chapters. Chapter 1 describes the overall rationale and objectives of this thesis. Chapter 2 is a detailed review of literature examining the current evidence on the diabetes-cancer association as well as the evidence on the use of incretin-based drugs (DPP-4 inhibitors and GLP-1-RAs) and the risk of skin cancer. Chapter 3 presents details on UK Clinical Practice Research Datalink (CPRD), the data source used for all three manuscripts, and additional details on the methodologies used in subsequent chapters. Chapters 4 through 6 are manuscripts that address each thesis objective listed in section 1.2. Chapter 4 examines the burden of cancer overall and 22 site-specific cancers, including skin cancer, among

patients of type 2 diabetes between 1988 through 2019 in the UK. Chapter 5 is an observational cohort study addressing whether DPP-4 inhibitor use is associated with the incidence of skin cancer compared to sulfonylurea use. Chapter 6 is an observational cohort study on the skin cancer safety of GLP-1 RAs compared to sulfonylureas. Finally, Chapter 7 summarizes the findings of the three manuscripts and provides a general discussion on the clinical implications and future directions. The references for the three manuscripts are listed in their corresponding chapters, while the remainder of the thesis has a general reference list at the end of this thesis.

Chapter 2. Literature review

2.1 Epidemiology of type 2 diabetes

The global burden of type 2 diabetes, a disease subtype constituting more than 95% of the disease load of diabetes worldwide, has increased substantially over the past decades.[29] Compared with 2000, when an estimated 151 million individuals worldwide were living with diabetes,[30] the case load is estimated to be 463 million in 2019,[30] signifying a tripling of the prevalence.[31] The number is expected to rise to 642 million by 2040, with most new cases predicted to occur in low- and middle-income countries.[32 33] In 2019, diabetes was the ninth leading cause of death,[34] was associated with 4.2 million deaths,[35] and was the direct cause responsible for 1.5 million deaths.[29] The International Diabetes Federation estimated that diabetes related health costs worldwide amounted to US$760 billion in 2019.[1] In Canada, type 2 diabetes is one of the fastest-growing diseases, with 2.3 million individuals living with this condition in 2017.[3] Type 2 diabetes is associated with high morbidity and mortality, and because of its costs to the healthcare system ($16 billion annually in Canada), it has been dubbed an "economic tsunami."[4]

2.2 Pathophysiology and complications of type 2 diabetes

Type 2 diabetes has a complex and multifactorial etiology.[36] The primary cause of development of type 2 diabetes is the inability of tissues to respond to the pancreatic hormone insulin, thus resulting in an inability of the tissues to metabolize blood sugar, raising the blood sugar.[36 37] In response to this tissue insulin resistance, there is a dysfunction of the beta cells of pancreas which are responsible for insulin secretion: initially the pancreas secretes excess insulin to compensate for the insulin resistance.[38] In later stages of the disease, however, there is fatigue of the beta cells, eventually resulting in the failure to secrete adequate insulin.[39] These parallel

pathophysiological processes, insulin resistance and beta cell dysfunction, are promoted because of multiple underlying factors, including obesity, lack of physical activity, genetic predisposition, inflammation, and imbalance in gut microbiota.[37 40 41] Once developed, the pathological changes accompanying type 2 diabetes are perpetuated by multiple pathways, including glucotoxicity and adipotoxicity on a systemic level, and oxidative stress, mitochondrial dysfunction, and epigenetic changes at a cellular level.[37]

Hyperglycemia, or high blood sugar, is a cardinal feature of diabetes, and is used to diagnose the disease. A diagnostic of diabetes can be made if any of the following criterion are met: 1. plasma glucose ≥126 mg/dL after fasting of at least 8 hours, 2. plasma glucose ≥200 mg/dL after 2 hours of orally taking 75 g anhydrous glucose dissolved in water, 3. the patient exhibiting classical symptoms of hyperglycemia and has a random plasma glucose ≥200 mg/dL, 4. glycated hemoglobin (HbA1c), which represents glycemic control over past three months, ≥6.5%.[42] The clinical symptoms of type 2 diabetes itself are often late to develop, and include polyphagia, polydipsia, and polyuria.[36] However, the clinical course is complicated by the development of microvascular, macrovascular, and nonvascular complications, which are responsible to the mortality and morbidity associated with type 2 diabetes.[36 43] The microvascular complications, which involve the small blood vessels, include retinopathy, nephropathy, and neuropathy.[36 43] In contrast, large vessels are involved in microvascular complications, which manifest as coronary heart disease, peripheral arterial disease, cerebrovascular disease.[36 43] Nonvascular complications include infections, dermatological changes, increased risk of dementia.[36 43] Furthermore, type 2 diabetes is associated with an increased risk of several types of cancer and cancer overall.[44]

2.3 Management of type 2 diabetes

Overall goals of management of type 2 diabetes are threefold: controlling hyperglycemia and its symptoms, preventing or treating long-term complications of diabetes, and enabling the patient to achieve a lifestyle as normal as possible.[36] The treatment usually involves a team of an endocrinologist/diabetologist, a diabetes educator, a nutritionist, a psychologist, and a social worker. Alongside, subspecialists including ophthalmologists, neurologists, nephrologists, podiatrists, cardiologists, and cardiovascular surgeons may be involved when complications arise.[36 45] Glycemic aims in type 2 diabetes management in non-pregnant adults include a glycated hemoglobin value of <7%, fasting blood glucose of 80-130 mg/dl, and postprandial blood glucose of <180 mg/dl.[36] Treatment options include a range of lifestyle interventions including diet, physical activity and psychosocial care. Pharmacological strategies include both oral and injectable medications.

2.4 Lifestyle changes

Medical nutrition therapy, or the approach to manage caloric intake with medications, exercise, and weight loss, is a cornerstone of diabetes therapy.[46 47] While the exact percentages of fat, carbohydrate, and protein in the diet requires individualization, the general advice is for modest caloric intake, using low-fat, low-carbohydrate, high-fiber food patterns.[48] Increasing physical activity has multiple benefits, including reducing blood glucose levels, blood pressure, and cardiovascular risk.[47 49] The recommended level of physical activity is 150 minutes/week of moderate aerobic exercises.[36] However, to avoid exercise induced hypoglycemia precautions such as monitoring of blood glucose before exercise, ingesting carbohydrate before exercise, and adjusting insulin doses should be considered.[36] Nuancing the psychosocial care to fit the specific situations and needs of the patients should be sought, with particular attention to development of

depression, anxiety, and eating disorders.[50] Generally, lifestyle changes such as medical nutrition therapy and exercise are the initial strategies for glucose reduction in patients with type 2 diabetes, upon the failure of which after 3-6 months, pharmacological management is considered.[36]

2.5 Pharmacological agents in type 2 diabetes

Several classes of anti-hyperglycemic agents are used in type 2 diabetes.

2.5.1 Biguanides

Metformin is the representative, and only approved, medication of the drug class biguanides.[51] It was approved by the United States (US) Food and Drugs Administration (FDA) for the treatment of type 2 diabetes in 1994.[52] The mechanism of action of this drug involves lowering of hepatic glucose production as well as increasing insulin sensitivity by better peripheral utilization of glucose.[36 51] There is some evidence that metformin produces these actions by inhibiting cyclic adenosine monophosphate generation in liver and intestinal cells.[36 51] It is highly efficacious in blood glucose reduction, resulting in a 1-2% reduction in HbA1c.[51] Long term, it reduces the risk of micro- and macrovascular outcomes as well as all-cause mortality.[53] Further advantages of this medication are its weight neutrality, and ability to cause weight loss among some. Finally, metformin does not cause glucose reduction when the patient is normoglycemic, thus having a low risk of hypoglycemia.[51] It is widely considered as the first-line treatment for type 2 diabetes, started after failure of lifestyle management alone when HbA1C is <9% and in combination with other agents when HbA1C is ≥9%.[36 42 46 51]

Being one of the earliest oral hypoglycemic agents approved, metformin enjoys the benefit of wide clinical experience. It is a relatively safe drug, with the most common side effects

being gastrointestinal disturbance (nausea, diarrhea, abdominal cramps or bloating).[36 51] It has also been associated with vitamin B12 deficiency. [36 51] While the most serious side effect of metformin is thought to be lactic acidosis,[36 51] recent analyses raise doubts as to whether the association is causal.[54 55] Contraindications for therapy with metformin include renal insufficiency, planned use of radiocontrast agents, and acidosis.[36 51]

2.5.2 Sulfonylureas

Sulfonylureas are one of the most common classes of glucose lowering agents used worldwide, comprising the rarely used first generation drugs (tolbutamide, tolazamide, and chlorpropamide) and the second-generation drugs (glyburide, glipizide, and glimepiride).[18 56-58] Sulfonylureas depolarize beta cells of pancreas by inhibiting K_{ATP} channel, leading to insulin secretion acutely.[36 51] Though the insulin level decline on chronic sulfonylurea administration, blood glucose levels are maintained. [51] The decrease in insulin secretion on chronic administration is thought to be due to beta cell failure.[59] Proper selection leads to 50-70% patients responding to these drugs, with all members of the class equally efficacious, resulting in 1-2% HbA1c reduction.[51] Differences in individual members of the class are in the pharmacokinetic properties, including duration of action.[51] Key advantages of this class are wide clinical experience, and wide accessibility due to low costs.

Important disadvantages are the risk of severe hypoglycemia, including coma.[36 51] These drugs also cause weight gain (1-3 kgs).[36 51] Rarer side effects include nausea, vomiting, agranulocytosis, and dermatological reactions. These drugs also may be associated with a higher cardiovascular mortality.[60] Contraindications of these drugs include pregnancy, lactation, hepatic and renal insufficiency.[36 51]

2.5.3 Meglitinides

Meglitinides, repaglinide and nateglinide, also promote insulin secretion by inhibiting K_{ATP} channels on pancreatic beta cells.[36 51 61] Due to their short duration of action, they are usually administered prior to meals to deal with postprandial glucose excursions.[36 51] Hypoglycemia is the major side effect of these drugs, though nateglinide may cause it less frequently than other insulin secretagogues.[36 51] Failure of insulin secretion after beta cell fatigue also occurs with these agents. Dosing of repaglinide and nateglinide should be titrated in renal and hepatic insufficiencies respectively.[36 51 61]

2.5.4 Alpha glucosidase inhibitors

These drugs, including acarbose, miglitol, and voglibose, inhibit conversion of oligosaccharides in the meal to simpler carbohydrates, thus reducing carbohydrate absorption in the gastrointestinal tract and postprandial glycemic surge. [36 51 62] Given the contribution of postprandial glucose rise to the hyperglycemic state in type 2 diabetes, before meal administration of alpha glucosidase inhibitors can produce modest reduction in blood glucose.[36 51] Treatment with this class is contraindicated in inflammatory bowel disease and with high serum creatinine.[36 51] Combining these agents with others such as sulfonylurea may precipitate hypoglycemia, which should be dealt with simple instead of complex carbohydrates. [36 51]

2.5.5 Thiazolidinediones

Thiazolidinediones, pioglitazone and rosiglitazone, bind to peroxisome proliferator activated receptor (PPARγ), nuclear hormone receptors mainly expressed in adipose and skeletal tissues, that regulate glucose and lipid metabolism.[36 51] As a result of PPARγ activation, there is an increased insulin sensitivity, enhancing glucose uptake by 30-50%.[36 51 63] Thiazolidinediones

also reduce hepatic neoglucogenesis and reduce plasma fatty acids. These drugs reduce HbA1c by 0.5-1.4% but increase low density lipoprotein levels.[36 51 64]

Recently, however, the use of thiazolidinediones has reduced considerably due to several safety-concerns.[65 66] The most common side effect of these drugs is weight gain, an average of 2-4 kilos in the first year of use, due to an increase in adiposity.[36 51] Moreover, there is dose related fluid retention and reduction in hematocrit. Fluid retention may be linked to the propensity of thiazolidinediones to cause peripheral edema and congestive heart failure.[36 51] Though there were past signals of increase of myocardial infarction risk with rosiglitazone,[67] this risk has not been substantiated in recent analyses.[68] Importantly, pioglitazone has been associated with an increased risk of bladder cancer.[69] Contraindications of this drug class includes hepatic insufficiency and congestive heart failure.[36 51]

2.5.6 Sodium-glucose cotransporter 2 inhibitors

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are a novel class of anti-hyperglycemic drugs that target the Na+-glucose cotransporter located in proximal tubules.[36 51 70] By inhibiting these molecules, SGLT-2 inhibitors stop glucose reabsorption, lower renal glucose threshold from 180 to 50 mg/dL and result in urinary excretion of both glucose and sodium.[36 51] Thus, these drugs not only reduce HbA1c by about 0.7-1%, but they also lead to a weight loss of 2-4 kgs, and a reduction in blood pressure by 3-6 mmHg. [36 51] Due to an increase in urinary glucose, there is also a higher risk of urinary and genital infections among recipients. [36 51 71] Hypotension is sometimes precipitated in older patients.[36 51 71] Although these drugs do not themselves precipitate hypoglycemia, in combination with other drugs they can.[36 51 71] Other side

effects include a potential increase in the risk of lower limb amputation with canagliflozin among elderly patients with cardiovascular risk factors.[72]

A major advantage of these agents is that they have been consistently shown to reduce cardiovascular events and cardiovascular mortality among those with cardiovascular risk factors.[73 74] As well, they have been shown to reduce progression of chronic kidney disease.[74 75] However, their use is contraindicated in advanced kidney disease.[36 51]

2.5.7 Incretin-based drugs

Incretins are gastrointestinal peptides that stimulate insulin release in response to food.[76] Glucose-dependent insulinotropic polypeptide (GIP), secreted from the K-cells of the proximal small intestine, and glucagon-like peptide-1 (GLP-1), secreted from the L-cells of the distal small intestine and colon, are the two best characterized incretins and are responsible for the "incretin effect": a phenomenon whereby glucose ingested orally elicits a stronger insulin surge than an isoglycemic glucose infusion delivered intravenously.[77 78] In health, GLP-1 and GIP are released when carbohydrate food comes in contact with the K- and L-cells of the intestine respectively, and are rapidly metabolized by the enzyme dipeptidyl peptidase after release.[76 79] However, in patients with type 2 diabetes, with a lower efficacy of GIP to incite the incretin effect and a lower secretion of GLP-1 (whose efficacy to incite the incretin effect is maintained in diabetes),[51] the net incretin effect is reduced, resulting in suboptimal insulin release in response to nutrients.[76] Thus, GLP-1, which is secreted at a lower level in patients with type 2 diabetes but whose efficacy to bring about incretin effect is maintained,[80] has become an important therapeutic target. Two major ways to enhance the effect of GLP-1 have been successful therapeutic strategies in type 2 diabetes: first, by decreasing the dipeptidyl peptidase-4

mediated metabolism of released GLP-1 by dipeptidyl peptidase-4 (DPP-4) inhibitors, and second, by stimulating the GLP-1 receptors on cells by molecules similar to endogenous GLP-1, called GLP-1 receptor agonists. Together they constitute incretin-based drugs.[51]

Indeed, the treatment landscape for type 2 diabetes has changed significantly since the mid-2000s, with the introduction of the incretin-based drugs.[81] Incretin-based drugs (first approved in Canada in 2005 and in the UK in 2007) are now well-established as standard second-to-third line antihyperglycemic drugs.[46] The mechanisms of action mentioned above enable these novel antihyperglycemic drugs to lower blood glucose levels without causing hypoglycemia.[82 83] Moreover, they are either weight neutral (DPP-4 inhibitors) or induce weight loss (GLP-1 RAs) and demonstrate cardiovascular safety.[83-85] Additionally, some GLP-1 RAs have been shown to reduce the risk of cardiovascular events and offer renal protection.[19] Key long-term cardiovascular outcome trials examining cardiovascular safety and benefits of incretin-based drugs are listed in **Table 2.1.** As a result of these clinical benefits, the incretin-based drugs together are the most commonly used second-to-third line antihyperglycemic drugs today, replacing older drugs such as sulfonylureas and thiazolidinediones.[18 19]

2.5.7.1 Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase is a widely expressed serine protease present as an ectoenzyme on endothelial cells and lymphocytes, as well has a circulating form.[51] It cleaves the N-terminal amino acids from peptides with proline or alanine in the second position, and thus metabolizes a wide range of peptide molecules.[36 51] However, it is essential for the degradation of GLP-1 and GIP, whose bioavailability increases substantially in presence of DPP-4 inhibitors.[36 51] Among the approved DPP-4 inhibitors, alogliptin, linagliptin, and sitagliptin are inhibit the enzyme

Table 2.1 Summary of cardiovascular outcome trials conducted on DPP-4 inhibitors and GLP-1 RAs

Trial, publication year	Study drug (n)	Comparator (n)	Median follow-up (years)	MACE, HR (95% CI)
DPP-4 inhibitors				
EXAMINE,[86] 2013	Alogliptin (n= 2701)	Placebo (n=2679)	1.5	0.96 (UL: 1.16)
SAVOR-TIMI 53,[87] 2013	Saxagliptin (n = 8280)	Placebo (n = 8212)	2.1	1.00 (0.89-1.12)
TECOS,[88] 2015	Sitagliptin (n = 7332)	Placebo (n = 7339)	3.0	0.98 (0.89-1.08)
CARMELINA,[89] 2018	Linagliptin (n = 3494)	Placebo (n = 3485)	2.2	1.02 (0.89-1.17)
CAROLINA,[90] 2018	Linagliptin (n = 3023)	Glimepiride (n = 3010)	6.3	0.98 (0.84-1.14)
GLP-1 RAs				
LEADER,[91] 2015	Liraglutide (n = 4668)	Placebo (n = 4672)	3.8	0.87 (0.78-0.97)
ELIXA,[92] 2015	Lixisenatide (n = 3034)	Placebo (n = 3034)	2.1	1.02 (0.89-1.17)
SUSTAIN-6,[93], 2016	Semaglutide (n = 1648)	Placebo (n = 1649)	2.1	0.74 (0.58-0.95)
EXSCEL,[94] 2017	Weekly exenatide (n = 7356)	Placebo (n = 7396)	3.2	0.91 (0.83-1.00)
HARMONY,[95] 2018	Albiglutide (n = 4731)	Placebo (n = 4732)	1.6	0.78 (0.68-0.90)
REWIND,[96] 2018	Dulaglutide (n = 4949)	Placebo (n = 4952)	5.4	0.88 (0.79-0.99)
PIONEER-6,[97] 2018	Oral semaglutide (n = 1591)	Placebo (n = 1592)	1.3	0.79 (0.57-1.11)

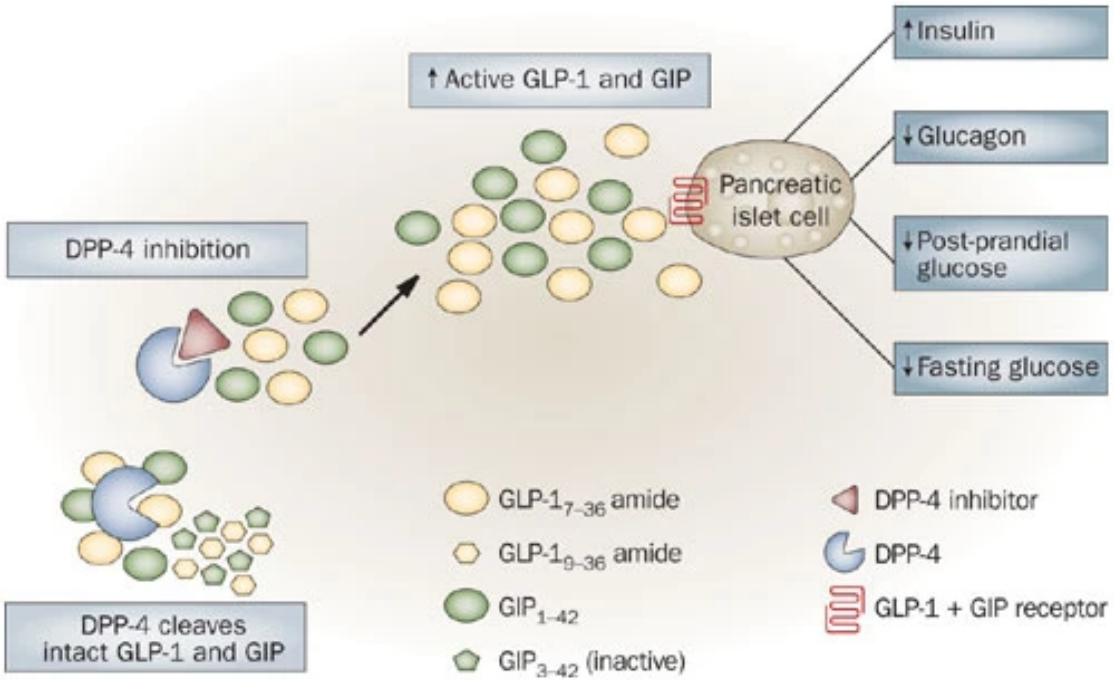
Abbreviations: DPP-4, dipeptidyl peptidase-4; CI, Confidence interval; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HR, Hazard ratio; MACE, major adverse cardiovascular event.

competitively, while saxagliptin and vildagliptin bind with it covalently, all lowering DPP-4 activity to more than 95% for 12 hours in tolerable doses and causing a 2-fold increase in the plasma level of GLP-1 and GIP, which is associated with an increase in insulin level, which seems to be the primary mechanism of glucose reduction by DPP-4 inhibitors (**Figure 2.1)**.[36 51] Overall, chronic treatment with DPP-4 inhibitors reduce the HbA1c by about 0.8% as monotherapy. When added to other antihyperglycemic agents, it additively reduces blood sugar by about 0.5%.[36 51] The primary mode of excretion of alogliptin, saxagliptin, sitagliptin, and vildagliptin is renal, thus requiring dose adjustment in renal insufficiency, while linagliptin is cleared through the hepatobiliary system, and thus can be used without dose adjustment in renal insufficiency.[36 51]

Apart from blood glucose reduction, DPP-4 inhibitors do not increase body weight with chronic treatment and have been found to have cardiovascular safety. [36 51 98] Allergic reactions, including anaphylaxis, angioedema, and Stevens Johnson syndrome, and joint pains have been reported as side effects.[36 51] The association of DPP-4 inhibitors with acute pancreatitis remains uncertain.[99] Importantly, DPP-4 is also a highly immunologically active molecule, with expression on multiple immunologic cells, including T lymphocytes.[100] This immunological activity of DPP-4 when inhibited long-term, can produce side effects. For example, DPP-4 inhibitors have been associated with skin autoimmune diseases such as bullous pemphigoids,[101] [102] and gastrointestinal autoimmune disorders such as inflammatory bowel disease.[103] Also, given the widespread expression of the DPP-4 molecule and that it cleaves peptides beyond incretins,[51] several off-target beneficial effects of DPP-4 inhibitors have been hypothesized,

including in the prevention/treatment of several cancers,[104] including rectal cancer and melanoma.[100 105]

Figure 2.1 The mechanism of action of DPP-4 inhibitors



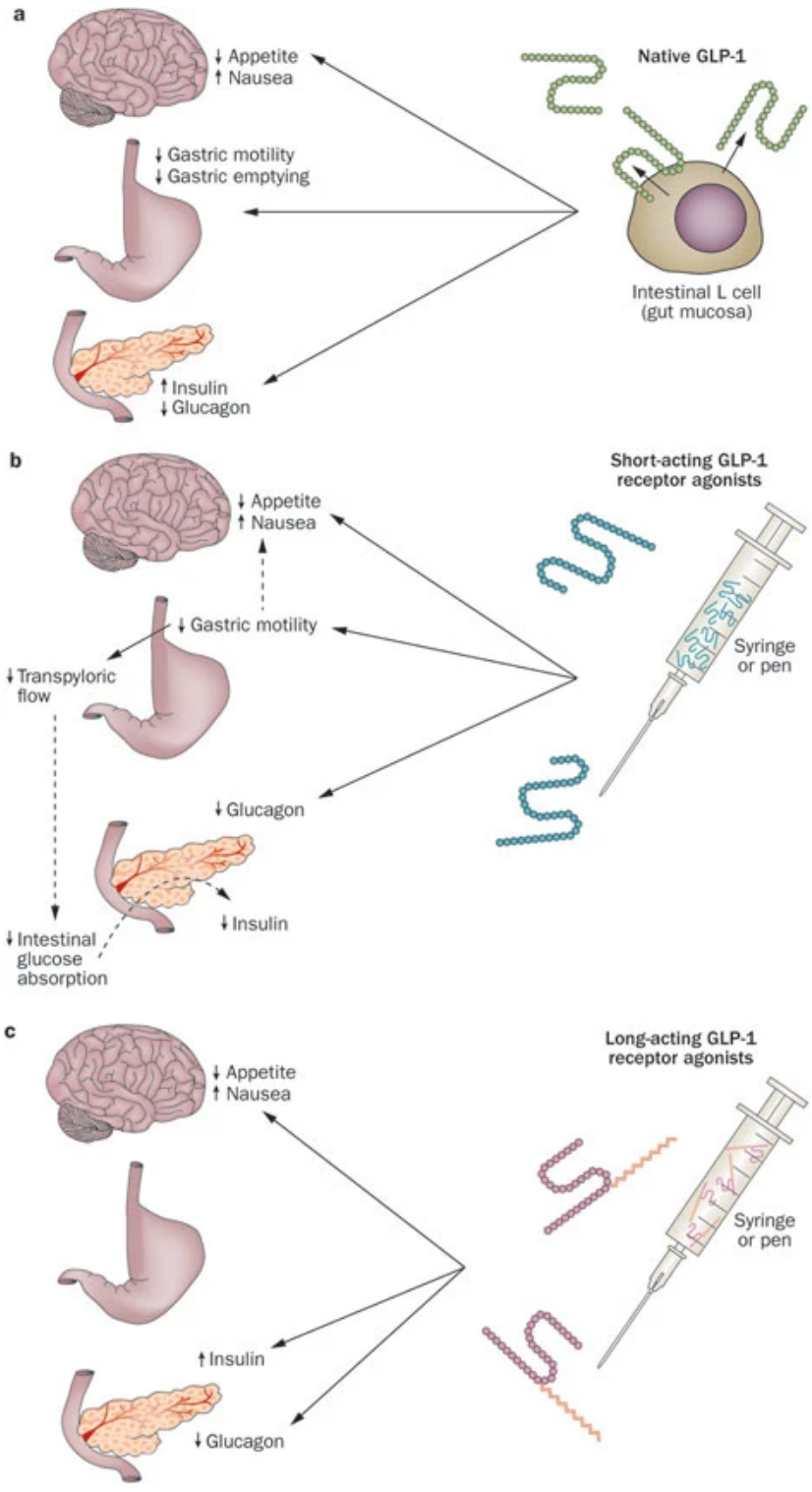
Reprinted with permission from Nature Reviews Endocrinology[106]

2.5.7.2 Glucagon like peptide-1 receptor agonists

Endogenous GLP-1 is rapidly metabolized by the DPP-4 enzyme, resulting in a half-life of 1-2 minutes, and thus is not useful as a therapeutic agent.[51] However, several GLP-1 RAs which are structurally similar to endogenous GLP-1 and thus can stimulate GLP-1 receptors, but are resistant to DPP-4 mediated degradation, have been approved for treatment in type 2 diabetes.[36 51] Approved GLP-1 RAs include exenatide (synthetic exendin-4, derived from saliva of Gila monster, with 50% homology with GLP-1), lixisenatide (another exendin-4 analog with 53% homology), liraglutide (97% homology, DPP-4 resistance due to fatty acid side chain), dulaglutide (90% homology, stabilization by linking to human immunoglobulin), albiglutide

(97% homology, stabilization by binding two GLP-1 moieties to albumin), semaglutide (94% homology, stabilization by linking amino acid modification and linking with fatty acid).[107 108] Among these, exenatide is available as twice daily and a weekly preparation, liraglutide and lixisenatide are once daily preparations, and dulaglutide, albiglutide, and semaglutide are once weekly preparations.[109] All are available as subcutaneous injections, although an oral preparation of semaglutide which undergoes gastric absorption to avoid intestinal degradation, has recently been approved.[109 110] All GLP-1 RAs stimulate the GLP-1 receptor (**Figure 2.2)**, which are expressed in beta cells of pancreas, but also in the central nervous system, cardiovascular system, kidney, and lung.[51] Stimulation of the GLP-1 receptors result in activation of multiple signaling pathways, including cAMP-PKA, GEFs, PKC, and PI3K pathways.[36 51] In the pancreatic beta cells, this leads to increased production and exocytosis of insulin. GLP-1 RAs result in the reduction of HbA1c by 0.5-1%.[36 51] Notably, beyond glycemic control, several GLP-1 RAs have been shown to have additional benefits, including weight reduction for all GLP-1 RAs, cardiovascular benefits for liraglutide, dulaglutide, albiglutide, and semaglutide, and renal benefits for liraglutide, dulaglutide, and semaglutide.[36 74] However, many GLP-1 RAs, including exenatide and lixisenatide, have significant renal clearance and thus are contraindicated in end stage renal disease.[36 51] Also, because of their expression on thyroid C cells, they are contraindicated in medullary carcinoma of the thyroid.[36 51] The most common side effects of these drugs are dose-dependent gastrointestinal upset (nausea, vomiting, diarrhea), which abates with time.[36 51] However, rarer but serious adverse associations include pancreatitis,[36 51] cholangiocarcinoma,[111] and anaphylaxis. [112]

Figure 2.2 Mechanism of action of GLP-1 and GLP-1 receptor agonists



Reprinted with permission from Nature Reviews Endocrinology[113]

2.5.8 Insulin

Replacement of insulin through exogenous delivery of the drug has been an important strategy in the treatment of both type 1 and type 2 diabetes.[114 115] In type 2 diabetes, insulin therapy is usually used in advanced disease when the body is no longer able to produce insulin: indeed, almost every type 2 diabetes patient will eventually need insulin therapy.[116] However, it can be used at any stage of the disease if the blood sugar is extremely high, those with severe weight loss, those with renal or hepatic diseases where oral antihyperglycemics may be contraindicated, and in hospitalized or acutely ill patients.[36 51] Several advantages of insulin therapy, including ability to lower blood glucose to any extent and smooth and predictable glucose control makes insulin particularly suitable for acute usage.[36 51] However, important side effects of the drug include hypoglycemia in relative overdosage, weight gain, and potential association with cancers in chronic usage.[36 51 117-119] Allergic reactions to insulin and insulin tolerance were earlier side effects of animal sourced insulin but are rarely encountered today with the widespread use of human insulin and insulin analogs.[120] As daily, long-term therapy, the ideal way to replace insulin is to be able to mimic physiological secretion of insulin throughout the day. [36 51] This need has led to the availability of insulin in short-acting forms (regular insulin, lispro, aspart, glulisine) for postprandial glycemia control, and long-acting forms (NPH, glargine, detemir, and degludec) for basal insulin replacement. [36 51] In certain type 2 diabetes patients, insulin infusion devices may be considered.[36 51]

In summary, a wide range of pharmacological therapies exist in type 2 diabetes, with specific advantages and disadvantages of each drug class (**Table 2.2)**, calling for personalization of the therapy.[36 51]

Table 2.2 Summary of the different anti-hyperglycemic drug classes

Drug Class	Route of Administration	Mechanism of Action	Advantages	Disadvantages
Metformin	Oral	Reducing hepatic gluconeogenesis	No hypoglycemia or weight gain, cardiovascular benefits, inexpensive	Gastrointestinal adverse effects, vitamin B12 deficiency, potential link with lactic acidosis
Sulfonylureas	Oral	Insulin secretion from pancreatic beta cells	Inexpensive, wide experience	Hypoglycemia, weight gain, potential link with adverse cardiovascular events
Meglitinides	Oral	Insulin secretion from pancreatic beta cells	Short duration of action enables its use to control postprandial glucose excursions	Hypoglycemia, weight gain
Alpha-glucosidase inhibitors	Oral	Reducing carbohydrate absorption in the gastrointestinal tract	No hypoglycemia or weight gain	Gastrointestinal adverse effects
Thiazolidinediones	Oral	Increased insulin sensitivity	Inexpensive, no hypoglycemia	Weight gain, edema, potential associations with bladder cancer and fractures

SGLT-2 inhibitors	Oral	Preventing glucose reabsorption in renal proximal tubules	No hypoglycemia, weight loss, associated with cardiorenal benefits	Genital and urinary tract infections, potential associations with lower extremity amputations
DPP-4 inhibitors	Oral	Increasing levels of biologically active GLP-1, which in turn causes glucose dependent insulin secretion from pancreatic beta cells	No hypoglycemia or weight gain, cardiorenal safety	Allergic reactions, joint pain, bullous pemphigoid
GLP-1 RAs	Parenteral (except for oral semaglutide)	Glucose dependent insulin secretion from pancreatic beta cells	No hypoglycemia, weight loss, associated with cardiorenal benefits	Gastrointestinal adverse effects, administered through injections, potential link with pancreatic side effects
Insulin	Parenteral	Increasing glucose uptake in tissues	Smooth and predictable glucose control, reduces the risk of microvascular complications	Hypoglycemia, weight gain, administered through injections, potential link with cancers

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; SGLT-2, sodium-glucose cotransporter 2

2.6 Type 2 diabetes and cancer

Traditionally, a major goal of treatment of type 2 diabetes, beyond reduction of surrogate markers such as blood glucose and HbA1c, has been to reduce the incidence and manage the macro and microvascular complications of diabetes.[36 51] These efforts have been relatively successful, with reduction in the death rates from cardiovascular diseases among patients with diabetes over the last four decades.[121 122] However, as a result, cancer has overtaken cardiovascular diseases as the leading cause of death among type 2 diabetes patients in many countries including the United Kingdom,[8] with similar trends in other countries such as Australia and Japan.[9 122] This highlights the need to better understand the association between diabetes and cancer.[10]

Indeed, cooccurrence of diabetes and cancer has been reported for more than 50 years, with a link found in population-based studies in the 1960s.[10] Over the years, several observational studies have examined the association between diabetes and different types of cancer to different degrees of certainty.[15 16] The biological basis of such an association has been extensively explored. It is thought that hyperinsulinemia, the body's response to relative insulin resistance of tissues in diabetes, leads to sustained stimulation of insulin receptors and mediates responses to other growth factors such as insulin-like growth factor (IGF).[10] Because cancer cells take up sugar constitutively, and do not need insulin for this purpose unlike noncancerous cells, it is thought that the purpose of insulin receptors on these cells is to promote cell survival.[123] Indeed, activation of the insulin and IGF-1 receptors stimulate multiple signalling pathways that lead to cell proliferation, invasion, and metastasis.[12] Other biological links between diabetes and cancer have also been proposed. For example, the Warburg hypothesis on cancer energetics indicates cancer cells need high amounts of glucose for cancer propagation, something which is

available in diabetes due to the hyperglycemia.[13] It is also hypothesized that diabetes, being a state of chronic inflammation, leads to production of cytokines including interleukin-6, plasminogen activator inhibitor-1, and tumor necrosis factor-alpha, molecules which are involved in carcinogenesis.[14]

However, for at least some of the cancers, the association with diabetes may not be causal.[124] [125] For example, several risk factors common to diabetes and cancer, including body weight, physical activity, alcohol intake, smoking, are often not measured properly in databases, which may lead to inadequate control of confounding.[124] [125] Other sources of bias include detection bias (whereby there is increased diagnosis of cancer due to enhanced contact with the health system after diabetes diagnosis) and reverse causality (particularly in case of pancreatic cancer which causes diabetes due to pancreatic dysfunction).[124] [125] Indeed, one recent meta-analyses of 151 cohorts comprising 32 million people reported that bias analysis for unmeasured confounding strongly suggested that the association between diabetes and cancers of the liver, pancreas, and endometrium was causal; with gallbladder cancer incidence likely; with kidney, colorectal, and thyroid cancer incidence less robust; and with leukemia, prostate, breast, bladder, stomach, ovarian, non-Hogkin lymphoma, melanoma, lung, or esophageal cancer unlikely to be causal.[16] In another umbrella review of meta-analyses, it was found that associations between only six types of cancer: breast cancer, intrahepatic cholangiocarcinoma, colorectal cancer, and endometrial cancer, had relatively low heterogeneity and hints of bias.[15] Importantly, the mortality gap between patients with and without type 2 diabetes is, in fact, higher in cancers with which diabetes is not thought to be etiologically related.[8] Thus accurate assessment of cancer burden in long-term and recent cohorts is an important, but often neglected, goal in research on diabetes-cancer links, beyond causal questions.[126]

The lack of well-conducted assessment of disease burden in diabetes is particularly stark in case of the most common form of human cancer, skin cancer. There is some evidence that patients with type 2 diabetes may be at a higher risk of both melanoma and nonmelanoma skin cancer.[127] [128] As patients with type 2 diabetes already have a significantly lower quality of life than the general population,[129] cancer diagnoses, over and above this, has been shown to disrupt diabetes care, with the rate of diabetic complications up to four times higher in the year following diagnosis.[130] Thus, cancer diagnoses can impart a more significant health burden and reduce the quality of life among these patients.[131] [132] Furthermore, type 2 diabetes has been shown to adversely impact survival among patients with skin cancers, including those diagnosed with nonmelanoma skin cancer.[133]

2.7 Skin Cancer

In Canada, skin cancer represents the most commonly diagnosed malignancy,[134] where its incidence has increased by 38.4% between 1992 and 2011.[135] This cancer can be divided into melanoma and nonmelanoma skin cancer.[28] Melanoma, caused by proliferation of melanocytes,[136] accounts for up to 4% of all skin cancers. It has a relatively poor prognosis, with a 5-year survival rate of 62% for regional disease and 16% for metastasized disease.[28] In Canada, melanoma is responsible for 80% of the deaths from skin cancer. On the other hand, nonmelanoma skin cancers, caused by mostly due to proliferation of keratinocytes,[137] are the most common skin cancer types, classified into basal cell carcinoma (80%), cutaneous squamous cell carcinoma (20%), and other rare variants. Together, they account for 28% of new cancer diagnoses in Canada;[138] one in eight Canadians will develop basal cell carcinoma, while one in twenty will develop squamous cell carcinoma in their lifetimes.[138] While the cure rate of these cancers is excellent (99%), mortality from this cancer continues to be high among individuals of

color, those with low socioeconomic status, and the immunocompromised.[139-141] Furthermore, the healthcare costs associated with the treatment of skin cancer are substantial. Indeed, the economic burden to treat skin cancer in Canada is projected to be nearly one billion dollars in 2031.[142]

2.8 Diabetes and skin cancer

Studies on the association between type 2 diabetes and skin cancer have shown an increased risk of both melanoma[128] and non-melanoma skin cancer.[127] A recent meta-analysis of nine observational studies conducted between 1980 and 2011 found an association between type 2 diabetes and malignant melanoma.[128] In contrast, a more recent study conducted in Taiwan found type 2 diabetes to be associated with non-melanoma skin cancer, but not melanoma.[128] However, these studies had important limitations including sampling from hospital-based cohorts, potential selection bias by looking into the future when selecting controls, and short durations of follow-up. Furthermore, given that the incidence of skin cancers has increased in Canada and worldwide,[135 143] whether the incidence of skin cancer has increased among patients with type 2 diabetes at a higher rate than in the non-diabetic population is a critical question that remains unanswered.

2.9 Incretin-based drugs and skin cancer

Incretin-based drugs, including DPP-4 inhibitors and GLP-1 RAs, have several advantages over other antihyperglycemic agents, including having a low risk of hypoglycemia, being weight neutral or promoting weight loss, and being safe with respect to cardiovascular effects.[46] These advantages have led to an increased use of incretin-based drugs in recent years.[18]

Wider use has also led to hypotheses of opportunities and concerns regarding off-target beneficial and harmful effects, including effects on skin cancer.[105]

2.9.1 DPP-4 inhibitors and skin cancer

2.9.1.1 DPP-4 inhibitors and skin cancer: clinical data

Regarding the DPP-4 inhibitors, clinical trial data on skin cancer is limited. Among the cardiovascular outcome trials, only the SAVOR-TIMI 53 trial of saxagliptin reported skin cancer events (**Table 2.3**). In this randomized controlled trial, no clear imbalance in melanoma events was reported with saxagliptin versus placebo (15/8280 vs. 11/8212, HR 1.33, 95% CI 0.62-2.98) or with nonmelanoma skin cancer (82/8280 vs. 79/8212, HR 1.03, 95% CI: 0.75-1.40).[144] To date, three meta-analyses have reported on the association of DPP-4 inhibitors and skin cancer events. In one, compiling data from 72 trials and 69,087 patients, the skin cancer events were reported under the categories "malignant melanoma", "basal cell carcinoma", and "skin cancer", with risk ratios of 0.87 (95% CI: 0.48–1.59), 0.95 (95% CI: 0.42–2.12), and 1.79 (95% CI: 0.86–3.71), respectively.[145] The other, analyzing 115 randomized controlled trials with 121,961 participants, reported "Skin neoplasm", "Skin benign neoplasm", and "Skin malignant neoplasm", with risk ratios of 0.85 (95% CI: 0 0.72-0.99), 0.46 (95% CI: 0.08-2.66), and 0.86 (95% CI: 0.73-1.00), respectively.[22] In a third meta-analysis of 157 trials, DPP-4 inhibitor use was not associated with melanoma (OR 1.13, 95% CI: 0.73-1.00).[146] Overall, it is important to note that none of the CVOTs or meta-analyses were designed to assess skin cancer as a safety endpoint. Furthermore, skin cancer was not always reported, and when reported, there was heterogeneity in the event adjudication process. Finally, the data in the meta-analyses were not always derived from peer reviewed publications, but often from clinical trial registries, which often have discrepant findings.[147]

2.9.1.2 DPP-4 inhibitors and skin cancer: Biological Plausibility

DPP-4 plays a complex role in skin cancer pathogenesis, both for melanoma and nonmelanoma skin cancer.[148] [149] In healthy melanocytes, DPP-4 is highly expressed. However, its expression is lost early on in the malignant transformation of melanocytes, while its re-expression is associated with reduced differentiation of the cells.[148] It is thought that DPP-4 exerts its anti-invasive effect by forming heterodimers with the fibroblast activation protein-alpha.[148] DPP-4 activity has also been shown to promote stroma formation in melanoma models.[148] Indeed, DPP-4 activity has been shown to be a good diagnostic marker to differentiate between tissue from melanoma and deep penetrating nevi. [148] However, whether these findings are relevant with respect to pharmacological inhibition of the DPP-4 activity with DPP-4 inhibitors is unclear. DPP-4 inhibitor use, in fact, results in enhanced DPP-4 expression early on which soon returns to baseline, with no long-term effect on expression levels.[150] In contrast, pharmacological DPP-4 inhibition leads to activation of a different pathway which has been shown to attract lymphocytes into the skin, leading to increased immune surveillance and tumor rejection.[105] This was shown to occur due to inhibition of DPP-4-mediated degradation of a chemokine called CXCL10 that leads to migration of CXCR3+ lymphocytes into tumor milieu. Of note, DPP-4 inhibitors also enhanced antitumor response of immunotherapy.[105]

On the other hand, the role of DPP-4 in nonmelanoma skin cancer is less well studied, often with contradictory findings.[148] Basal cell carcinoma expressed higher levels of DPP-4 activity compared with noncancerous skin. Contrarily, in cutaneous squamous cell carcinoma, DPP-4 expression was more significant in the peritumoral region compared with the tumoral stroma.[148] Interestingly, CXCR3, upregulated on DPP-4 inhibition, results in proliferation of

keratinocytes.[151] Thus, it is unclear whether CXCR3 infiltrate leads to regression or progression of basal and squamous cell carcinoma.

2.9.2 GLP-1 RAs and skin cancer

2.9.2.1 GLP-1 RAs and skin cancer: clinical data and regulatory concerns

Imbalances in skin cancer incidence were initially reported in a large post-approval cardiovascular outcome trial of GLP-1 RAs (**Table 3**). In the LEADER trial of liraglutide, there was a statistically significant imbalance in investigator-reported skin cancer events with liraglutide versus placebo (96/4668 vs. 68/4672, odds ratio [OR] 1.42, 95% CI 1.03-1.94).[21 152] Although the findings were no longer statistically significant after classifying the adjudicated skin cancer events into the melanoma and nonmelanoma skin cancer subtypes, the imbalance remained, with a numerically elevated number of events with liraglutide versus placebo for both melanoma (13/4668 vs. 5/4672, HR 2.59, 95% CI: 0.92-7.27) and nonmelanoma skin cancer (78/4668 vs. 62/4672, HR 1.25, 95% CI 0.90-1.75).[17] Moreover, a sensitivity analysis excluding skin cancer events in the first year after randomization (to reduce the effect of drug-unrelated prevalent cases and differential detection between groups) led to elevated HRs for both melanoma (11/4599 vs. 1/4601, HR 10.95, 95% CI 1.41-84.82) and nonmelanoma skin cancer (61/4599 vs. 48/4601, HR 1.26, 95% CI 0.87-1.84).[17] A similar pattern was observed in the SUSTAIN-6 trial of semaglutide, but for all skin cancers combined (24/1624 vs. 17/1632, HR 1.41, 95% CI 0.76-2.63).[153] To date, a breakdown by skin cancer subtypes in SUSTAIN-6 has not been published, and publications of other GLP-1 RA cardiovascular outcome trials (exenatide, lixisenatide, dulaglutide, and albiglutide)[95 154-156] did not report on skin cancer events.

Taken together, the available evidence on a possible association between GLP-1 RAs and skin cancer has raised regulatory concerns. In their safety assessment of GLP-1 RAs, the US

FDA classified skin cancer risk as uncertain, particularly with melanoma. [152] Although the US FDA has not issued any formal safety warning regarding skin cancer, this safety issue was raised as a source of concern during the Endocrinologic and Metabolic Drugs Advisory Committee Meeting, which was tasked to consider the final approval of liraglutide.[157] Similarly, the EMA's independent assessment deemed routine pharmacovigilance activity for melanoma insufficient and classified it as an "important potential risk" of GLP-1 RAs, calling for further research on the topic.[20]

2.9.2.2 GLP-1 RAs and skin cancer: Biological Plausibility

Skin cells such as melanocytes and keratinocytes express the GLP-1 receptor.[26 27] Importantly, GLP-1 RAs have been shown to stimulate the phosphoinositol-3-kinase (PI3K)-Akt signaling pathway in both melanocytes[27 158] and keratinocytes.[26] The activation of the PI3K-Akt pathway plays a critical role in the malignant transformation of melanocytes and keratinocytes.[159] GLP-1 RAs also upregulate vascular endothelial growth factor (VEGF) in skin cells.[160] VEGF is a potent promoter of blood vessel formation and has also been linked with multiple cancers, including skin cancer.[71,72] In the case of melanoma and nonmelanoma skin cancer, VEGF promotes carcinogenesis by increasing blood supply to the tumor and by inducing proliferation of skin cells and metastasis.[161 162] However, there is no evidence that these changes lead to proliferation of melanocytes or keratinocytes, or tumorigenesis of melanoma or nonmelanoma skin cancer in vivo.

Table 2.3 Reporting of skin cancer in cardiovascular outcome trials conducted on DPP-4 inhibitors and GLP-1 RAs

Trial, publication year	Skin cancer type, HR (95% CI)
EXAMINE,[86] 2013	Not reported
SAVOR-TIMI 53,[87] 2013	Melanoma: HR 1.33 (95% CI 0.62-2.98) Skin cancer: HR 1.03 (95% CI 0.75-1.40)
TECOS,[88] 2015	Not reported
CARMELINA,[89] 2018	Not reported
CAROLINA,[90] 2018	Not reported
LEADER,[91] 2015	Melanoma: No lag: HR 2.59 (95% CI 0.92-7.27); 1-year lag: HR 10.95 (95% CI 1.41-84.82); 2-year lag: HR 4.97 (95% CI 0.58-42.54) Non-melanoma skin cancer: No lag: HR 1.25 (95% CI 0.90-1.75); HR 1-year lag: 1.26 (95% CI 0.87-1.84); 2-year lag: HR 1.22 (95% CI 0.78-1.90)
ELIXA,[92] 2015	Not reported
SUSTAIN-6,[93], 2016	Skin cancer: HR 1.41 (95% CI 0.76-2.63)
EXSCEL,[94] 2017	Not reported
HARMONY,[95] 2018	Not reported
REWIND,[96] 2018	Not reported
PIONEER-6,[97] 2018	Not reported

Abbreviations: DPP-4, dipeptidyl peptidase-4; CI, Confidence interval; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HR, Hazard ratio

2.10 Knowledge gaps

Millions of patients worldwide are living with diabetes. As overall mortality in this population decreases, patients are more prone to develop cancer, which has often been causally linked with diabetes. However, studies examining the burden of cancer in diabetes, specifically skin cancer, are dated and methodologically limited. Moreover, several unanswered questions regarding the diabetes-cancer association remain unanswered, including whether there has been any change in the burden of cancer diagnoses in recent years, and what the risk of multiple cancers is in patients with diabetes. The uncertainties regarding diabetes-skin cancer link are particularly concerning given the recent safety signals concerning the most commonly used second-to-third line therapy, incretin-based drugs, with skin cancer. While an randomized controlled trial assessing the association between incretin-based drugs and skin cancer would provide the most definitive results, such a trial would require a large sample size (>100,000 patients) and a prolonged follow-up (>5 years). As such, it would be prohibitively expensive and raise important ethical concerns given the known clinical benefits of incretin-based drugs. In such circumstances, regulatory agencies recommend conducting real-world studies to investigate associations between drugs and possible adverse events.[80] In the case of incretin-based drugs, despite being on the market for more than 15 years, no large-scale real-world study has been conducted to address this safety concern. Given that an estimated 300 million individuals live with type 2 diabetes worldwide, and the use incretin-based drugs is increasing,[18] any increased risk of skin cancer caused by incretin-based drugs would have significant public health consequences. Overall, this thesis addressed these gaps in knowledge on the diabetes-cancer association and skin cancer safety of incretin-based drugs through several observational studies using real-world data.

Chapter 3. Methods

Individual chapters describe the respective methods in detail. This chapter presents an overview of the data source used and elaborates on some of the methods used for this thesis.

3.1 Clinical Practice Research Datalink

The National Health Service (NHS) in the United Kingdom provides publicly funded health care paid out of general taxation since 1948.[163] Services cover all four UK nations, namely, England, Scotland, Wales, and Northern Ireland. Almost 98% of the UK population are registered with general practices, to which visits are free of charge.[164] The CPRD is a UK government, not-for-profit service that compiles this general practice data, producing one of the largest longitudinal electronic health record datasets focusing on primary care data in the world.[164] The CPRD has anonymized data from patients registered at general practices participating in the CPRD, who have not dissented from secondary use of their health data. CPRD captures demographics, diagnoses, symptoms, signs, prescriptions, referrals, immunizations, behavioral factors, and tests. General practitioners are trained and incentivized to record key data elements to ensure quality and completeness.[164 165]

The CPRD has two sections, CPRD Gp OnLine Data (GOLD) and CPRD Aurum, this thesis utilized both datasets.[164 166] Overall, the CPRD GOLD covers about 7% of the UK population from all four UK nations and includes data from patients registered at general practices participating in the CPRD, who have not dissented from secondary use of their health data. CPRD GOLD records data from 1987 onwards, and has been shown to have data representative of the UK population as per the 2011 national census with respect to age, sex, ethnicity, and body mass index.[164] In CPRD GOLD, diagnoses are recorded with Read codes,

which is a hierarchical clinical classification system consisting of about 96,000 codes,[167] and prescriptions recorded using the UK Pricing Authority Dictionary, with information on substance and product names, British National Formulary codes, quantity, and dose.[164] Two sets of quality criteria are provided for the data: at the patient level, acceptability (based on registration status, recorded events, and valid age and gender) and, at the practice level, up to standard time (based on the continuity of recording and the number of deaths within the practice). [164]

CPRD Aurum comprises data from about 10% of English practices, representing 13% of the population of England, and records data from 1995 onwards.[166] The data is broadly representative of the English population in terms of age, sex, deprivation, and geographical spread.[166] Diagnoses are recorded using the SNOMED Clinical Terms (CT) codes as well as Read Version 2 codes, and prescription information (including substance and product names from the British National Formulary, days of supply, quantity, and dose) using the Dictionary of Medicines and Devices under the SNOMED CT.[168] The data quality is assured by more than 900 checks, on three levels: collection, research quality, and patient level.[166] The final binary 'acceptability' flag is based on the consistent recording of date of birth, practice registration, and transfer out date. In case of overlap between CPRD GOLD and Aurum patients, occurring in situations where a practice moved from one electronic health record system to the other, the patients in Aurum were considered after deduplication, given the longer follow-up in this dataset.

Together, CPRD GOLD and Aurum have over 2000 general practices across the United Kingdom and longitudinal data for >60 million patients.[164 166] General practitioners in the UK act as gatekeepers to health, dealing with all non-emergency contacts and referring patients for secondary care as necessary. Secondary care teams report back to the general practitioners

completing the loop, who in turn record the diagnoses and provides follow-ups and long-term care for most chronic conditions, including diabetes.[164 166] Laboratory values are automatically linked to records, and secondary care diagnoses are manually entered.[164] CPRD has a particular advantage in that it contains rich data on anthropometric, lifestyle, clinical, and laboratory variables, which are often missing in administrative data, but serve as important covariates in diabetes research.[164 166]

Beyond data quality checks, diagnoses in the CPRD have been validated in multiple studies.[169-175] For example, a systematic review investigating validation studies on CPRD diagnoses found that of the 183 diagnoses studied, 89% were associated with confirmed cases.[176] Indeed, CPRD diagnoses also have a high concordance with disease prevalence recorded in the UK national statistics.[177] Importantly, cancer diagnoses in general have a high degree of validity in the CPRD, with medical profile review confirming 93% of cancer diagnoses.[178] Skin cancer diagnoses in UK primary care databases, the outcomes of interest in Objectives 2 and 3, also have high degree of validity.[178-180] Indeed, recording of both melanoma and nonmelanoma skin cancer has been shown to be more complete in the CPRD compared with the UK national cancer registry.[172 181] Importantly, the NHS imposes a fixed co-pay for all drugs, minimizing the impact of socioeconomic factors on the access to and the use of medications.

3.2 Cohort formation for objective 1 and risk set sampling

3.2.1 Base cohort for objective 1

Within the CPRD, we constructed a base cohort of patients not having a history of cancer or diabetes at cohort entry. This was done to follow such patients up until they developed

diabetes and compare their cancer outcomes with those who at the time did not have diabetes. Base cohort entry was defined as the latest of the following:

1. the establishment of the datasets,
2. the patient's 18th birthday (to exclude pediatric patients as pediatric cancers have different epidemiology than adult cancer and are not thought to be associated with diabetes),
3. completing one year of medical history in the general practice (to ensure patients with stable registrations in the CPRD to ensure proper follow-up)

At this stage, patients with type 1 or type 2 diabetes or prescriptions for antihyperglycemic drugs, and a history of any cancer (including receipt of chemotherapy or radiation therapy), ever before cohort entry, were excluded. We excluded patients with a history of antihyperglycemic drugs and chemotherapy even if they did not have a diabetes or cancer diagnosis, respectively, to allow for omissions in noting the diagnoses, to obtain a clean cohort. These patients were then followed until the first of the following events:

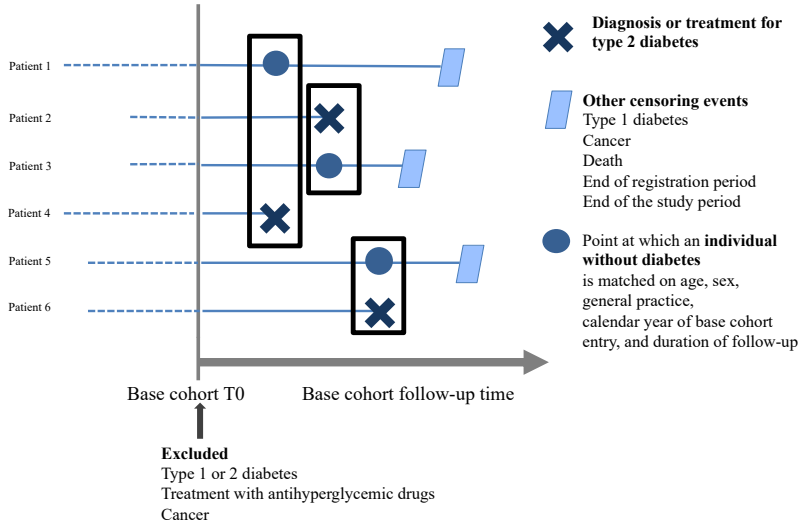
1. an incident diagnosis of type 2 diabetes or a new prescription for an antihyperglycemic drug,
2. an incident diagnosis of type 1 diabetes (as this condition may influence
3. an incident diagnosis of any cancer, death from any cause, end of registration with the general practice, or end of the study accrual period (September 30, 2019).

3.2.2 Risk set sampling for objective 1

Risk set sampling was used to sample patients with type 2 diabetes and randomly match them with patients without diabetes at that point in time (**Figure 3.1)**.[182] Matching was done on age, sex, general practice, year of base cohort entry, and duration of follow-up in the base cohort,

to ensure comparability of cancer detection between the groups and for stratified analyses,[182] but not to control for confounding as we were not asking a causal question. This sampling scheme allowed for selection of controls who, at a comparable time point, did not have diabetes, thus avoiding looking into the future to select patients who never have diabetes during the follow-up, thus selecting healthier patients, a method that is common in this literature. Therefore, patients with type 2 diabetes could be selected as comparators before their diagnosis, and comparators could have been selected for more than one patient with type 2 diabetes.

Figure 3.1 Sampling strategy



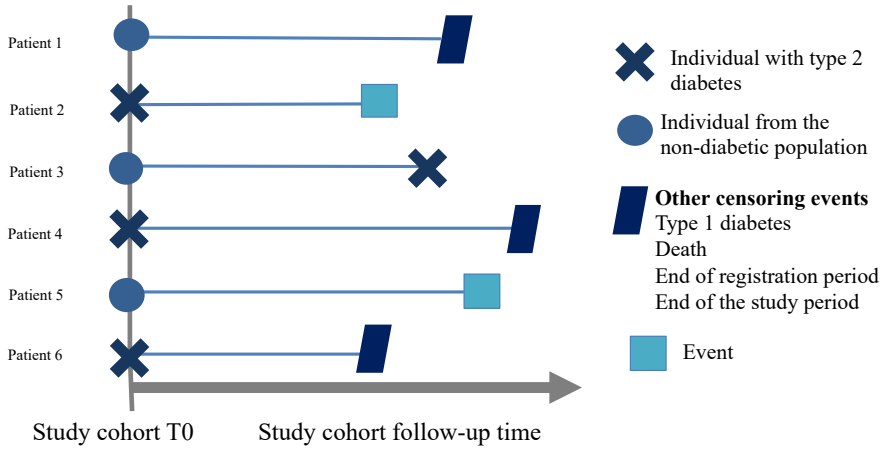
3.2.3 Study cohort for objective 1

Using this sampling scheme, a study cohort was constructed of patients with and without type 2 diabetes, the cohort entry for patients with type 2 diabetes being the date of diabetes diagnosis (**Figure 3.2**). This date was assigned as cohort entry to the comparators. All patients in the matched cohort were followed from study cohort entry until the earliest of the following:

1. the occurrence of an incident cancer event
2. incident diagnosis of type 1 diabetes,

3. an incident diagnosis of type 2 diabetes or initiation of an antihyperglycemic drug (for the matched patients who did not have type 2 diabetes at cohort entry),
4. death
5. end of registration with the general practice
6. end of the study period (30 September 2020), whichever occurred first.

Figure 3.2 Study population



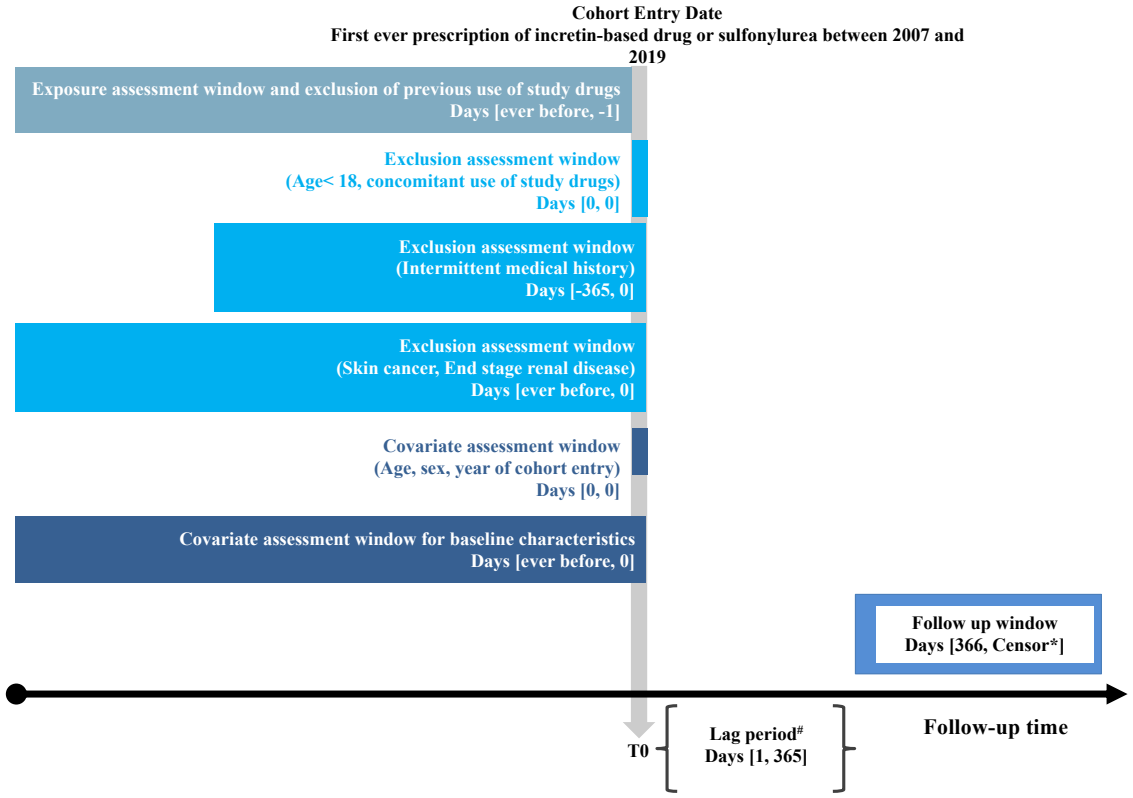
3.3 Cohort construction for objectives 2 and 3

Using CPRD, we assembled new-user, active comparator cohorts from January 1, 2007 (the year the first incretin-based drugs entered the UK market) through July 31, 2019 (**Figure 3.3**). A new-user, active comparator design has several advantages over other designs in pharmacoepidemiology: a new-user approach avoids biases from using prevalent users, including survival bias and confounding, as well as time-related biases.[183 184] It also allows implementation of latency period important in cancer pharmacoepidemiology.[185 186] Comparing with another drug class used at the same stage of the disease ensures clinical meaningfulness of the comparison, in addition to reducing confounding and possibilities of differential detection. [183 184] For objective 2, the cohort consisted of initiators of GLP-1 RAs (dulaglutide, exenatide,

liraglutide [except the 6 mg/ml formulation indicated for weight loss], lixisenatide, semaglutide) and initiators of sulfonylureas (Objective 2). For objective 3, the cohort consisted of initiators of DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin, vildagliptin) and initiators of sulfonylureas (Objective 3). The fact that we only used drugs indicated in type 2 diabetes allowed construction of the cohorts without using diabetes diagnoses, which might be inaccurately noted, particularly for sulfonylureas which are older drugs, potentially resulting in selection bias. [175] [187] In both objectives, cohort entry was defined by the date of either the first prescription of the incretin-based drug class of interest or a sulfonylurea during the study period. This avoided hierarchically classifying exposure, thus reducing the possibility of immortal time bias.[188] To be included, all patients were required to be at least 18 years of age (to ensure we had adult patients, as pediatric approvals for the drugs of interest are not uniform[189]) and have at least one year of medical history in the CPRD before cohort entry (to ensure stability in the database for follow-up, covariate assessment, as well as allowing for a minimum washout period to identify new users). Because the mechanism of inducing skin cancer may be incretin-mediated, we excluded patients with a history of use of incretin-based drugs (i.e., patients with a history of DPP-4 inhibitors in the GLP-1 RA versus sulfonylurea cohort, and patients with a history of GLP-1 RAs in the DPP-4 inhibitor versus sulfonylurea cohort). We also excluded individuals with prior end stage renal disease as several drugs of interest are contraindicated in this condition. We then excluded patients previously diagnosed with any type of skin cancer ever before cohort entry (as these represent prevalent cases) and those with less than one year of follow-up. The latter represents a lag period that addressed two design elements.[124] [125] First, it allowed for a minimum latency period, as skin cancer events diagnosed soon after treatment initiation are unlikely to be associated with the exposures. Second, this approach minimized detection bias resulting from

increased interaction with physicians in the early months after treatment initiation. This implementation of lag period also resulted in formation of two cohorts each for the two objectives, depending on the outcome.

Figure 3.3 New-user, active comparator cohorts[190]



Patients experiencing any censoring event are excluded during lag period

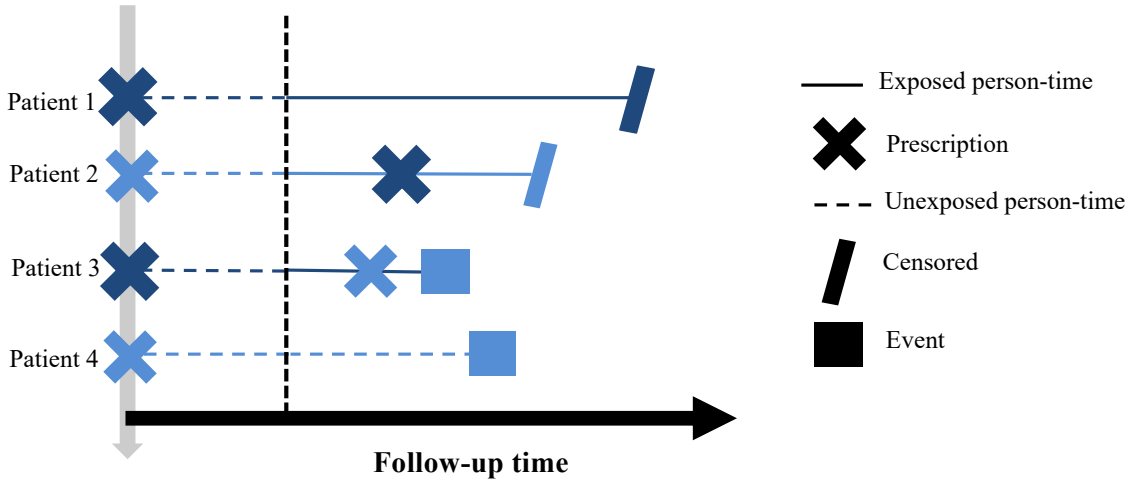
* Incident diagnosis of melanoma or nonmelanoma skin cancer, one year after crossover or switch to one of the study drugs, death, end of registration with the general practice, or the end of the study period (July 31, 2020), whichever occurs first

3.4 Exposure definition for objectives 2 and 3

All patients were followed starting one year after cohort entry (i.e., after the lag period) until an incident diagnosis of melanoma or nonmelanoma skin cancer, one year after crossover or switch to one of the study drugs (i.e., sulfonylurea to an incretin-based drug, an incretin-based

drug to a sulfonylurea, or switch between incretin-based drug classes), death, end of registration with the general practice, or the end of the study period (July 31, 2020), whichever occurs first (**Figure 3.4**). We used an intention-to-treat exposure definition to account for the potentially irreversible mechanism of influencing cancer outcomes that the drugs are associated with.[185 191] This definition also has advantages in reducing bias due to informative censoring and allows the implementation of a lag period to account for cancer latency. However, this exposure definition ignores discontinuation of drugs and thus may result in exposure misclassification, which may bias the results towards the null value.[185 191]

Figure 3.4 Exposure definition



3.5 Propensity score fine stratification

Propensity score, or the predicted probability of receiving a treatment based on measured covariates, is a well-recognized mean to analyze observational data using the potential outcome framework, allowing comparison between treated and reference populations in a manner similar to randomized controlled trials.[192 193] Propensity score methods provide two important advantages in observational research: it clarifies the target population of inference, and helps

exclude patients who are unlikely to receive either treatment (thus excluding those for whom exchangeability is hard to establish).[194] There are several methods to condition on propensity score to adjust for confounding, including matching, stratification, adjustment, and weighting.[195] Propensity score fine stratification is a relatively novel method which is suitable for situations of low exposure prevalence as it does not need to exclude patients who do not match on propensity score.[196 197] After calculating the propensity scores, patients in the nonoverlapping propensity score regions were trimmed from the cohorts to ensure exchangeability. Fifty strata based on the propensity score distribution of the patients receiving the drugs of interest (GLP-1 RA or DPP-4 inhibitors) were then created. Within each stratum, the exposed individuals received a weight of 1, while sulfonylurea users were weighted in proportion to the number exposed in the corresponding stratum.

- Weight for patients on incretin-based drugs =1

- Weight for patients on sulfonylureas= $\frac{(N_{\text{exposed in PS stratum i}}/N_{\text{total exposed}})}{(N_{\text{reference in PS stratum i}}/N_{\text{total referece}})}$

Being a weighting method in essence, it aims to balance the covariate distribution in each stratum, which is the motivation behind granulating into fine strata. The strata were based on the smaller exposure groups ensuring minimal loss of patients. The estimand generated with this approach is the average treatment effect among the treated.

3.6 Confounders

We considered a wide range of potential confounders, all measured before or at cohort entry (**Table 3.1**). These included age (modeled using cubic splines with five interior knots to account for a possible non-linear relation with the exposure), sex, lifestyle-related factors (body

mass index, alcohol-related disorders, smoking status), calendar year (as a proxy for temporal trends in prescribing and changes in ultraviolet radiation, categorized as 2007-2010, 2011-2014, 2015-2019) and region (as a proxy for exposure to sunlight). We considered known skin cancer risk factors, including pre-cancerous photodermatoses (serving as markers of sun exposure), and use of photosensitizing and immunosuppressive drugs. We also considered diabetes-related variables such as hemoglobin A1c, duration of diabetes (calculated as the time between cohort entry and the earliest of a diabetes diagnosis, use of an antihyperglycemic drug, or an HbA1c value of $\geq$ 6.5%), as well as microvascular [nephropathy, neuropathy, retinopathy] and macrovascular [myocardial infarction, stroke, peripheral arteriopathy] complications of diabetes. Furthermore, we adjusted for the use of antihyperglycemic drugs ever before cohort entry (including metformin, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, sodium-glucose cotransporter-2 inhibitors, and insulin), common comorbidities (heart failure, cancer, obstructive sleep apnea, osteoarthritis, chronic obstructive pulmonary disease, depression, dyslipidemia, gastrointestinal reflux disease, cardiac arrhythmia, hypertension, hypothyroidism) and comedications (antihypertensives, antiarrhythmics, antiplatelet agents, statins, non-steroidal anti-inflammatory drugs, corticosteroids, biologics, proton pump inhibitors), and markers of healthcare-seeking behavior (uptake of cancer screening [fecal occult blood testing or colonoscopy, mammography, prostate-specific antigen testing] and vaccinations [including influenza and pneumococcal vaccinations] in the year before cohort entry).

Table 3.1 Summary of covariates

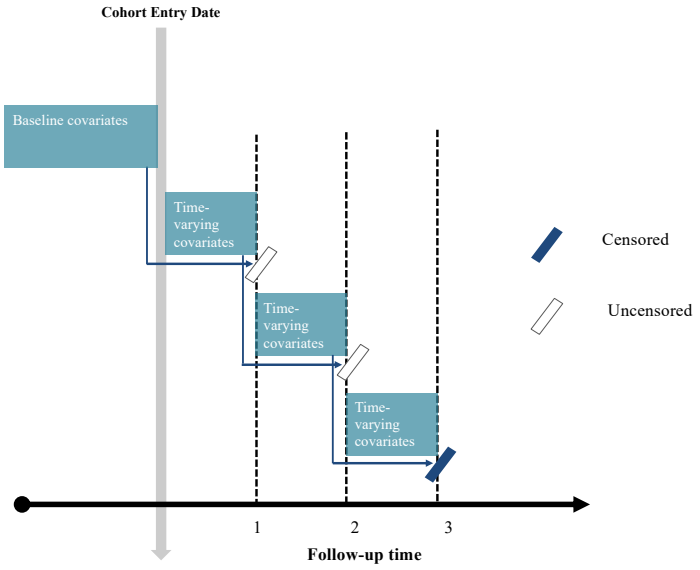
Covariate	Variable Type	Definition	Covariate Assessment Period
Demographic/lifestyle variables			
Age	Continuous	Cohort entry year minus birth year	Cohort entry
Sex	Categorical	Male/female	CPRD master file
Practice region	Categorical	Thirteen CPRD region categories	CPRD master file
Ethnicity	Categorical	White, South Asian, black, mixed other, unknown	Any record associated with patient
Body mass index	Categorical	≤ 24.9 kg/m², 25.0 - 29.9 kg/m², ≥ 30.0 kg/m², unknown	Last measure before cohort entry
Smoking status	Categorical	Ever, never, unknown	Cohort entry
Alcohol-related disorders	Binary	Present/absent	Ever before cohort entry
Year of cohort entry	Categorical	2007-2010, 2011-2014, 2015-2019	Cohort entry
Diabetes-related variables			
Hemoglobin A1c	Categorical	≤7.0%, 7.1%-8.0%, >8.0%, unknown	Last measure before cohort entry
Duration of diabetes	Continuous	Defined by the date of the first of either an HbA1c ≥6.5%, a diagnosis of type 2 diabetes, or prescription for an anti-hyperglycemic drug to the date of cohort entry	Cohort entry
Peripheral vascular disease	Binary	Present/absent	Ever before cohort entry
Stroke	Binary	Present/absent	Ever before cohort entry
Myocardial infarction	Binary	Present/absent	Ever before cohort entry
Renal disease	Binary	Present/absent	Ever before cohort entry
Retinopathy	Binary	Present/absent	Ever before cohort entry
Neuropathy	Binary	Present/absent	Ever before cohort entry
Anti-hyperglycemic drugs			
Metformin	Binary	Present/absent	Ever before cohort entry
Thiazolidinediones	Binary	Present/absent	Ever before cohort entry
Meglitinides	Binary	Present/absent	Ever before cohort entry
Alpha-glucosidase inhibitors	Binary	Present/absent	Ever before cohort entry
SGLT-2 inhibitors	Binary	Present/absent	Ever before cohort entry
Insulin	Binary	Present/absent	Ever before cohort entry

Skin cancer related variables			
Photodermatoses	Binary	Present/absent	Ever before cohort entry
Phototoxic drugs	Binary	Present/absent	Ever before cohort entry
Immunosuppressants	Binary	Present/absent	Ever before cohort entry
Common comorbidities			
Heart failure	Binary	Present/absent	Ever before cohort entry
Cancer	Binary	Present/absent	Ever before cohort entry
Obstructive sleep apnea	Binary	Present/absent	Ever before cohort entry
Osteoarthritis	Binary	Present/absent	Ever before cohort entry
Chronic obstructive pulmonary disease	Binary	Present/absent	Ever before cohort entry
Depression	Binary	Present/absent	Ever before cohort entry
Dyslipidemia	Binary	Present/absent	Ever before cohort entry
Gastrointestinal esophageal reflux disease	Binary	Present/absent	Ever before cohort entry
Arrhythmia	Binary	Present/absent	Ever before cohort entry
Hypertension			
Common prescription drugs			
Antihypertensives	Binary	Present/absent	Ever before cohort entry
Antiarrhythmics	Binary	Present/absent	Ever before cohort entry
Antiplatelet agents	Binary	Present/absent	Ever before cohort entry
Statins	Binary	Present/absent	Ever before cohort entry
Non-steroidal anti-inflammatory drugs	Binary	Present/absent	Ever before cohort entry
Corticosteroids	Binary	Present/absent	Ever before cohort entry
Biologics	Binary	Present/absent	Ever before cohort entry
Proton-pump inhibitors	Binary	Present/absent	Ever before cohort entry
Opioids	Binary	Present/absent	Ever before cohort entry
Healthcare seeking behavior			
Colon cancer screening	Binary	Present/absent	Ever before cohort entry
Mammogram	Binary	Present/absent	Ever before cohort entry
Prostate specific antigen	Binary	Present/absent	Ever before cohort entry
Pneumococcal vaccine	Binary	Present/absent	Ever before cohort entry
Influenza vaccine	Binary	Present/absent	Ever before cohort entry

3.7 Inverse probability of censoring weighting

Differential censoring due to switching of treatments or death may lead to selection bias.[198-200] One way to reduce such bias is to create a pseudopopulation where the censoring rates are equal between exposure groups, by inverse probability of censoring weighting (**Figure 3.5**).[200] It was conducted by initially dividing the follow-up into intervals of one year separately for each exposure group. We then calculated separately the probability of remaining uncensored[201 202] and probability of remaining alive[203] at each interval by using two separate logistic regression models, conditional on covariates updated in the previous interval. We then took the product of the weights (defined as the inverse of the predicted probabilities of remaining uncensored and alive) across all intervals for each patient. Intercept only models were used as numerators to stabilize the weights, and further. These stabilized weights were multiplied with the propensity score fine stratification weights to generate final weights for each patient to compute the hazard ratios of skin cancer associated with the use of incretin-based drugs versus sulfonylureas.

Figure 3.5. Inverse probability of censoring weighting



Chapter 4. Long-Term Patterns of Cancer Incidence Among Patients With and Without Type 2 Diabetes in the United Kingdom

4.1 Preface

A link between type 2 diabetes and cancer has been reported since 1960s. In a meta-analysis of all studies published on the topic till 2019, including 155 cohorts and 32 million patients, patients with diabetes were found to have a 15% higher risk of all cancers than patients without diabetes.[16] However, the literature on this topic has several shortcomings, including methodological drawbacks such as potential selection bias.[15] In particular, studies examining the association between diabetes and skin cancer, the most commonly diagnosed human cancer, have been few. Furthermore, there have been many shifts in the management and prognosis of diabetes since most of the included studies were conducted, including introduction of new drugs, better glycemic control, and longer life expectancies of diabetes patients, all of which could contribute to a change in the cancer burden in diabetes. Accordingly, the first objective of this thesis was to examine the long-term patterns of cancer incidence among patients with diabetes in the UK. This paper was published in *Diabetes Res Clin Pract*. *2022;185:109229*.[204]

4.2 Title Page

Long-Term Patterns of Cancer Incidence Among Patients With and Without Type 2 Diabetes in the United Kingdom

Richeek Pradhan MD MS[1,2], Oriana Yu MD MSc[3], Robert W. Platt PhD[1,2], Laurent Azoulay PhD[1,2,4]

[1] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada

[2] Center for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Canada

[3] Division of Endocrinology, Jewish General Hospital, Montreal, Canada

[4] Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada

Running title: Cancer Incidence in Patients with Type 2 Diabetes

Main text word count: 3233

Figures: 2;

Tables: 2

Correspondence:

Dr Laurent Azoulay

Centre for Clinical Epidemiology, Jewish General Hospital, Lady Davis Institute

3755 Cote Sainte-Catherine, H425.1, Montreal, Canada, H3T 1E2

Tel.: (514) 340-8222 ext. 28396

Email: laurent.azoulay@mcgill.ca;

Twitter: @LaurentAzoulay0

January 12, 2021

4.3 ABSTRACT

Aims: Studies using contemporary cohorts are needed to assess the association between type 2 diabetes and cancer.

Methods: Using the United Kingdom Clinical Practice Research Datalink, we matched patients with type 2 diabetes between 1988 to 2019 to patients without type 2 diabetes. Poisson regression models were fit to estimate incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for cancer. In secondary analyses, we determined whether the strength of the association varied with calendar time and whether patients with type 2 diabetes had a higher incidence of being diagnosed with multiple cancers during the follow-up period.

Results: 890,214 patients with type 2 diabetes were matched to an equal number of patients without type 2 diabetes. Patients with type 2 diabetes had a higher cancer incidence than patients without type 2 diabetes (IRR 1.19, 95% CI 1.18-1.21). The IRR was higher 2010 onwards (IRR: 1.25, 95% CI: 1.23-1.28) compared with the association in previous years. Overall, patients with type 2 diabetes had a 5% higher incidence of being diagnosed with multiple cancers (IRR: 1.05, 95% CI: 1.04-1.07).

Conclusions: The results of this large population-based study indicate that type 2 diabetes is associated with an increased risk of several cancers.

Keywords: Type 2 diabetes, Cancer, Detection patterns, Multiple cancer, Cohort

4.4 INTRODUCTION

The prevalence of type 2 diabetes is steadily rising worldwide.[1, 2] In 2019, this disease accounted for more than 90% of the 463 million patients living with diabetes,[3] and 1.5 million excess deaths.[4] With declining vascular mortality among patients with type 2 diabetes, cancer has become the foremost cause of death in this population.[5, 6]

Over the years, several observational studies have reported a higher incidence of cancer among patients with type 2 diabetes when compared with patients without this disease.[7, 8] However, several aspects of this association have remained understudied, such as patterns of cancer detection with the duration of diabetes and the risk of multiple cancers occurring in the same patient. Moreover, several factors influencing cancer incidence among patients with type 2 diabetes have changed in recent decades. These include better control of cancer risk factors[9, 10] and the introduction of novel antidiabetic drugs. While the improved glycemic control by these drugs could have led to a decreased cancer incidence, certain antidiabetic drugs could have increased the incidence of specific cancers.[11, 12] Finally, the implementation of various cancer screening programs[13, 14] and increasing life expectancy of patients with type 2 diabetes may have created an opportunity for increased cancer detection.[15] Indeed, it is unclear whether the association between type 2 diabetes and cancer incidence has changed over time.

To address these uncertainties, we conducted a large population-based study to compare the incidence of cancer overall, site-specific cancers, and multiple cancers among patients with and without type 2 diabetes. We also assessed the patterns of cancer detection with the duration of diabetes and the temporal trends over a 32-year period.

4.5 MATERIALS AND METHODS

4.5.1 Data source

This study was conducted using the GOLD and Aurum datasets of the Clinical Practice Research Datalink (CPRD). The CPRD is a representative, population-based primary care database containing detailed records for >50 million patients seen at over 2000 general practices in the United Kingdom (UK).[16] In the UK, general practitioners function as the primary caregivers of the healthcare system and are responsible for the long-term management of patients with type 2 diabetes.[17] Moreover, reports from secondary care providers are sent to them and entered into the CPRD. Consequently, the recording of type 2 diabetes and its management is of high quality. Diagnoses and procedures are recorded using the Read code and SNOMED-CT classification, while drug prescriptions are recorded using the UK Prescription Pricing Authority Dictionary. The data and practices are audited regularly to ensure high quality. Finally, cancer diagnoses have been shown to be well recorded in the CPRD, with positive predictive values ranging between 92% to 98%.[18, 19] The study protocol was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol No. 20_152) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

4.5.2 Study population

Within the CPRD population, we first identified a base cohort composed of patients who did not have a history of cancer or diabetes at cohort entry. Entry into the base cohort was defined as the latest of the following events: January 1, 1988 for CPRD GOLD or January 1, 1996 for CPRD Aurum (i.e., one year after these datasets were

established), the calendar date of a patient's 18th birthday, or achieving one year of medical history in the general practice. At this stage, we excluded patients if they had a diagnosis of type 1 or type 2 diabetes, prescriptions for antidiabetic drugs (including metformin, sulfonylureas, meglitinides, thiazolidinediones, acarbose, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists, sodium-glucose co-transporter-2 inhibitors, or insulin), and a history of any cancer (including receipt of chemotherapy or radiation therapy), all assessed ever before cohort entry. Patients meeting these criteria were then followed until the first of the following events: an incident diagnosis of type 2 diabetes or a new prescription for an antidiabetic drug, an incident diagnosis of type 1 diabetes, an incident diagnosis of any cancer, death from any cause, end of registration with the general practice, or end of the study accrual period (September 30, 2019).

4.5.3 Matching patients with and without type 2 diabetes

Using the base cohort defined above, we used risk set sampling to randomly match each patient newly diagnosed with type 2 diabetes with one patient without type 2 diabetes on factors that may impact cancer detection, including age, sex, general practice, year of base cohort entry, and duration of follow-up in the base cohort. According to this sampling scheme, patients with type 2 diabetes could have been selected as comparators before their diagnosis, and comparators could have been selected for more than one patient with type 2 diabetes. Study cohort entry for patients with type 2 diabetes was defined as the date of diabetes, which was assigned to the matched patients without type 2 diabetes. Thus, both patients with and without type 2 diabetes had the same duration of follow-up in the base cohort. Importantly, this sampling scheme ensured that none of the

patients were diagnosed with type 1 or type 2 diabetes or any cancer at any time before study cohort entry.

All patients in the matched cohort were followed from study cohort entry until the occurrence of an incident cancer event (detailed below) or censored upon an incident diagnosis of type 1 diabetes, an incident diagnosis of type 2 diabetes or initiation of an antidiabetic drug (for the matched patients who did not have type 2 diabetes at cohort entry), death from any cause, end of registration with the general practice, or end of the study period (30 September 2020), whichever occurred first.

The primary outcome was cancer overall (except non-melanoma skin cancer) (**Supplementary Table 1)**. We excluded non-melanoma skin cancer in this analysis because this cancer has relatively good prognosis, and represents the most common cancer regardless of diabetes status.[20] The secondary outcomes consisted of 22 site-specific cancers, including cancers of the breast, prostate, lung, colon and rectum, kidney, head and neck, central nervous system, pancreas, bladder, esophagus, stomach, liver and biliary tract, ovary, uterus, cervix, testes, and thyroid, melanoma and non-melanoma skin cancer, non-Hodgkin lymphoma, leukemia, and myeloma.[8]

4.5.4 Statistical Analyses

Poisson regression models were fit to estimate incidence rate ratios (IRRs) with 95% confidence intervals (CIs) of cancer overall and site-specific cancers, comparing patients with and without type 2 diabetes. The models were conditioned on the matched pairs and used the logarithm of the person-years as the offset. Additionally, we calculated incidence rate differences as absolute measures of excess risk between the groups. We

also plotted Kaplan-Meier curves to display the cumulative incidence of time to first cancer.

We conducted four secondary analyses. First, we computed age- and sex-stratified IRRs given that both age and sex has been associated with the incidence of certain cancers and has been found to influence cancer screening rates among patients with type 2 diabetes.[21-23] Second, we determined whether the IRRs of cancer overall and site-specific cancers varied with the following duration of follow-up categories: ≤1.9, 2-3.9, 4-5.9, 6-7.9, 8-9.9, ≥10 years. Third, we examined whether the strength of association the association between type 2 diabetes and cancer has varied over the different decades of the study period (≥2010, 2000-2009, <2000). Finally, we examined whether patients with type 2 diabetes were more likely to be diagnosed with more than one cancer during the follow-up period (excluding non-melanoma skin cancer), compared with patients without type 2 diabetes, using Poisson regression for event count. As a measure of cumulative incidence, we plotted Kaplan-Meir curves from the time of the first cancer to the second cancer over the follow-up.

All analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC), STATA version 14 (StataCorp LP, College Station, TX, USA), and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

4.6 RESULTS

4.6.1 General results

Overall, the base cohort included 31,782,771 patients without a history of cancer or diabetes before cohort entry. After a median follow-up of 4.8 years, 990,290 patients were newly-diagnosed with type 2 diabetes (cumulative incidence 3.1% and incidence rate: 433.8 per 100,000 person-years, CI: 433.0-434.7 per 100,000 person-years). A total of 890,214 (89.9%) of these patients were matched to an equal number of patients without type 2 diabetes. The inability to match on the general practice was the reason for nearly all of the unmatched patients with type 2 diabetes (**Figure S4.1**). Overall, the mean (standard deviation) age was 58.1 (15.5) years, 51.8% were males, and most patients entered the study cohort after 2000 (**Table 4.1**).

Table 4.2 presents the results for cancer overall and by site-specific cancers. After a median follow up of 6.0 years (interquartile range 2.8-10.7 years), patients with type 2 diabetes had an 19% higher incidence of cancer overall compared with patients without type 2 diabetes (1145.8 vs. 960.1 per 100,000 person years, respectively; IRR 1.19, 95% CI: 1.18-1.21). The cumulative incidence curves diverged early in the follow-up and remained separated throughout the follow-up (**Figure 4.1.A**).

Strong associations were observed for cancers of the pancreas (IRR: 2.82, 95% CI: 2.66-2.99), liver and biliary tree (IRR: 2.54, 95% CI: 2.37- 2.72), and uterus (IRR: 2.20, 95% CI: 2.04-2.37). Moderate associations were observed for cancers of the kidney, stomach, bladder, cervix, colon and rectum, esophagus, thyroid, lymphoma, head and neck, lungs, leukemia, central nervous system, breast, and ovary, with IRRs ranging between 1.09 and 1.47. In contrast, inverse associations were observed with cancers of

the testes, prostate, and non-melanoma skin cancer. The IRRs were generally higher among females than males (**Figure S4.2**), and increased with age at the time of study cohort entry (**Figure S4.3**).

4.6.2 Patterns of cancer detection during the follow-up period

Compared with patients without type 2 diabetes, those with type 2 diabetes had a higher incidence of cancer in the first two years of follow-up (IRR: 1.29, 95% CI: 1.26-1.31). The IRR remained above null value during the remainder of the follow-up period, although the strength of the association decreased over time (IRRs ranging from 1.11 to 1.15, **Figure 4.2**). The IRRs over the follow-up period varied according to the site-specific cancer (**Figure S4.4**). For example, there were cancers for which the IRR remained high throughout the follow-up [cancers of pancreas (IRR range: 1.08 to 7.06), liver and biliary tree (IRR range: 2.15 to 2.98), uterus (IRR range: 2.04 to 2.36), colon and rectum (IRR range: 1.19 to 1.27), bladder (IRR range: 1.46 to 1.18), kidney (IRR range: 1.20 to 1.82). On the other hand, for prostate cancer, the IRR was high initially but below the null for the rest of the follow-up (IRR 1.18 at ≤1.9 years and IRR range: 0.80 to 0.88 during the rest). Finally, there were cancers for which there was no initial rise in the IRR, and it remained below the null for most of the rest of the follow-up, such as non-melanoma skin cancer (IRR range: 0.84 to 0.94).

4.6.3 Temporal trends in cancer incidence

The association between type 2 diabetes and cancer was highest in patients who entered the cohort from 2010 onwards (IRR: 1.25, 95% CI: 1.23-1.28), followed by those entering the cohort between 2000 to 2009 (IRR: 1.18, 95% CI: 1.16-1.20), and those

before 2000 (IRR: 1.16, 95% CI: 1.13-1.19) (**Figure 4.5**). Among specific cancers, pancreatic and lung cancer were associated with higher IRRs from 2010 onwards (IRR: 4.07, 95% CI: 3.61-4.59 2010 and IRR: 1.35, 95% CI: 1.26-1.43 2010, respectively), compared with earlier time periods. For prostate cancer, the IRR was inclusive of the null value 2010 onwards (IRR: 0.98, 95% CI: 0.93-1.03) and below the null in previous decades (IRR 0.89, 95% CI: 0.86-0.92 in 2000 to 2009 and IRR 0.89, 95% CI: 0.83-0.95 before 2000). The CIs of estimates by cohort entry years overlapped for other site-specific cancers (**Figure S4.5**).

4.6.4 Multiple cancer incidence

Patients with type 2 diabetes had a higher risk of being diagnosed with multiple cancers during the follow-up period than patients without type 2 diabetes (792.2 vs. 751.7 per 100,000 person years, respectively; IRR 1.05, 95% CI 1.04-1.07). The cumulative incidence of the second cancer cancer for those with a first cancer was higher among patients with type 2 diabetes early in the follow-up. However, the cumulative incidence curves converged at around 15 years of follow-up (**Figure 4.1.B**). The most frequent cancer combination in males was bladder and prostate cancers, while that in females was cancers of the head and neck and pancreas.

4.7 DISCUSSION

In this large population-based study, patients with type 2 diabetes had a 19% increased incidence of cancer overall compared with patients without diabetes. Among the different cancers, pancreatic cancer had the highest excess incidence. Distinct detection patterns were observed over duration of follow-up, which also varied with specific cancers. Importantly, the excess cancer incidence among patients with type 2 diabetes increased after 2010 compared with previous decades. Finally, patients with type 2 diabetes were more likely to be diagnosed with multiple cancers during the follow-up period compared with patients without type 2 diabetes.

Overall, our finding of a 19% increased incidence of cancer overall among patients with type 2 diabetes is consistent with what has been reported in a comprehensive meta-analysis of 151 observational studies involving 32 million patients (IRR: 1.15, 95% CI 1.10-1.21).[7] However, over and above the individual cancers for which a biological link with diabetes has been ascertained to be likely in previous studies (liver and biliary tree, pancreas, uterus,[7] breast, colon and rectum[8]), we found several other cancers positively associated with type 2 diabetes (lung, bladder, kidney, lymphoma, esophagus, stomach, leukemia, head and neck, ovary, cervix, central nervous system, and thyroid), as well as some negative associations (prostate, non-melanoma skin cancer, and the hitherto unreported, testicular cancer). Together, these findings indicate that, whether or not biologically related, type 2 diabetes is associated with a higher burden of several cancers. Importantly, our findings suggest a high incidence of cancer in the initial years after a diagnosis of type 2 diabetes, as has already been reported previously.[24, 25] A potential reason for this may be an increased cancer detection due

to enhanced contact with the health system, including receiving several screening tests, immediately following diabetes diagnosis.[26, 27] However, this was followed by a sustained increase in incidence compared with patients without diabetes, indicating that the long-term association between type 2 diabetes and cancer cannot simply be explained by increased surveillance only.

Our results shed light on hitherto unexplored areas in the diabetes-cancer association. For example, whether the strength of the diabetes-cancer association has changed over calendar time is unclear. One meta-analysis analysing 203 cohorts found an increased association between diabetes and cancer in the 2000s compared to 1980s (relative risk ratio for 1990 vs 1980: 1.24, 95% CI: 1.16-1.34; 2000 vs 1990: 1.23, 95% CI 1.15-1.31; and 2010 vs 2000 1.06, 95% CI: 0.99-1.13).[28] However, this study included cohorts from different countries, rendering the results difficult to interpret. We found that the IRR of cancer overall was higher after 2010 compared to previous decades, a finding that was driven by an increasing incidence of lung, pancreas and prostate cancers among patients with type 2 diabetes. Several factors may explain this, including improved survival of patients with type 2 diabetes in recent decades, with reduced cardiovascular mortality, and thus an increased potential to develop cancer.[29, 30] In addition, potentially improving surveillance among patients with type 2 diabetes, individuals already at increased contact with the health system, may also contribute to increased cancer detection.[31] Whether these trends represent a true increase in cancer incidence in patients with type 2 diabetes or an artefact of increased surveillance will need to be investigated in future studies. Finally, to our knowledge, this is the first study reporting on the incidence of being diagnosed with multiple cancers in patients with and

without type 2 diabetes. Our findings suggest a high burden of multiple cancers in this population, implying that surveillance should continue among patients with type 2 diabetes after their first cancer diagnosis. Interestingly, we found that the cumulative incidence of a second cancer was initially higher among patients with type 2 diabetes, but eventually became comparable with patients without type 2 diabetes. A possible reason for this is depletion of patients susceptible to develop a second cancer over time.[32]

Cancer has overtaken cardiovascular diseases as the leading cause of death among patients with type 2 diabetes in the United Kingdom,[6] with similar trends in other countries.[33] This emphasizes the need to better understand the joint occurrences of diabetes and cancer. The current study was designed to investigate the patterns of cancer incidence in patients with type 2 diabetes, and not to isolate the biological association between diabetes and cancer by adjusting for cancer risk factors. This is important, given that the mortality gap between patients with and without type 2 diabetes is, in fact, higher in cancers with which diabetes is not thought to be etiologically related.[6-8] Indeed, the unadjusted incidence of cancer represents the real-world experience of patients, a culmination of not only the biological effect of diabetes itself, but also the myriad elements that converge in patients with type 2 diabetes, including other cancer risk factors, antidiabetic drugs, and increased cancer surveillance. At a patient level, this knowledge allows planning of additional treatments and testing associated with a cancer diagnosis in this vulnerable population. From a policy perspective, the knowledge of the excess incidence of individual cancers during the course of diabetes may allow prioritization of screening programs of different cancers and ascertainment of the appropriate time to implement them.

Our study has several strengths. First, our findings are based on a large primary care cohort with over 13 million person-years of experience and a maximum follow-up of 32 years. This makes it one of the largest studies on the topic to date. Second, we assembled patients without diabetes using risk set sampling, which only few other studies have done,[34, 35] rather than cumulative incidence sampling,[36] which has been the dominant sampling approach in this literature.[7] The latter selects individuals without diabetes at the end of the base cohort follow-up as comparators. This results in a potentially healthier control population that may have had lower prevalence of risk factors for both diabetes and cancer, thus incurring selection bias. Third, this is the first study to use a contemporaneous cohort to examine changes in the association of type 2 diabetes and cancer over time.

This study has some limitations. First, we did not link our data with the national cancer registry. However, cancer diagnoses identified in the CPRD have a high degree of concordance with the national cancer registry.[37] Second, our study was unable to account for increased detection of cancer among patients with diabetes due to their more frequent contact with the healthcare system. However, by matching on the general practice, we mitigated this potential issue as patients from the same general practice would likely experience a similar level of surveillance. Finally, our results on pattern analysis based on age and duration of follow-up should be interpreted with caution given possibility of chance findings with multiple testing and varying numbers at risk throughout follow-up.

In summary, in this large population-based study, we found that patients with type 2 diabetes had a higher incidence of cancer overall and several site-specific cancers,

compared with patients without this disease. This association increased in magnitude after 2010 compared with previous decades. Future studies will be needed to investigate the mechanisms behind these patterns.

4.8 ACKNOWLEDGEMENTS

R Pradhan is the recipient of a Doctoral Award from the Fonds de Recherche du Québec – Santé. OHYY holds a Chercheur-Boursier Clinicien Junior 1 award from the Fonds de Recherche du Québec - Santé. R Platt holds the Albert Boehringer I Chair in Pharmacoepidemiology at McGill University LA holds a Chercheur-Boursier Senior award from the Fonds de Recherche du Québec - Santé and is the recipient of a William Dawson Scholar Award from McGill University.

4.9 COMPETING INTEREST STATEMENT

R Platt received consulting fees from Amgen, Biogen, Merck, Nant Pharma, Pfizer, and Reckitt Benckise for work unrelated to this study. LA received consulting fees from Janssen and Pfizer for work unrelated to this study. Other authors have no conflict of interest to declare.

4.10 FUNDING

This study was funded by a Foundation Scheme grant from the Canadian Institutes of Health Research (FDN-143328). The sponsors had no influence on design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

4.11 DATA STATEMENT

No additional data available.

4.12 References

[1] Zghebi SS, Steinke DT, Carr MJ, Rutter MK, Emsley RA, Ashcroft DM. Examining trends in type 2 diabetes incidence, prevalence and mortality in the UK between 2004 and 2014. Diabetes, Obesity & Metabolism. 2017;19:1537-45.

[2] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Research and Clinical Practice. 2019;157:107843.

[3] International Diabetes F. Diabetes Atlas, 9th edition 2019.

[4] World Health Organization: Key facts on diabetes.

[5] Song M. Cancer overtakes vascular disease as leading cause of excess death associated with diabetes. The Lancet Diabetes & Endocrinology. 2021;9:131-3.

[6] Pearson-Stuttard J, Bennett J, Cheng YJ, Vamos EP, Cross AJ, Ezzati M, 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. Lancet Diabetes Endocrinol. 2021;9:165-73.

[7] Ling S, Brown K, Miksza JK, Howells L, Morrison A, Issa E, 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;43:2313-22.

[8] Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JPA. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ (Clinical research ed). 2015;350:g7607.

[9] Alcohol statistics. Alcohol Change UK.

[10] Public Health E. Adult smoking habits in the UK: 2019. 2019.

[11] Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. BMJ (Clinical research ed). 2016;352:i1541.

[12] Abrahami D, Douros A, Yin H, Yu OH, Faillie J-L, Montastruc F, et al. Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study. BMJ (Clinical research ed). 2018;363:k4880.

[13] Klil-Drori AJ, Azoulay L, Pollak MN. Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? Nature Reviews Clinical Oncology. 2017;14:85-99.

[14] Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. British Journal of Cancer. 2016;115:1147-55.

[15] Eliasson M, Talbäck M, Rosén M. Improved survival in both men and women with diabetes between 1980 and 2004--a cohort study in Sweden. Cardiovascular Diabetology. 2008;7:32.

[16] Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44:827-36.

[17] Dambha-Miller H, Griffin SJ, Kinmonth AL, Burt J. Provision of services in primary care for type 2 diabetes: a qualitative study with patients, GPs, and nurses in the East of England. The British Journal of General Practice. 2020;70:e668-e75.

[18] Margulis AV, Fortuny J, Kaye JA, Calingaert B, Reynolds M, Plana E, et al. Validation of Cancer Cases Using Primary Care, Cancer Registry, and Hospitalization Data in the United Kingdom. Epidemiology (Cambridge, Mass). 2018;29:308-13.

[19] Dregan A, Moller H, Murray-Thomas T, Gulliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. Cancer Epidemiol. 2012;36:425-9.

[20] Samarasinghe V, Madan V. Nonmelanoma Skin Cancer. Journal of Cutaneous and Aesthetic Surgery. 2012;5:3-10.

[21] Davis JL, Buchanan KL, Katz RV, Green BL. Gender differences in cancer screening beliefs, behaviors, and willingness to participate: implications for health promotion. Am J Mens Health. 2012;6:211-7.

[22] Friedemann-Sánchez G, Griffin JM, Partin MR. Gender differences in colorectal cancer screening barriers and information needs. Health Expect. 2007;10:148-60.

[23] Institute NC. Age and Cancer Risk.

[24] De Bruijn KMJ, Ruiter R, de Keyser CE, Hofman A, Stricker BH, van Eijck CHJ. Detection bias may be the main cause of increased cancer incidence among diabetics: results from the Rotterdam Study. Eur J Cancer. 2014;50:2449-55.

[25] Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia. 2011;54:2263-71.

[26] Bowker SL, Richardson K, Marra CA, Johnson JA. Risk of breast cancer after onset of type 2 diabetes: evidence of detection bias in postmenopausal women. Diabetes Care. 2011;34:2542-4.

[27] Colmers IN, Majumdar SR, Yasui Y, Bowker SL, Marra CA, Johnson JA. Detection bias and overestimation of bladder cancer risk in type 2 diabetes: a matched cohort study. Diabetes Care. 2013;36:3070-5.

[28] Ling S, Brown K, Miksza JK, Howells LM, Morrison A, Issa E, et al. Risk of cancer incidence and mortality associated with diabetes: A systematic review with trend analysis of 203 cohorts. Nutrition, metabolism, and cardiovascular diseases: NMCD. 2021;31:14-22.

[29] Færch K, Carstensen B, Almdal TP, Jørgensen ME. Improved survival among patients with complicated type 2 diabetes in Denmark: a prospective study (2002-2010). J Clin Endocrinol Metab. 2014;99:E642-6.

[30] Maruthur NM. The growing prevalence of type 2 diabetes: increased incidence or improved survival? Curr Diab Rep. 2013;13:786-94.

[31] Suh M, Choi KS, Park B, Lee YY, Jun JK, Lee DH, et al. Trends in Cancer Screening Rates among Korean Men and Women: Results of the Korean National Cancer Screening Survey, 2004-2013. Cancer Res Treat. 2016;48:1-10.

[32] Renoux C, Dell'Aniello S, Brenner B, Suissa S. Bias from depletion of susceptibles: the example of hormone replacement therapy and the risk of venous thromboembolism. Pharmacoepidemiol Drug Saf. 2017;26:554-60.

[33] Islam Z, Akter S, Inoue Y, Hu H, Kuwahara K, Nakagawa T, et al. Prediabetes, Diabetes, and the Risk of All-Cause and Cause-Specific Mortality in a Japanese Working Population: Japan Epidemiology Collaboration on Occupational Health Study. Diabetes Care. 2021;44:757-64.

[34] Lega IC, Austin PC, Fischer HD, Fung K, Krzyzanowska MK, Amir E, et al. The Impact of Diabetes on Breast Cancer Treatments and Outcomes: A Population-Based Study. Diabetes Care. 2018;41:755-61.

[35] de Jong RGPJ, Peeters PJHL, Burden AM, de Bruin ML, Haak HR, Masclee AAM, et al. Gastrointestinal cancer incidence in type 2 diabetes mellitus; results from a large population-based cohort study in the UK. Cancer Epidemiology. 2018;54:104-11.

[36] Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. American Journal of Epidemiology. 1982;116:547-53.

[37] Boggon R, van Staa TP, Chapman M, Gallagher AM, Hammad TA, Richards MA. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. Pharmacoepidemiology and drug safety. 2013;22:168-75.

4.13 FIGURE LEGENDS

Figure 4.1 Cumulative Incidence of A. First Cancer, and B. From First to Second Cancer Among Patients With and Without Type 2 Diabetes Over a 20-Years Period

Figure 4.2 Incidence Rate Ratios Comparing the Incidence of All Cancers Among Patients With and Without Type 2 Diabetes Over Duration of Follow-Up

Table 4.1 Baseline Characteristics of Patients with and without Type 2 Diabetes

Characteristics*	Patients with type 2 diabetes	Patients without type 2 diabetes
Number of patients	890,214	890,214
Age in years, mean (SD)	58.1 (15.5)	58.1 (15.5)
Male, n (%)	460,765 (51.8)	460,765 (51.8)
Time in base cohort in years, mean (SD)	8.4 (6.1)	8.4 (6.1)
Year of study cohort entry		
<2000	83,128 (9.3)	83,128 (9.3)
2000-2010	408,177 (45.8)	408,177 (45.8)
>2010	398,909 (44.8)	398,909 (44.8)

*Patients were matched on age, sex, time in the base cohort, and year of cohort entry.

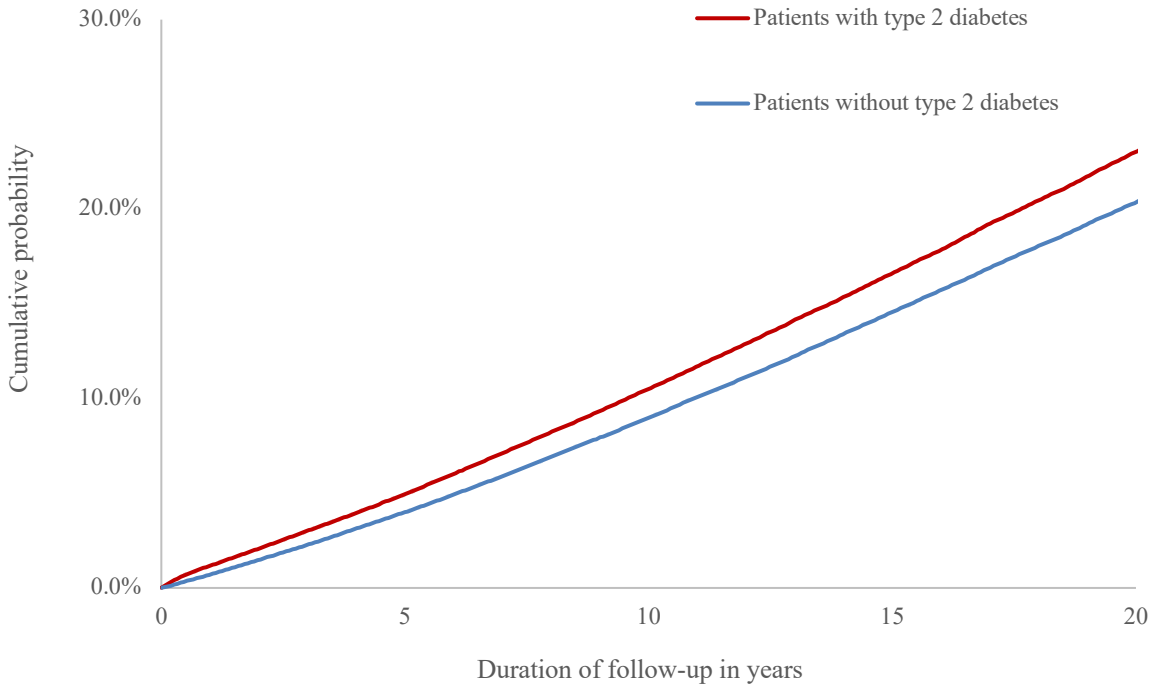
Table 4.2 Comparing the Incidence of Cancer Overall and Site-Specific Cancers Between Patients with and without Type 2 Diabetes

Cancer Type	Patients with Type 2 Diabetes			Patients without Type 2 Diabetes			Incidence rate ratio (95% CI)	Rate difference (95% CI)
	Events	Person years	Incidence Rate* (95% CI)	Events	Person years	Incidence Rate* (95% CI)		
All cancers	74,068	6,464,341	1145.8 (1137.6-1154.1)	61,300	6,384,646	960.1 (952.5-967.7)	1.19 (1.18-1.21)	185.7 (174.5 - 196.9)
Pancreas	4322	6,714,738	64.4 (62.5-66.3)	1510	6,610,861	22.8 (21.7-24)	2.82 (2.66-2.99)	41.6 (39.4 - 43.8)
Liver and biliary tree	2876	6,714,413	42.8 (41.3-44.4)	1116	6,610,632	16.9 (15.9-17.9)	2.54 (2.37-2.72)	25.9 (24 - 27.8)
Uterus †	2152	3,186,194	67.5 (64.7-70.5)	974	3,167,530	30.7 (28.8-32.7)	2.20 (2.04-2.37)	36.8 (33.4 - 40.2)
Kidney	2531	6,708,802	37.7 (36.3-39.2)	1695	6,605,751	25.7 (24.5-26.9)	1.47 (1.38-1.56)	12 (10.1 - 13.9)
Stomach	1630	6,714,866	24.3 (23.1-25.5)	1205	6,610,007	18.2 (17.2-19.3)	1.33 (1.24-1.43)	6.1 (4.5 - 7.7)
Bladder	5905	6,693,090	88.2 (86-90.5)	4503	6,593,670	68.3 (66.3-70.3)	1.29 (1.24-1.34)	19.9 (16.9 - 22.9)
Cervix †	425	3,194,558	13.3 (12.1-14.6)	333	3,170,383	10.5 (9.4-11.7)	1.27 (1.10-1.46)	2.8 (1.1 - 4.5)
Colon and rectum	9797	6,682,992	146.6 (143.7-149.5)	7685	6,584,215	116.7 (114.1-119.4)	1.26 (1.22-1.29)	29.9 (26 - 33.8)
Esophagus	2398	6,714,689	35.7 (34.3-37.2)	1895	6,609,251	28.7 (27.4-30)	1.25 (1.17-1.32)	7 (5.1 - 8.9)
Thyroid	408	6,716,297	6.1 (5.5-6.7)	330	6,610,482	5 (4.5-5.6)	1.22 (1.05-1.41)	1.1 (0.3 - 1.9)
Lymphoma	3244	6,705,683	48.4 (46.7-50.1)	2667	6,601,545	40.4 (38.9-42)	1.20 (1.14-1.26)	8 (5.7 - 10.3)
Head and neck	1808	6,712,182	26.9 (25.7-28.2)	1484	6,606,639	22.5 (21.3-23.6)	1.20 (1.12-1.28)	4.4 (2.7 - 6.1)
Lung	9988	6,706,212	148.9 (146-151.9)	8468	6,601,831	128.3 (125.5-131)	1.16 (1.13-1.20)	20.6 (16.6 - 24.6)
Leukemia	3543	6,705,510	52.8 (51.1-54.6)	3095	6,600,800	46.9 (45.3-48.6)	1.13 (1.07-1.18)	5.9 (3.5 - 8.3)
Central nervous system	1220	6,716,271	18.2 (17.2-19.2)	1086	6,610,573	16.4 (15.5-17.4)	1.11 (1.02-1.2)	1.8 (0.4 - 3.2)
Breast	9789	6,669,742	146.8 (143.9-149.7)	8803	6,565,840	134.1 (131.3-136.9)	1.09 (1.06-1.13)	12.7 (8.7 - 16.7)
Ovary †	1098	3,193,046	34.4 (32.4-36.5)	997	3,169,029	31.5 (29.5-33.5)	1.09 (1.00-1.19)	2.9 (0.1 - 5.7)
Myeloma	1447	6,713,503	21.6 (20.5-22.7)	1419	6,607,559	21.5 (20.4-22.6)	1.00 (0.93-1.08)	0.10 (−1.5 - 1.7)

Melanoma	3446	6,701,556	51.4 (49.7-53.2)	3526	6,594,474	53.5 (51.7-55.3)	0.96 (0.92-1.01)	−2.1 (−4.6 - 0.4)
Prostate ††	12,281	3,465,749	354.4 (348.1-360.7)	13,132	3,377,589	388.8 (382.2-395.5)	0.91 (0.89-0.93)	−34.4 (−43.5 - −25.3)
Non-melanoma skin	26,068	6,585,383	395.8 (391.0-400.7)	28,480	6,461,269	440.7 (435.6-445.9)	0.90 (0.88-0.91)	−44.9 (−51.9 - −37.9)
Testis ††	96	3,521,299	2.7 (2.2-3.3)	132	3,439,203	3.8 (3.2-4.6)	0.71 (0.55-0.92)	−1.1 (−2.0 - −0.20)

Abbreviation: CI, confidence interval. * Per 100,000 person years, † Analyzed only among females, †† Analyzed only among males

Figure 4.1.A. Cumulative incidence of first cancer among patients with and without type 2 diabetes



Number at risk

890,214	502,624	244,529	92,939	20,474
890,214	511,512	254,394	95,007	18,584

Figure 4.1.B Cumulative incidence from first to second cancer among patients with and without type 2 diabetes

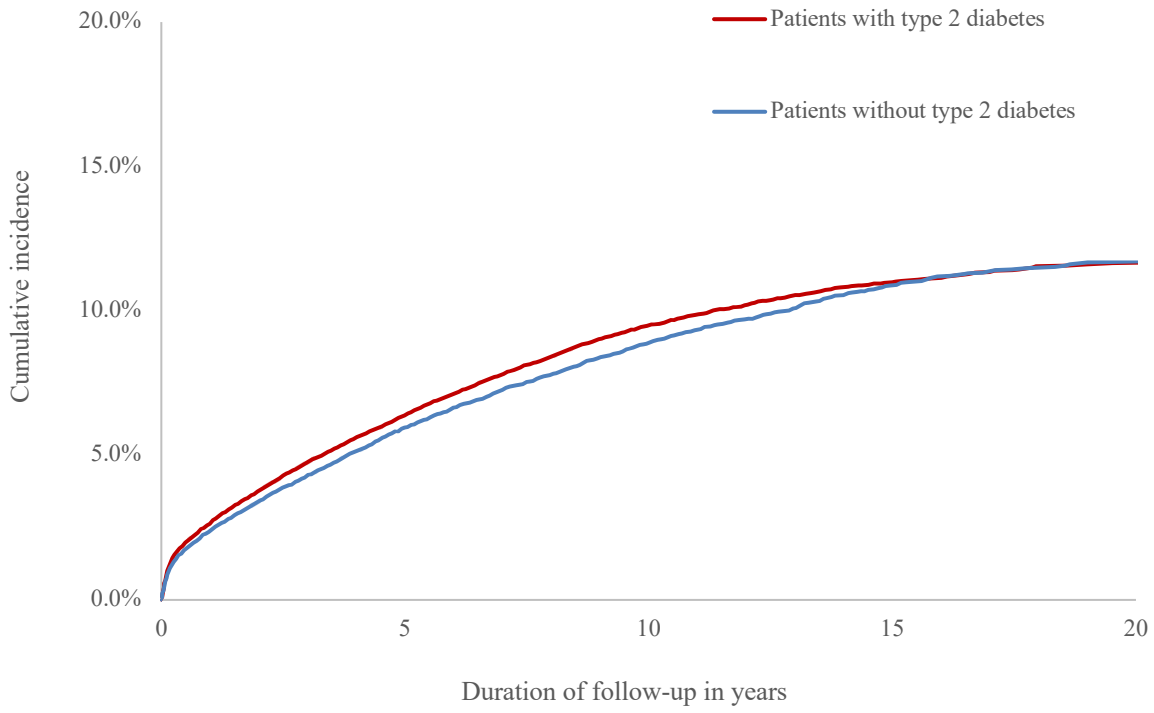
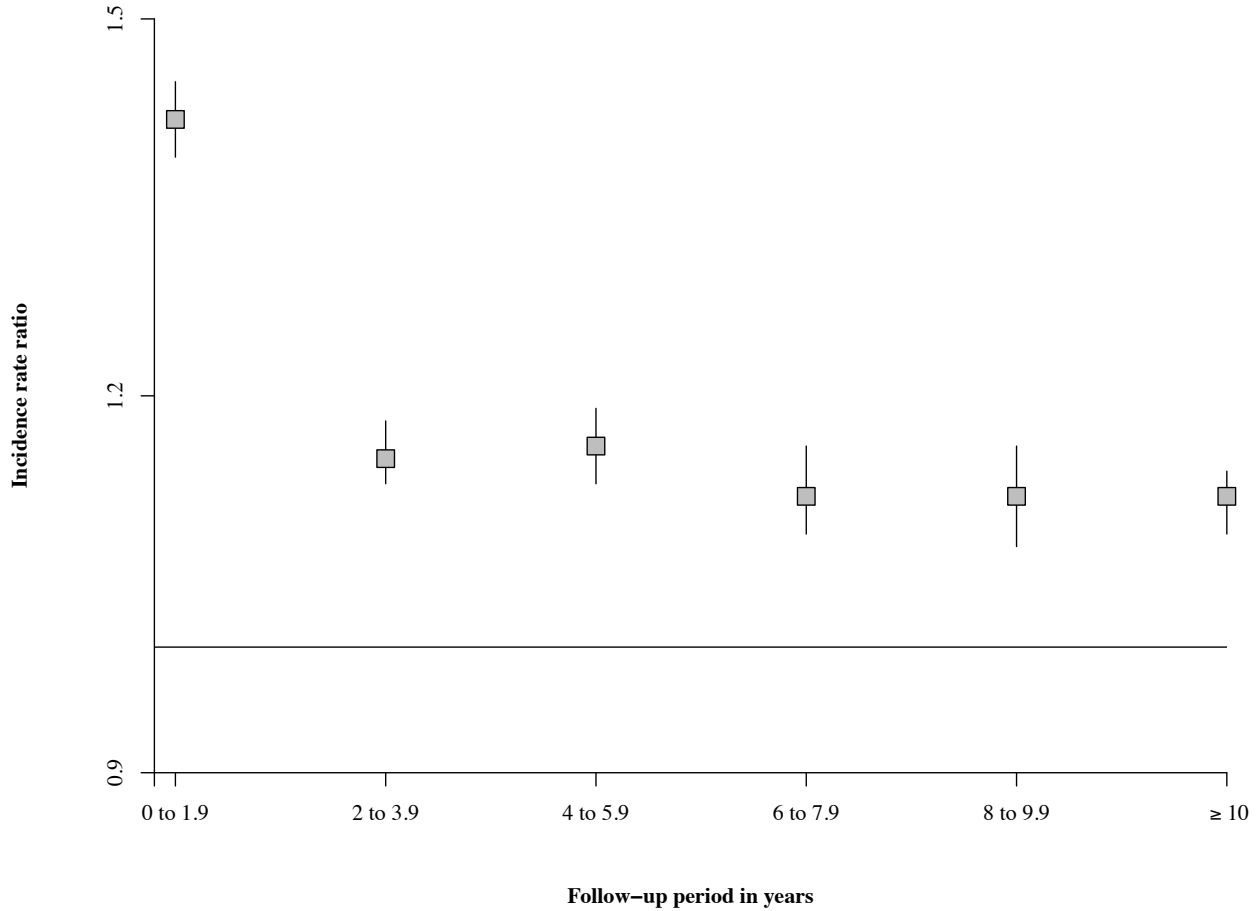


Figure 4.2. Incidence rate ratios comparing the incidence of all cancers among patients with and without type 2 diabetes over duration of follow-up



S4. Long-Term Patterns of Cancer Incidence Among Patients With and Without Type 2 Diabetes in the United Kingdom: Supplementary material

Figure S4.1 Study flow chart

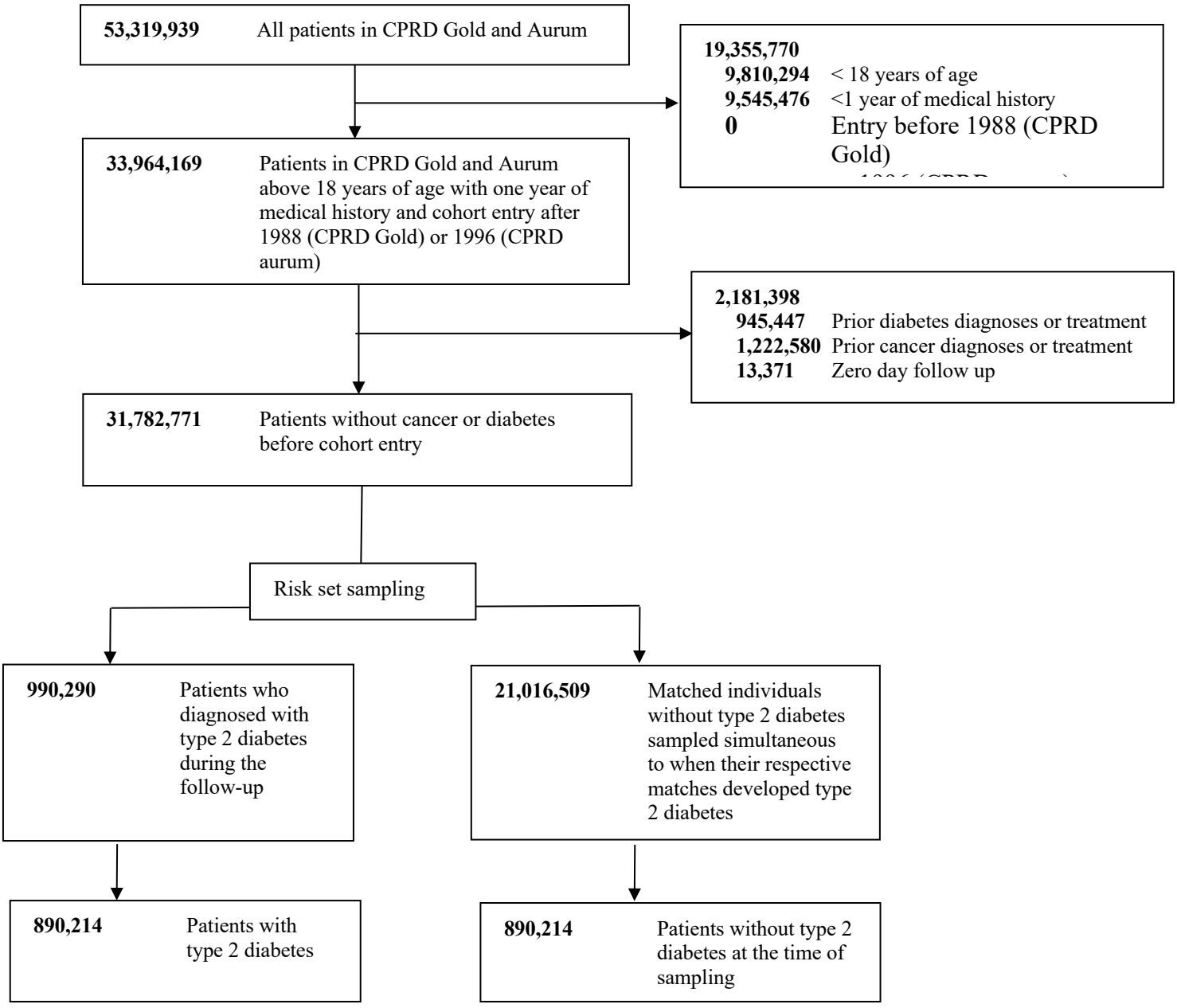
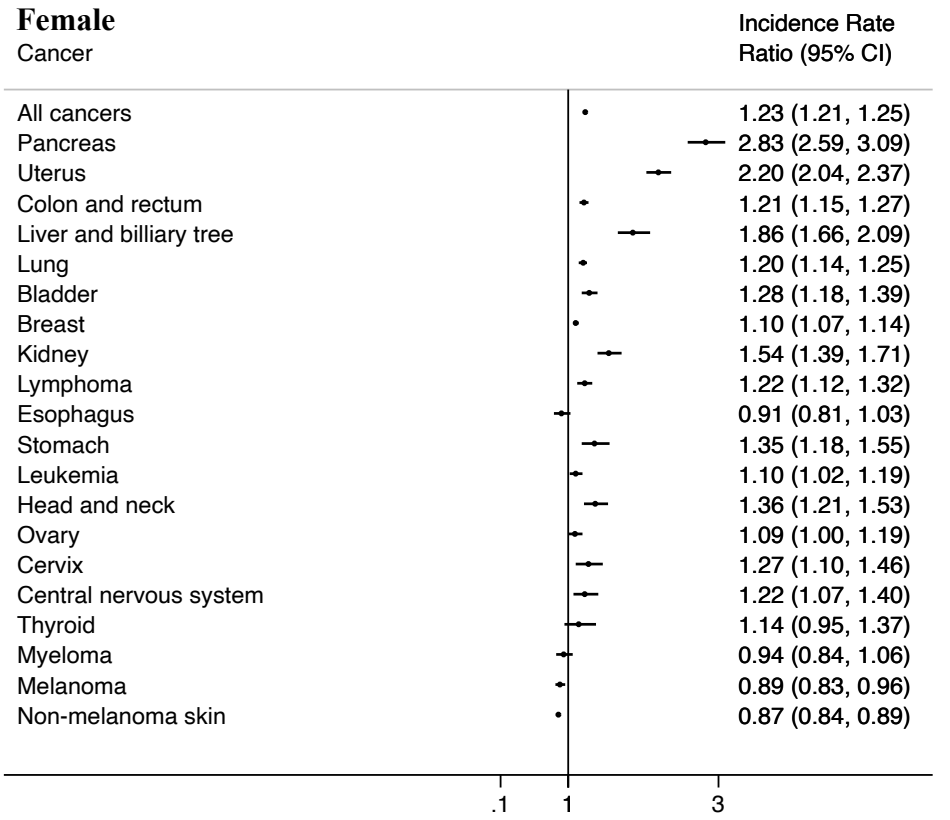


Figure S4.2 Association of type 2 diabetes and cancer incidence by sex



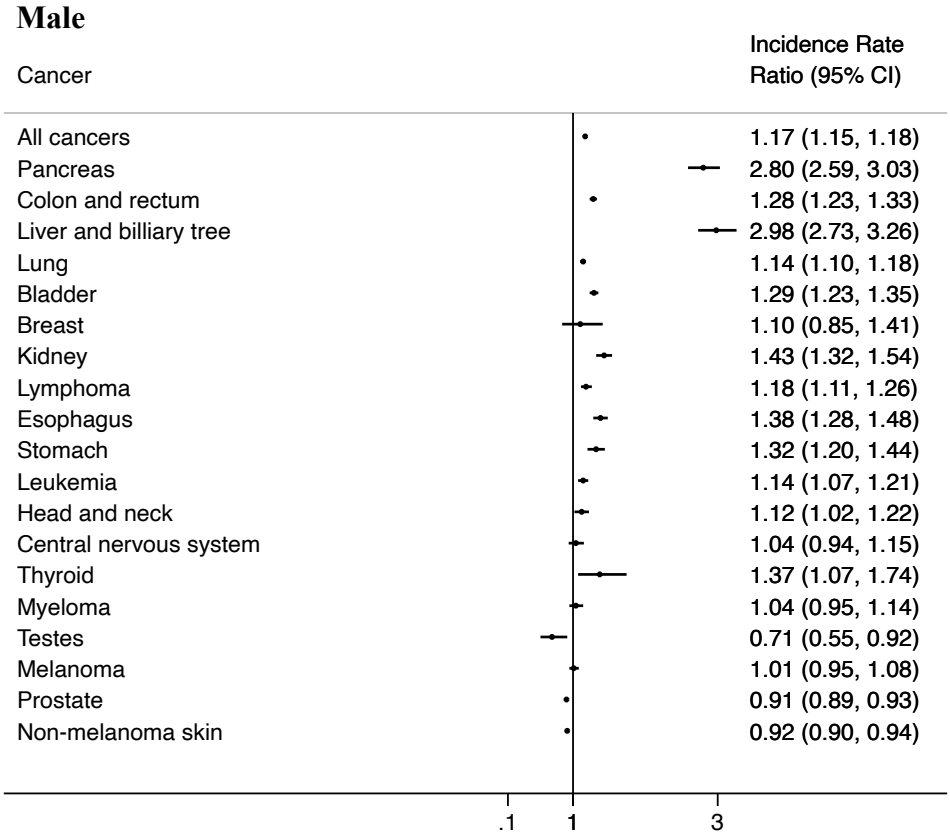
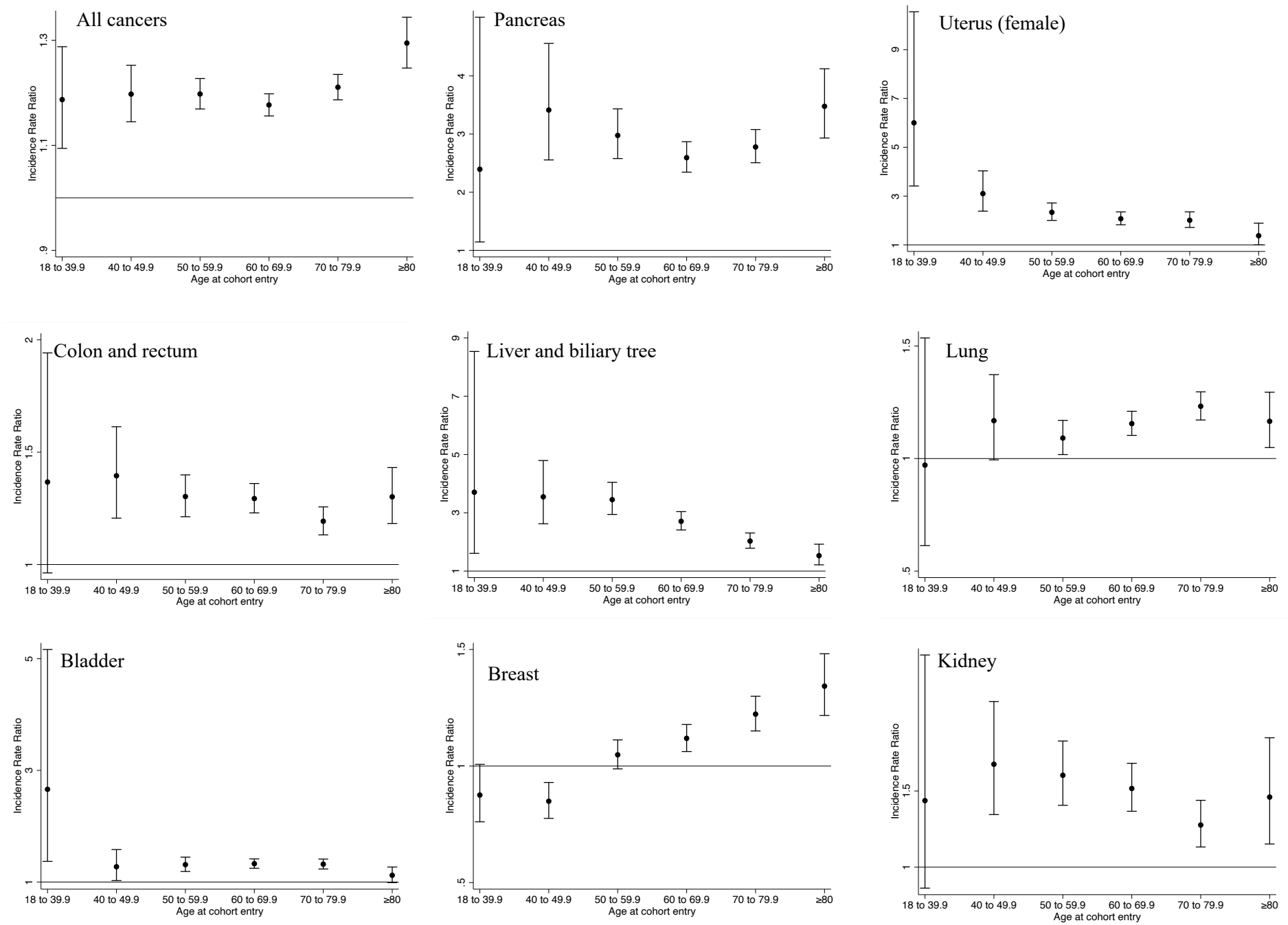
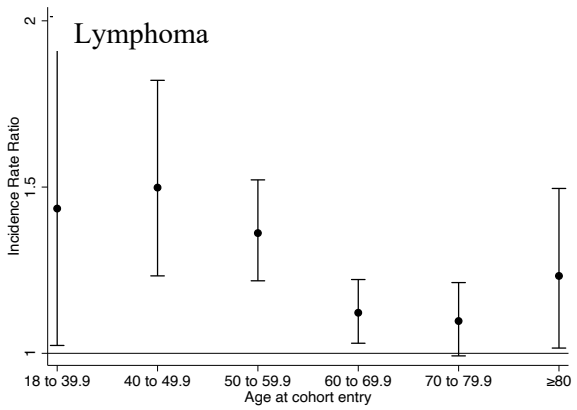
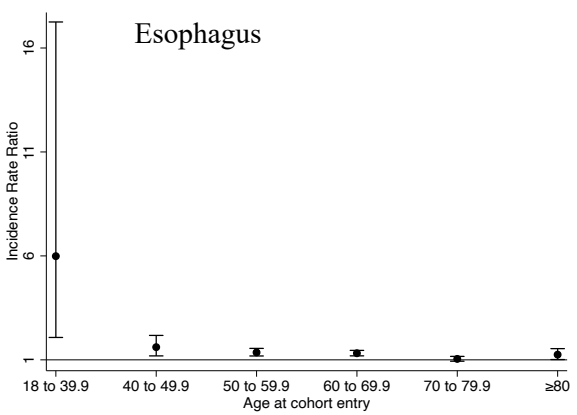
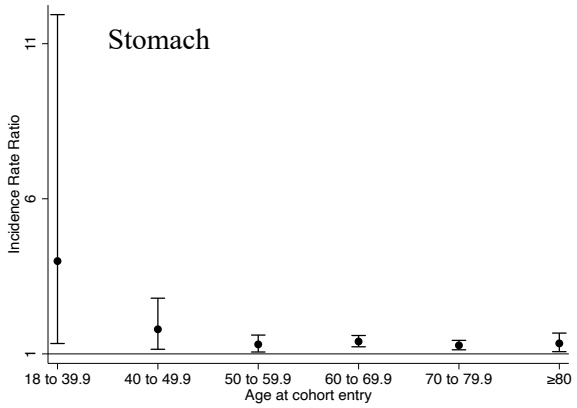


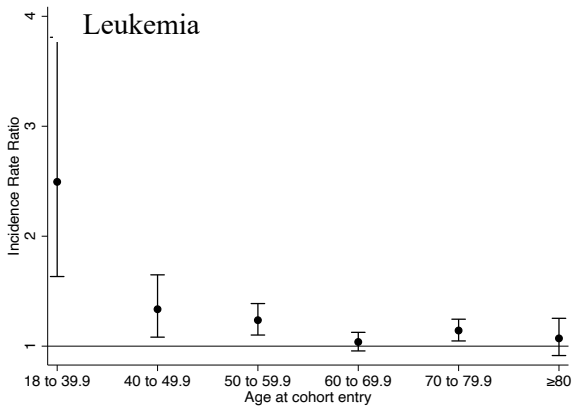
Figure S4.3 Association between type 2 diabetes and cancer incidence based on age at diabetes onset

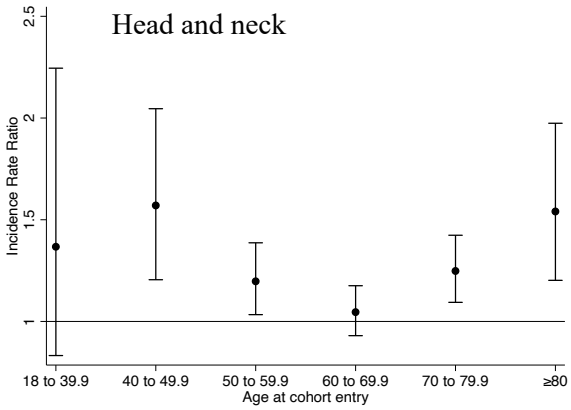


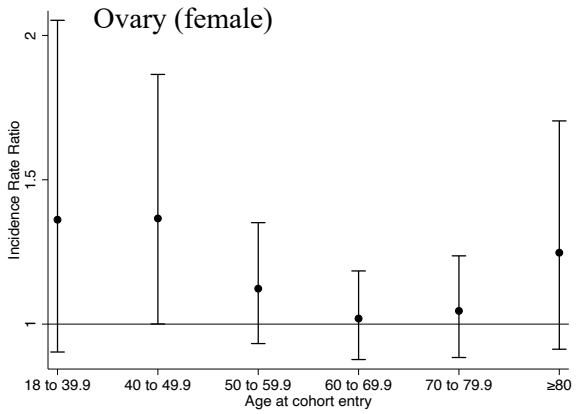

Lymphoma
Incidence Rate Ratio
1
1.5
2
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

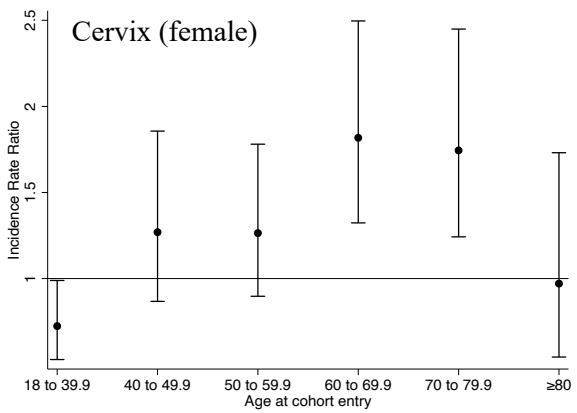

Esophagus
Incidence Rate Ratio
1
6
11
16
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

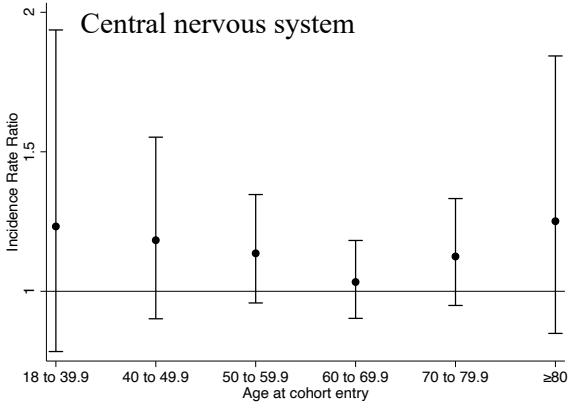

Stomach
Incidence Rate Ratio
1
6
11
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

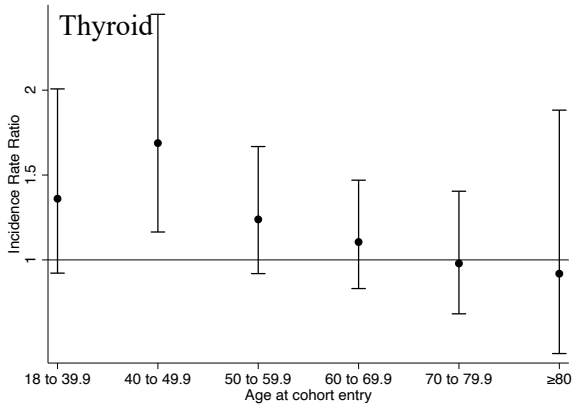

Leukemia
Incidence Rate Ratio
1
2
3
4
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

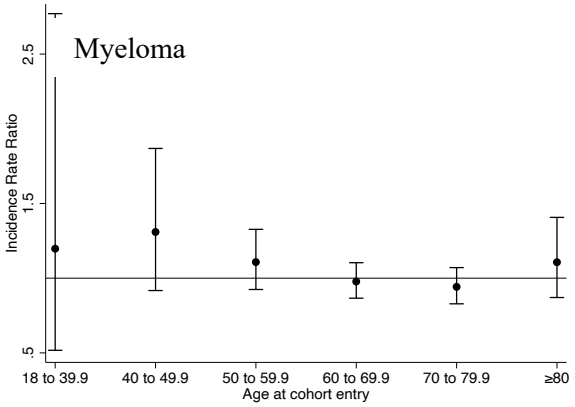

Head and neck
Incidence Rate Ratio
1
1.5
2
2.5
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

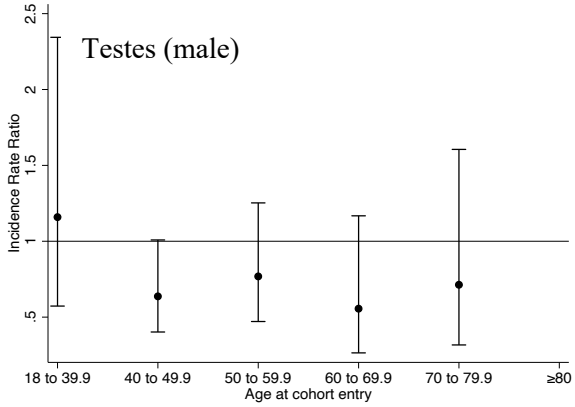

Ovary (female)
Incidence Rate Ratio
1
1.5
2
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

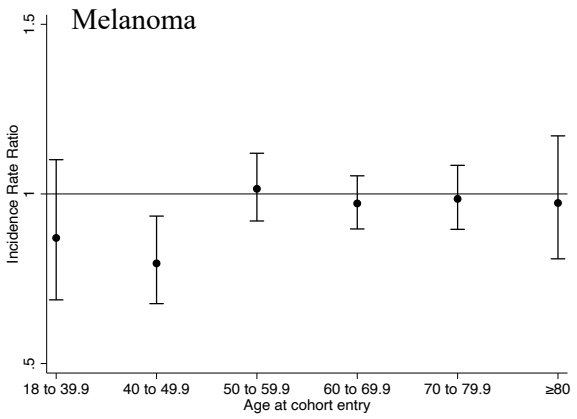

Cervix (female)
Incidence Rate Ratio
1
1.5
2
2.5
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

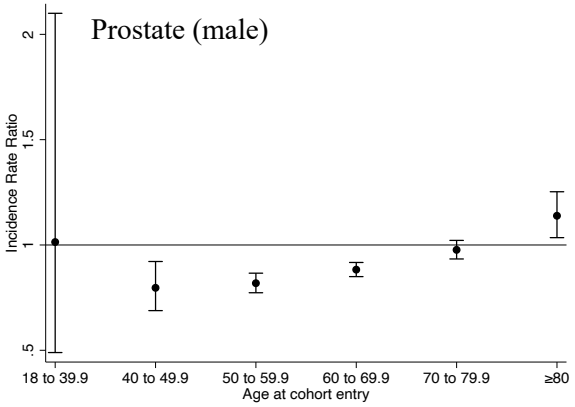

Central nervous system
Incidence Rate Ratio
1
1.5
2
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry


Thyroid
Incidence Rate Ratio
1
1.5
2
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry


Myeloma
Incidence Rate Ratio
.5
1
1.5
2.5
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry


Testes (male)
Incidence Rate Ratio
.5
1
1.5
2
2.5
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry


Melanoma
Incidence Rate Ratio
.5
1
1.5
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry


Prostate (male)
Incidence Rate Ratio
.5
1
1.5
2
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

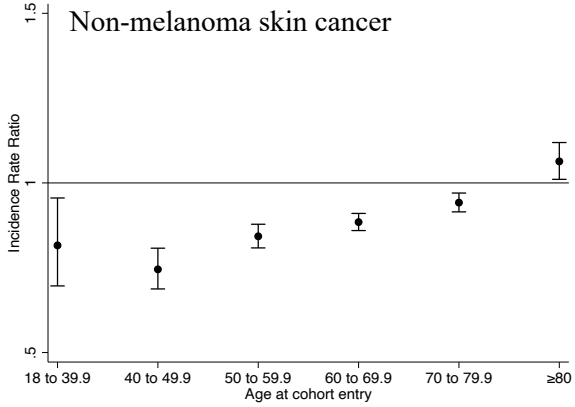
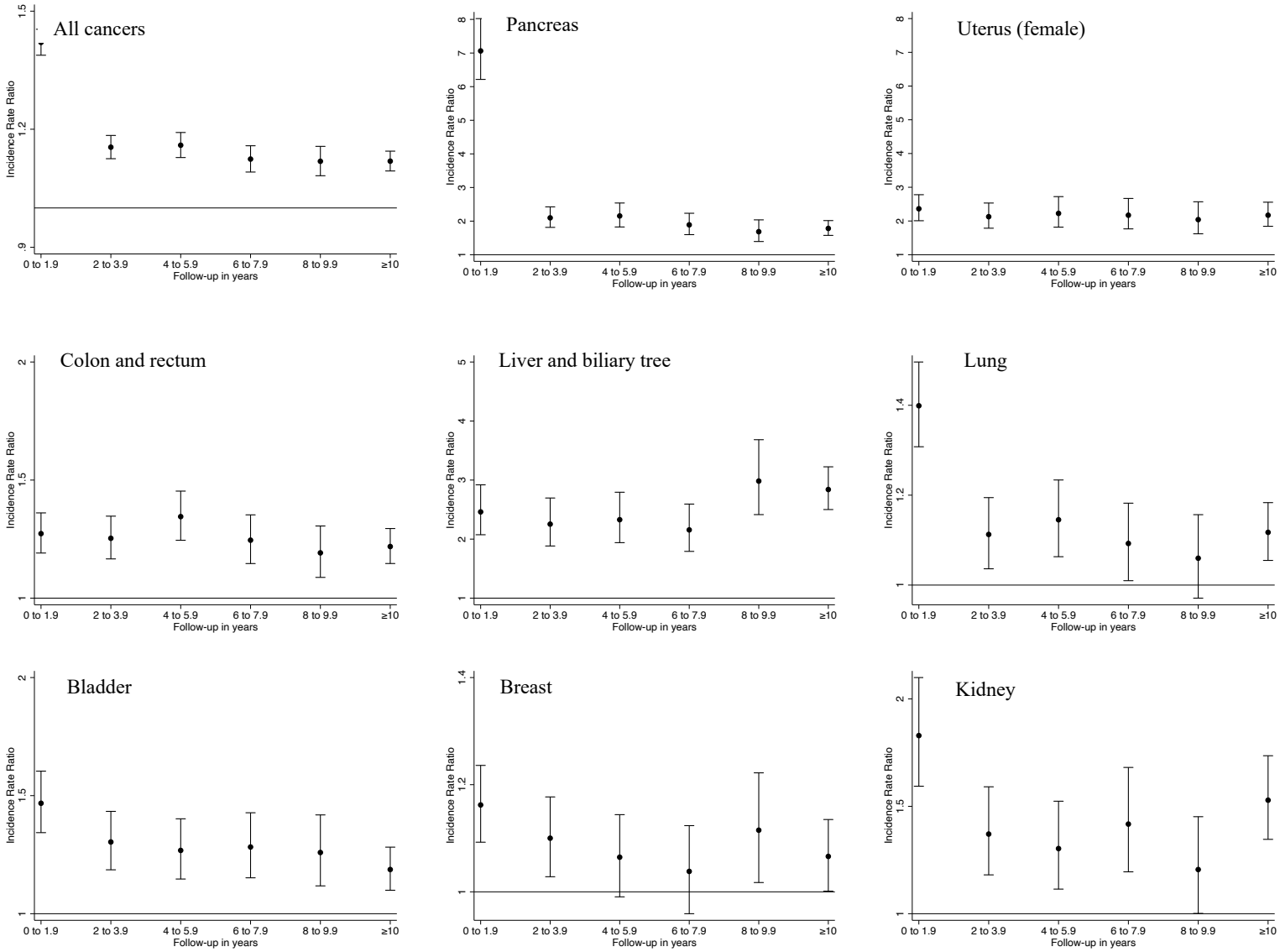
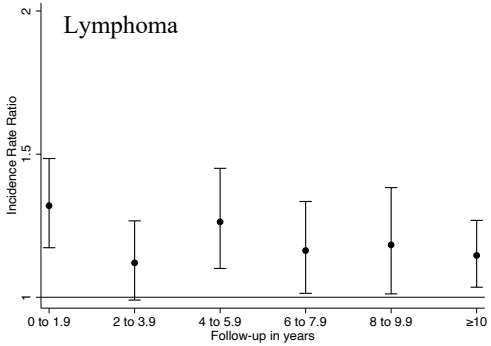
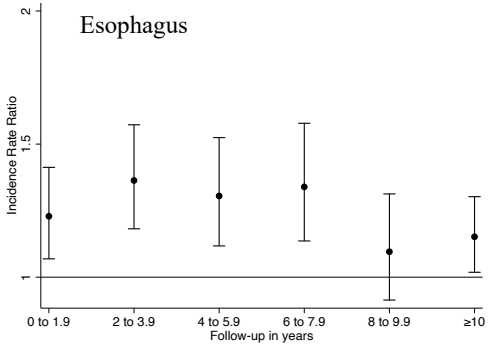
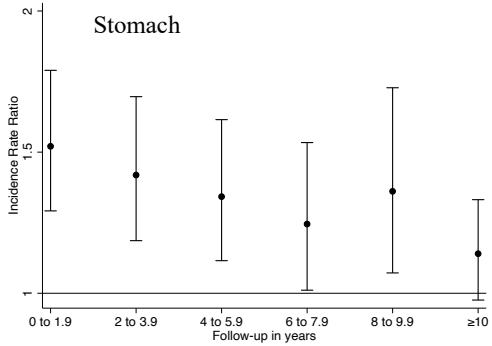

Non-melanoma skin cancer
Incidence Rate Ratio
.5
1
1.5
18 to 39.9
40 to 49.9
50 to 59.9
60 to 69.9
70 to 79.9
≥80
Age at cohort entry

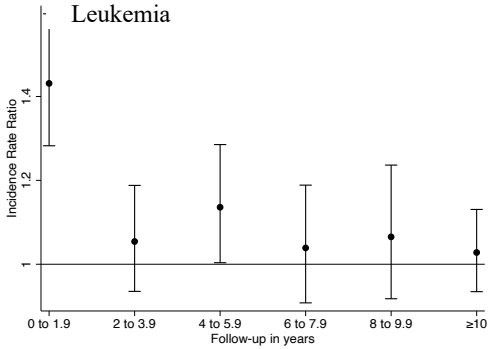
Figure S4.4 Association between type 2 diabetes and cancer incidence based on follow-up period

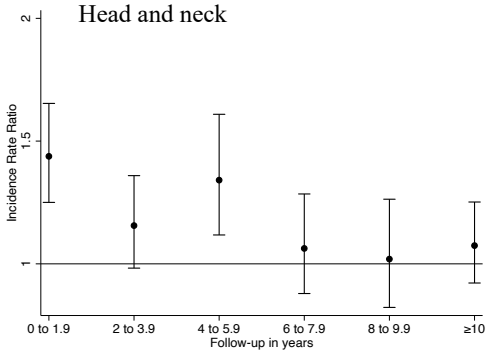


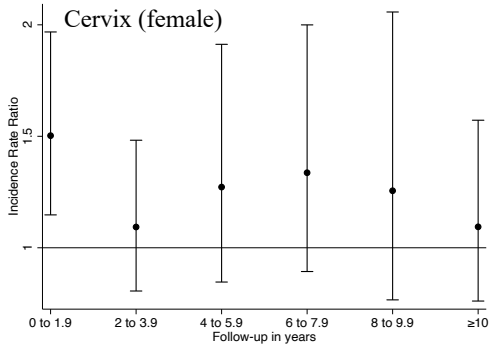

Lymphoma
Incidence Rate Ratio
1
1.5
2
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

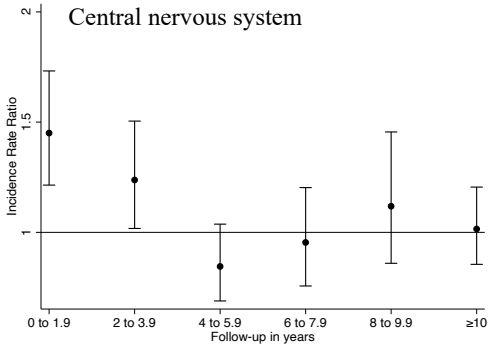

Esophagus
Incidence Rate Ratio
1
1.5
2
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

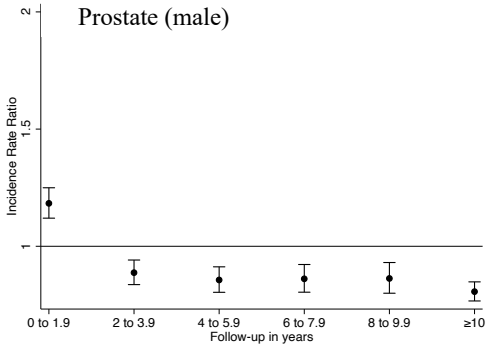

Stomach
Incidence Rate Ratio
1
1.5
2
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

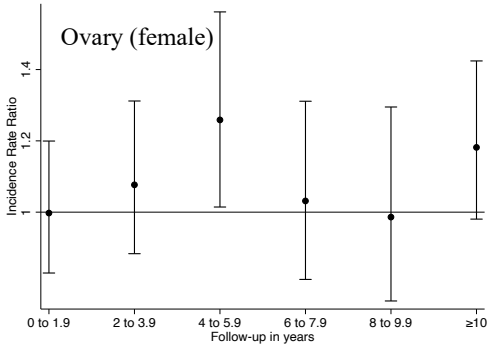

Leukemia
Incidence Rate Ratio
1
1.2
1.4
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

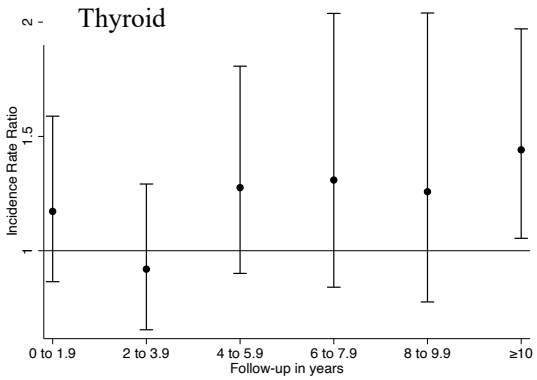

Head and neck
Incidence Rate Ratio
1
1.5
2
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

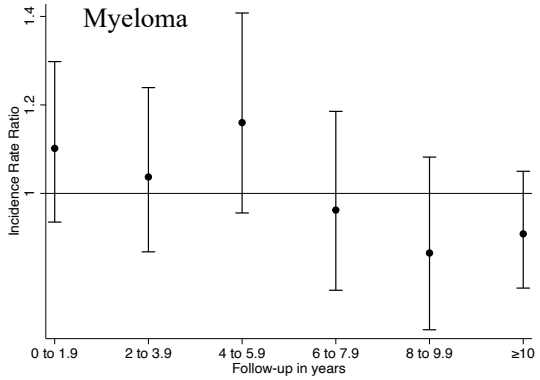

Cervix (female)
Incidence Rate Ratio
1
1.5
2
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

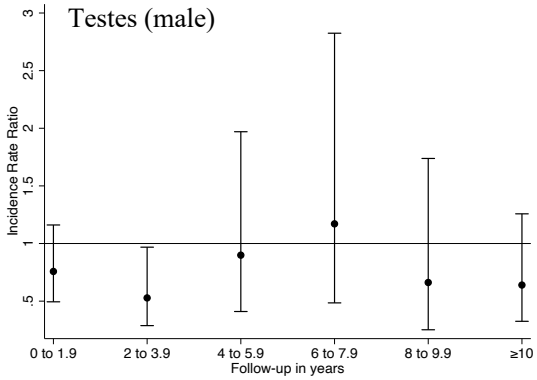

Central nervous system
Incidence Rate Ratio
1
1.5
2
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

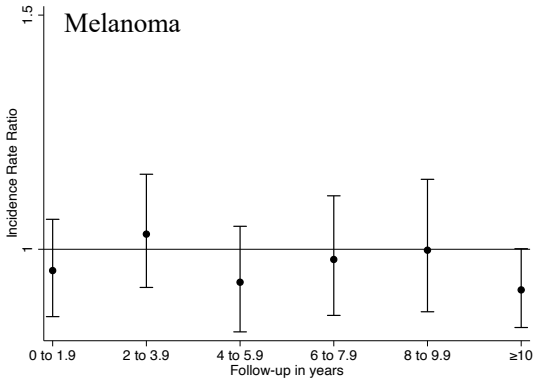

Prostate (male)
Incidence Rate Ratio
1
1.5
2
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years


Ovary (female)
Incidence Rate Ratio
1
1.2
1.4
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years


Thyroid
Incidence Rate Ratio
1
1.5
2
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years


Myeloma
Incidence Rate Ratio
1
1.2
1.4
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years


Testes (male)
Incidence Rate Ratio
.5
1
1.5
2
2.5
3
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years


Melanoma
Incidence Rate Ratio
1
1.5
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

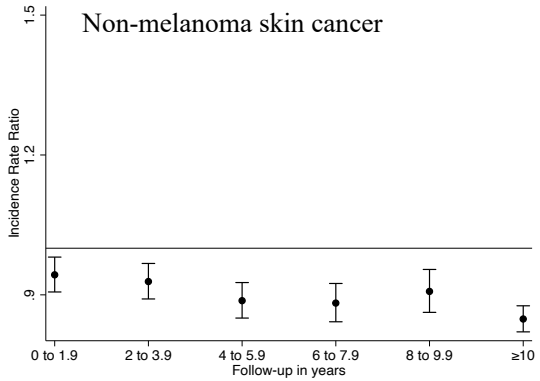
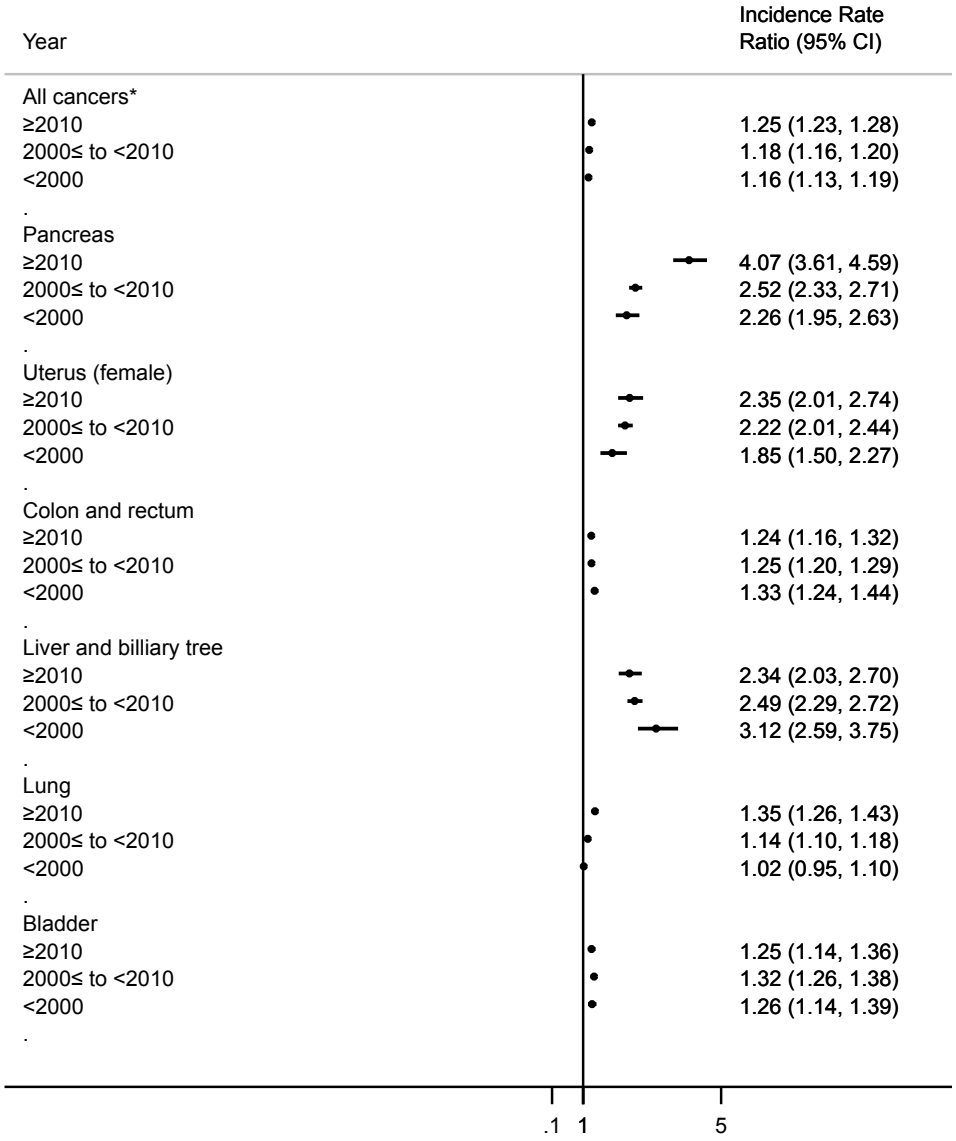
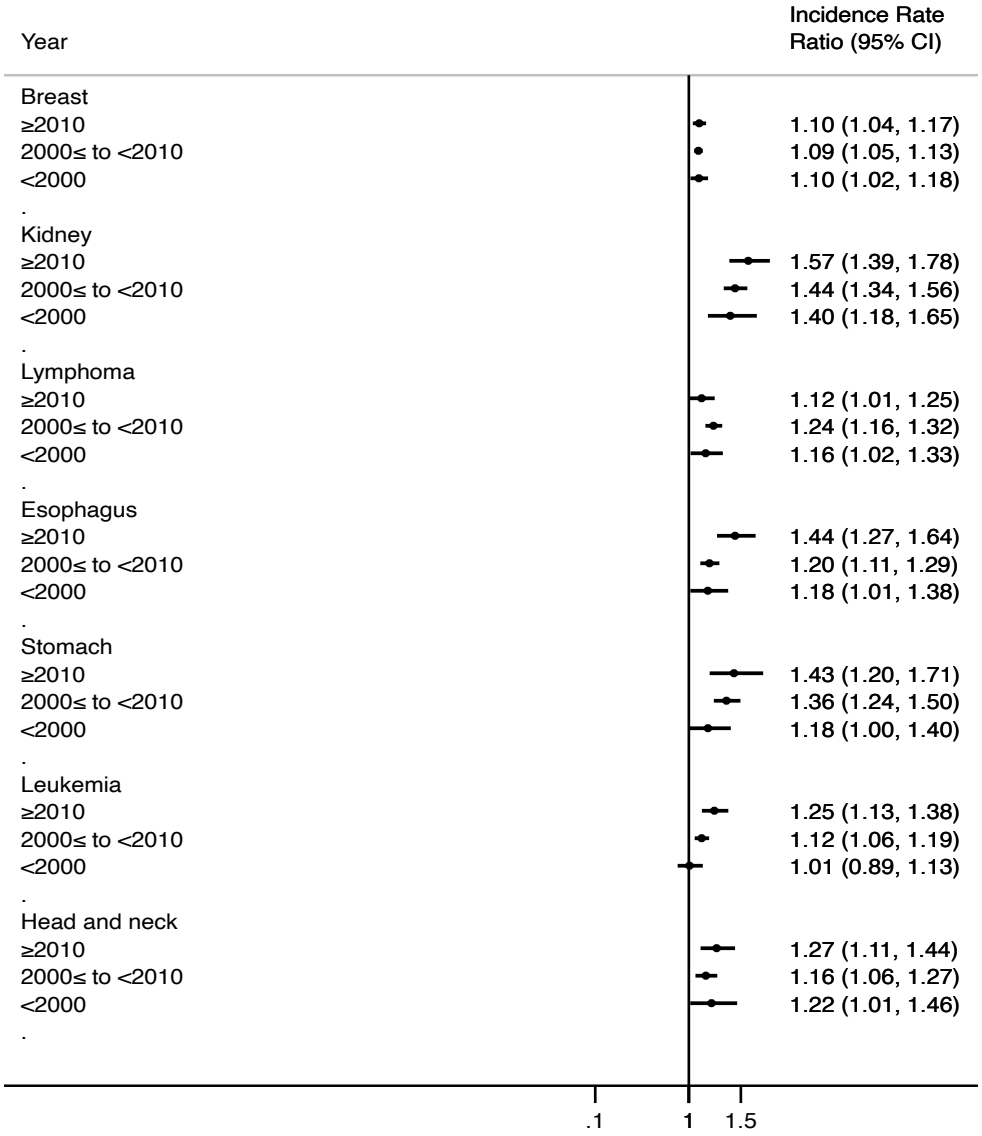
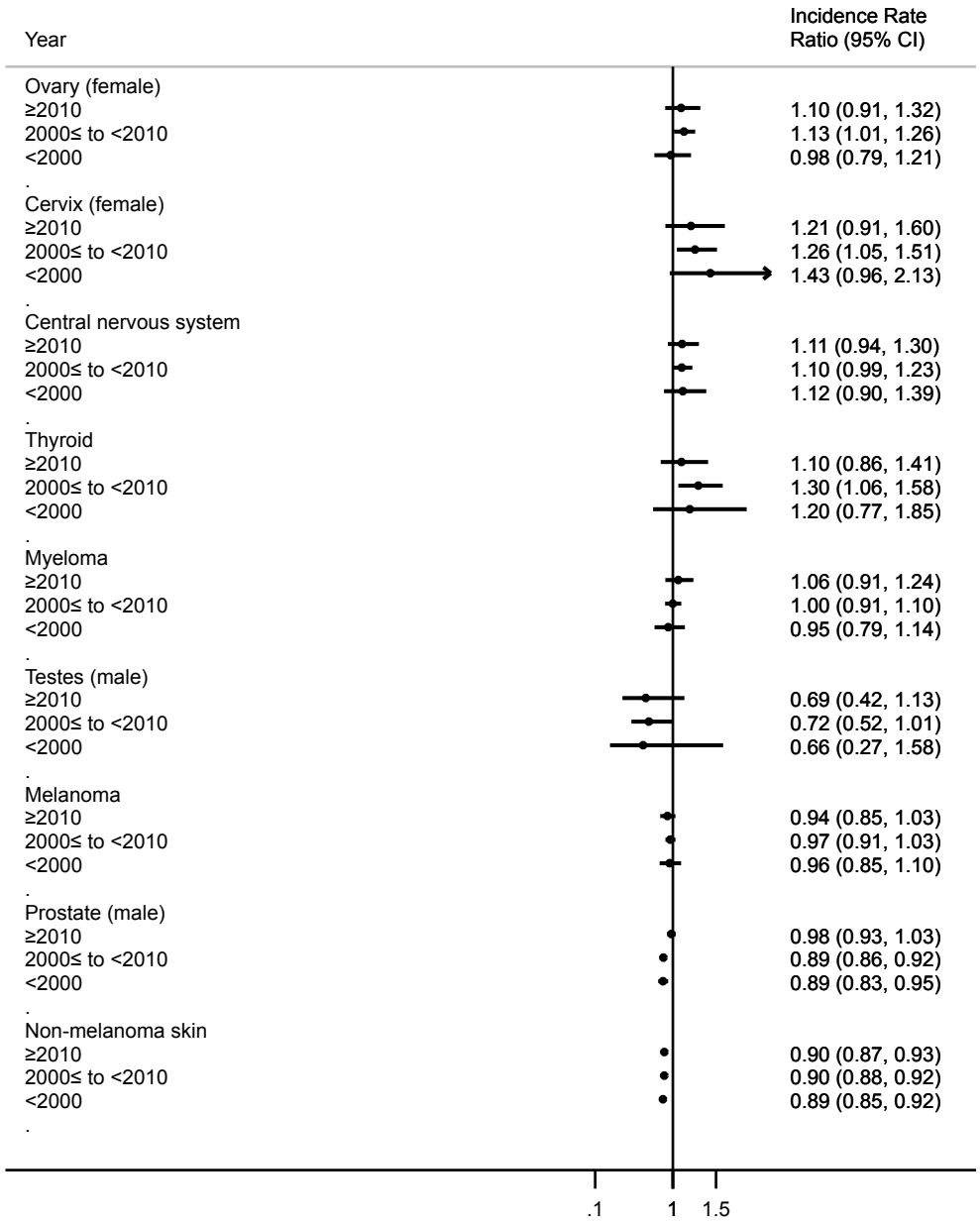

Non-melanoma skin cancer
Incidence Rate Ratio
.9
1.2
1.5
0 to 1.9
2 to 3.9
4 to 5.9
6 to 7.9
8 to 9.9
≥10
Follow-up in years

Figure S4.5 Association between type 2 diabetes and cancer incidence based on cohort entry year



*Median follow up time for those with cohort entry year ≥2010, 2000 to <2010, and <2000 were 4.2 years, 9.5 years, and 9.0 years, respectively


Year
Incidence Rate Ratio (95% CI)
Breast
≥2010
1.10 (1.04, 1.17)
2000≤ to <2010
1.09 (1.05, 1.13)
<2000
1.10 (1.02, 1.18)
.
Kidney
≥2010
1.57 (1.39, 1.78)
2000≤ to <2010
1.44 (1.34, 1.56)
<2000
1.40 (1.18, 1.65)
.
Lymphoma
≥2010
1.12 (1.01, 1.25)
2000≤ to <2010
1.24 (1.16, 1.32)
<2000
1.16 (1.02, 1.33)
.
Esophagus
≥2010
1.44 (1.27, 1.64)
2000≤ to <2010
1.20 (1.11, 1.29)
<2000
1.18 (1.01, 1.38)
.
Stomach
≥2010
1.43 (1.20, 1.71)
2000≤ to <2010
1.36 (1.24, 1.50)
<2000
1.18 (1.00, 1.40)
.
Leukemia
≥2010
1.25 (1.13, 1.38)
2000≤ to <2010
1.12 (1.06, 1.19)
<2000
1.01 (0.89, 1.13)
.
Head and neck
≥2010
1.27 (1.11, 1.44)
2000≤ to <2010
1.16 (1.06, 1.27)
<2000
1.22 (1.01, 1.46)
.
.1
1
1.5


Year
Incidence Rate Ratio (95% CI)
Ovary (female)
≥2010
1.10 (0.91, 1.32)
2000≤ to <2010
1.13 (1.01, 1.26)
<2000
0.98 (0.79, 1.21)
Cervix (female)
≥2010
1.21 (0.91, 1.60)
2000≤ to <2010
1.26 (1.05, 1.51)
<2000
1.43 (0.96, 2.13)
Central nervous system
≥2010
1.11 (0.94, 1.30)
2000≤ to <2010
1.10 (0.99, 1.23)
<2000
1.12 (0.90, 1.39)
Thyroid
≥2010
1.10 (0.86, 1.41)
2000≤ to <2010
1.30 (1.06, 1.58)
<2000
1.20 (0.77, 1.85)
Myeloma
≥2010
1.06 (0.91, 1.24)
2000≤ to <2010
1.00 (0.91, 1.10)
<2000
0.95 (0.79, 1.14)
Testes (male)
≥2010
0.69 (0.42, 1.13)
2000≤ to <2010
0.72 (0.52, 1.01)
<2000
0.66 (0.27, 1.58)
Melanoma
≥2010
0.94 (0.85, 1.03)
2000≤ to <2010
0.97 (0.91, 1.03)
<2000
0.96 (0.85, 1.10)
Prostate (male)
≥2010
0.98 (0.93, 1.03)
2000≤ to <2010
0.89 (0.86, 0.92)
<2000
0.89 (0.83, 0.95)
Non-melanoma skin
≥2010
0.90 (0.87, 0.93)
2000≤ to <2010
0.90 (0.88, 0.92)
<2000
0.89 (0.85, 0.92)
.1
1
1.5

Chapter 5. Dipeptidyl Peptidase-4 Inhibitors and the Risk of Skin Cancer Among Patients with Type 2 Diabetes: Population-Based Cohort Study

5.1 Preface

In chapter four, we observed that patients with diabetes had a higher burden of cancer overall, a similar burden of melanoma, and a lower burden of nonmelanoma skin cancer when compared with patients without diabetes.[204] Nevertheless, we found that skin cancers are the most commonly diagnosed cancers in patients with diabetes.[204] This is significant, given that skin cancer diagnosis has substantial impact on management and prognosis of co-existent diabetes. Importantly, novel drugs such as DPP-4 inhibitors, currently the most used second-to-third line antihyperglycemic drug,[18] might influence biological pathways involved in skin carcinogenesis. Indeed, DPP-4 expression is lost early in the malignant transformation of melanocytes, resulting in melanomas.[205] Paradoxically, pharmacological inhibition of DPP-4 by DPP-4 inhibitors has been shown to inhibit melanoma development in mice.[105] Role of DPP-4 inhibition in nonmelanoma skin cancers is understood yet less clearly.[206] No observational study has been conducted to examine the effect of DPP-4 inhibitor use on the incidence of skin cancer. Thus, in this chapter, using data from the UK, we examined whether DPP-4 inhibitors are associated with melanoma and nonmelanoma skin cancer, separately, in patients with diabetes. This paper has been submitted to *Diabetes Care*.

5.2 Title Page

Dipeptidyl Peptidase-4 Inhibitors and the Risk of Skin Cancer Among Patients with Type 2 Diabetes: Population-Based Cohort Study

Richeek Pradhan MD MS,[1,2] Oriana H. Y. Yu MD MSc,[2,3] Robert W. Platt PhD,[1,2] Laurent Azoulay PhD[1,2,4]

[1] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada.

[2] Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Canada.

[3] Division of Endocrinology, Jewish General Hospital, Montreal, Canada.

[4] Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada.

Word count: 3278

Running title: DPP-4 inhibitors and Skin Cancer

Number of tables: 4

Number of figures: 0

Keywords: Dipeptidyl peptidase-4 inhibitors, Skin Cancer, Drug Effects, Drug Safety, Pharmacoepidemiology

Correspondence:

Dr. Laurent Azoulay

Centre for Clinical Epidemiology, Jewish General Hospital, Lady Davis Institute

3755 Cote Sainte-Catherine, H425.1, Montreal, Canada, H3T 1E2

Tel.: (514) 340-8222 ext. 28396

Email: laurent.azoulay@mcgill.ca

Twitter: @LaurentAzoulay0

December 15, 2022

5.3 ABSTRACT

INTRODUCTION: The dipeptidyl peptidase-4 (DPP-4) enzyme influences carcinogenic pathways in the skin, although its exact role remains uncertain. The objective of this study was to determine whether DPP-4 inhibitors are associated with the incidence of melanoma and nonmelanoma skin cancer, compared with sulfonylureas.

RESEARCH DESIGN AND METHODS: Using the United Kingdom Clinical Practice Research Datalink, we assembled two new-user active comparator cohorts for each skin cancer outcome from 2007 to 2019. For melanoma, the cohort included 96,739 DPP-4 inhibitor users and 209,341 sulfonylurea users, and 96,411 DPP-4 inhibitor users and 208,626 sulfonylurea users for nonmelanoma skin cancer. Propensity score fine stratification weighted Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of melanoma and nonmelanoma skin cancer, separately.

RESULTS: Overall, DPP-4 inhibitors were associated with a 23% decreased risk of melanoma compared with sulfonylureas (49.7 vs. 65.3 per 100,000 person-years, respectively; HR 0.77, 95% CI 0.61-0.96). The HR progressively reduced with increasing cumulative duration of use (0-2 years HR 1.14, 95% CI 0.84-1.54; 2.1-5 years HR 0.44, 95% CI 0.29-0.66; >5 years HR 0.33, 95% CI 0.14-0.74). In contrast, these drugs were not associated with the incidence of nonmelanoma skin cancer, compared with sulfonylureas (448.1 vs. 426.1 per 100,000 person-years, respectively; HR 1.06, 95% CI 0.98-1.15).

CONCLUSIONS: In this large, population-based cohort study, DPP-4 inhibitors were associated with a reduced risk of melanoma but not nonmelanoma skin cancer, compared with sulfonylureas.

5.4 INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors are the most prescribed second to third line antihyperglycemic drugs that work by reducing blood glucose without causing hypoglycemia or inducing weight gain.[1 2] These drugs that act by prolonging the action of incretins which results in the release of insulin.[1 2] With increasing use, several pleiotropic as well as adverse effects of this drug class have been reported,[3] including a potential association with skin cancer.[4]

The role of the DPP-4 enzyme and its inhibition in skin cancer remains unclear.[5] In murine models of melanoma, DPP-4 expression is lost early during the malignant transformation of melanocytes.[4 6 7] Indeed, DPP-4 expression has been suggested as a biomarker differentiating between malignant melanoma and nevi.[8] In contrast, DPP-4 inhibition by sitagliptin in mice resulted in potent anti-tumor effects mediated through lymphocyte trafficking.[9] In nonmelanoma skin cancer, DPP-4 enzyme activity is high in basal cell carcinomas, while variable findings have been reported in squamous cell carcinomas with both higher and lower DPP-4 activity compared to non-cancerous skin.[4 10] To date, clinical studies examining the association between DPP-4 inhibitors and skin cancer have been limited. In a meta-analysis of randomized controlled trials (RCTs), DPP-4 inhibitors were associated with a reduced risk of skin cancer overall (odds ratio 0.85, 95% confidence intervals (CIs) 0.72–0.99) and malignant skin cancer (odds ratio 0.86, 95% CIs 0.73–1.00),[11] although in two other meta-analyses, an association with skin cancer was not found.[12 13] To our knowledge, no observational study has been conducted to address the association between DPP-4 inhibitor use and skin cancer in the real-world setting.

Thus, the objective of this study was to determine whether the use of DPP-4 inhibitors is associated with the incidence of melanoma and nonmelanoma skin cancer, separately, among

patients with type 2 diabetes, compared with use of sulfonylureas, another class of second-to-third line antihyperglycemic drugs.[1 2]

5.5 METHODS

5.5.1 Data Source

We used the Clinical Practice Research Datalink (CPRD), a representative, electronic health records database containing detailed information for more than 50 million patients seen at over 2000 general practices in the United Kingdom (UK).[14] In this database, clinical diagnoses are recorded using Read and SNOMED-CT classification system and drug prescriptions are recorded using UK Prescription Pricing Authority Dictionary.[14] Importantly, this database also records lifestyle, clinical, and anthropometric variables. These variables have been validated and the data and practices are audited regularly to ensure high quality.[15-18] Our study protocol was approved by the CPRD Research Data Governance (Protocol 22_001715) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

5.5.2 Study Population

We assembled two new-user, active comparator cohorts, each investigating a specific skin cancer outcome, from January 1, 2007 (the year the first DPP-4 inhibitors entered the UK market) through July 31, 2019. These cohorts compared initiators of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) with initiators of sulfonylureas (glibenclamide, gliclazide, glimepiride, glipizide, and tolbutamide). Cohort entry was defined by the date of either the first prescription of a DPP-4 inhibitor or a sulfonylurea during the study period. Patients below 18 years of age, those having concomitant use of the study drugs at cohort entry, and those with less than one year of medical history in the CPRD before cohort entry were excluded. The latter served as a washout period to identify new users. We then excluded patients previously diagnosed with any type of skin cancer ever before cohort entry and those with end-stage renal disease as it constitutes a relative contraindication to sulfonylurea use. We also

excluded patients with a history of use of the study drugs (DPP-4 inhibitors and sulfonylureas), as well as glucagon-like peptide-1 receptor agonist users, as these drugs share a similar mechanism of action with DPP-4 inhibitors.[19] Finally, we excluded patients with less than one year of follow-up for cancer latency purposes (i.e., lag period). Patients diagnosed with the skin cancer of interest during this lag period were excluded, resulting in two cohorts, one specific to each outcome of interest.

We used sulfonylureas as the comparator as they are widely used second to third line drugs among patients with type 2 diabetes, and have not been linked to skin cancer in both clinical[20] and laboratory settings.[21] We did not use other comparators such as metformin (typically initiated at early stage of the disease), insulin (used at an advanced stage), thiazolidinediones (as they are infrequently used due to their association with serious adverse events), GLP-1 receptor agonists (which have been potentially linked with skin cancers), or sodium glucose co-transporter-2 inhibitors (which are relatively new molecules whose use would have restricted the cohort to 2013 and later, which would be prohibitive due to small sample size).

5.5.3 Follow-Up

All patients were followed starting one year after cohort entry (i.e., after the lag period) until an incident diagnosis of the skin cancer of interest, one year after switching to one of the study drugs, death from any cause, end of registration with the general practice, or the end of the study period (July 31, 2020), whichever occurred first. Melanoma diagnoses have been previously validated in the CPRD, with a positive predictive value of 85% compared to medical review.[22] On the other hand, CPRD has a better documentation of nonmelanoma skin cancer, including basal cell carcinoma and cutaneous squamous cell carcinoma, than the UK national

cancer registry.[23 24] Moreover, validation studies of UK primary care databases have shown the positive predictive value to be 93%[25] and 83%[26] for basal cell carcinoma and cutaneous squamous cell carcinoma, respectively.

5.5.4 Potential Confounders

We considered a wide range of potential confounders, all measured before or at cohort entry. These included age (modeled using cubic splines with five interior knots to account for a possible non-linear relation with the exposure), sex, lifestyle-related factors (body mass index, alcohol-related disorders, smoking status), calendar year (as a proxy for temporal trends in prescribing and changes in ultraviolet radiation, categorized as 2007-2010, 2011-2014, 2015-2019) and region (as a proxy for exposure to sunlight). We considered known skin cancer risk factors, including pre-cancerous photodermatoses (serving as markers of sun exposure), and use of photosensitizing and immunosuppressive drugs. We also considered diabetes-related variables such as hemoglobin A1c, duration of diabetes (calculated as the time between cohort entry and the earliest of a diabetes diagnosis, use of an antihyperglycemic drug, or an HbA1c value of ≥ 6.5%), as well as microvascular [nephropathy, neuropathy, retinopathy] and macrovascular [myocardial infarction, stroke, peripheral arteriopathy] complications of diabetes. Furthermore, we adjusted for the use of antihyperglycemic drugs ever before cohort entry (including metformin, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, sodium-glucose cotransporter-2 inhibitors, and insulin), common comorbidities (heart failure, cancer, obstructive sleep apnea, osteoarthritis, chronic obstructive pulmonary disease, depression, dyslipidemia, gastrointestinal reflux disease, cardiac arrhythmia, hypertension, hypothyroidism) and comedications (antihypertensives, antiarrhythmics, antiplatelet agents, statins, non-steroidal anti-inflammatory drugs, corticosteroids, biologics, proton pump inhibitors), and markers of

healthcare-seeking behavior (uptake of cancer screening [fecal occult blood testing or colonoscopy, mammography, prostate-specific antigen testing] and vaccinations [including influenza and pneumococcal vaccinations] in the year before cohort entry).

5.5.5 Statistical Analysis

We used propensity score fine stratification to adjust for confounding.[27] In each cohort, we estimated the predicted probability of receiving a DPP-4 inhibitor versus a sulfonylurea by using multivariable logistic regression conditional on the covariates listed above. After trimming patients in the non-overlapping regions of the propensity score distributions, we created 50 strata based on the propensity score distribution of the DPP-4 inhibitor users. In each stratum, DPP-4 inhibitor users were assigned a weight of one, while sulfonylurea users were weighted in proportion to the number exposed in the corresponding stratum. This method estimates the average treatment effect among the treated, that is, the DPP-4 inhibitor group.

We used descriptive statistics to summarize the exposure groups' characteristics before and after weighting. Covariate balance before and after weighting were assessed using standardized differences, with a difference of less than 0.10 indicative of good balance.[28] Weighted incidence rates of melanoma and nonmelanoma skin cancer, with 95% CIs based on the Poisson distribution, were calculated for each exposure group. Weighted Kaplan-Meier curves were used to display the cumulative incidence of melanoma and nonmelanoma skin cancer for the exposure groups over the follow-up period. Finally, weighted Cox proportional hazards models were fit to estimate hazard ratios (HRs) with 95% CIs of incident melanoma and nonmelanoma skin cancer in the respective cohorts, comparing DPP-4 inhibitors with sulfonylureas. We also calculated the number needed to treat/harm for both outcomes after five years of follow-up by applying the Kaplan-Meier method.[29]

5.5.6 Secondary Analyses

We conducted four secondary analyses. In the first two analyses, we assessed whether the association varied with time since treatment initiation and cumulative duration of use of DPP-4 inhibitors. In these analyses, the exposure was defined in a time-varying manner, updated every person-day of follow-up. Specifically, the time since initiation was calculated as the difference between cohort entry date and end of follow-up, while the cumulative duration of use was the sum of prescription durations since cohort entry until the risk set event. In the third analysis, we assessed whether the association varied with individual drugs (sitagliptin, alogliptin, saxagliptin, linagliptin, vildagliptin). Lastly, we examined potential effect measure modification on the multiplicative scale by age (<65 vs. ≥ 65 years), sex, and use of immunosuppressive drugs. Effect modification was tested by including interaction terms between exposures and these variables in the models.

5.5.7 Sensitivity Analyses

We conducted two sensitivity analyses to assess the robustness of our findings. First, we repeated the analysis by lengthening the exposure lag period to three and five years to address uncertainties regarding the appropriate duration of cancer latency. Second, we used stabilized inverse probability of censoring weighting to investigate the potential for informative censoring from (1) drug crossover or switching during follow-up and (2) competing risk of death from any cause.[30-32] All analyses were conducted with SAS version 9.4 (SAS institute, Cary, NC).

5.6 Results

5.6.1 Melanoma outcome cohort

The melanoma outcome cohort included 96,739 new users of DPP-4 inhibitors and 209,341 new users of sulfonylureas (**Figure S5.1**). Before weighting, DPP-4 inhibitor users were more likely to be obese, have a longer duration of diabetes, have microvascular diseases, and enter at a later cohort entry year, than sulfonylurea users. After weighting, all covariates were well balanced, with the standardized difference varying between 0.01 to 0.03 (**Table 5.1**). Over a median follow-up of 2.6 years (interquartile range 1.1-5.0 years), a total of 634 melanoma events occurred generating a crude incidence rate of 60.5 per 100,000 person-years (95% CI 56.0-65.4).

Overall, after weighting, the use of DPP-4 inhibitors was associated with a 23% decrease in the incidence of melanoma compared with the use of sulfonylureas (49.7 vs. 65.3 per 100,000 person-years, respectively; HR 0.77, 95% CI 0.61-0.96) (**Table 5.2**). The cumulative incidence curves diverged after almost two years of use (**Figure S5.2**), with the number needed to treat being 880 at 5 years. The time since initiation analysis revealed no association early in the follow-up period (0-2 years HR 1.24, 95% CI 0.83-1.86), followed by HRs below the null value but with wide CIs (2.1-5 years HR 0.59, 95% CI 0.41-0.84; >5 years HR 0.69, 95% CI 0.42-1.13) (**Table 5.2**). Similarly, with cumulative duration of use, the HRs decreased with longer durations of use, with at least five years of use associated with a 67% decreased risk (HR 0.33, 95% CI 0.14-0.74) (**Table 5.2**).

The results were consistent across the individual drugs, with HRs below null value with wide CIs, except sitagliptin (the most common DPP-4 inhibitor in the cohort), where the CIs excluded the null value (**Table 5.2**). The association was not modified by age, sex, or prior use of immunosuppressants (**Figure S5.3**). Overall, the sensitivity analyses aligned with the primary

results, although the inverse probability of censoring weighted analysis generated wide CIs (**Figure S5.4**).

5.6.2 Nonmelanoma skin cancer outcome cohort

The nonmelanoma skin cancer cohort included 96,411 DPP-4 inhibitor new users and 208,626 sulfonylurea new users (**Figure 5.5**). As noted in the melanoma cohort, there were imbalances in terms of obesity, microvascular diseases, diabetes duration, and cohort entry year. After weighting, the covariates were well balanced between the exposure groups (standardized difference between 0.01 to 0.03) (**Table 5.3**). There were 4,702 nonmelanoma skin cancer events during a median of 2.6 years (interquartile range 1.1-5.0 years), generating an incidence rate of 455.7 per 100,000 (95% CI 442.8-468.9) person-years.

Overall, the use of DPP-4 inhibitors was not associated with the incidence of nonmelanoma skin cancer (448.1 vs. 426.1 per 100,000 person-years, respectively; HR 1.06, 95% CI 0.98-1.15) (**Table 5.4**). The cumulative incidence curves overlapped throughout the follow-up period (**Figure 5.6**). The HR remained close to the null value in all categories of time since initiation analysis (0-2 years HR 1.09, 95% CI 0.93-1.28; 2.1-5 years HR 1.10, 95% CI 0.98-1.24; >5 years HR 1.04, 95% CI 0.88-1.22). Similarly, there was no consistent pattern with cumulative duration of use, with all HRs around the null value (0-2 years HR 0.98, 95% CI 0.87-1.11; 2.1-5 years HR 1.16, 95% CI 1.02-1.31; >5 years HR 0.85, 95% CI 0.68-1.08).

The analysis stratified by individual drugs generated effect estimates similar to the primary analysis, with CIs including the null value for all drugs (**Table 5.4**). While there was a 13% increased risk in the subgroup of patients above 65 years, the CIs overlapped with the estimate for patients below 65 years (**Figure S5.7**). Effect measure modification by sex or

immunosuppressant use was also not detected (**Figure S5.7**). Sensitivity analyses resulted in estimates largely overlapping with the primary analysis results (**Figure S5.8**).

5.7 CONCLUSION

The results of this population-based cohort study suggest that, compared with sulfonylureas, DPP-4 inhibitors were associated with a reduced risk of melanoma, with evidence of a duration-response relationship. In contrast, these drugs were not associated with the incidence of nonmelanoma skin cancer. Overall, these results remained consistent in several sensitivity analyses.

To our knowledge, no clinical study has examined the use of DPP-4 inhibitors and skin cancer as a standalone outcome. One meta-analysis of 72 RCTs including 35,768 patients on DPP-4 inhibitor and 33,319 on comparison drugs/placebo reported a numerically lower risk of malignant melanoma (relative risk 0.87, 95% CI 0.48–1.59) but a numerically higher risk of skin cancer overall (relative risk 1.79, 95% CI 0.86–3.71).[12] A larger meta-analysis of 115 RCTs with 65,740 patients in the DPP-4 inhibitor group and 56,221 in the control group reported a lower overall risk of cancer (odds ratio 0.91, 95% CI 0.85–0.97), all skin cancers (odds ratio 0.85, 95% CIs 0.72–0.99), and malignant skin cancer (odds ratio 0.86, 95% CIs 0.73–1.00), although the type of skin cancer was not specified.[11] In another meta-analysis of 157 RCTs with 66,825 patients on DPP-4 inhibitor treatment and 61,524 patients in the control group, DPP-4 inhibitor use was not associated with melanoma (OR 1.13, 95% CI: 0.73-1.00).[13] However, all the meta-analyses included data from clinical trial reports published in trial registries in absence of publications, which may be a source of inconsistent event numbers.[33] Furthermore, all meta-analyses included short term studies (<52 weeks), which may be inadequate to uncover cancer risk.[11 12] Our study found that DPP-4 inhibitor use was associated with a 23% lower risk of melanoma skin cancer, the risk reduction occurring after 2 years of use. We did not find any consistent association of DPP-4 inhibitor use with nonmelanoma skin cancer.

The DPP-4 enzyme has a complex role in the melanocyte malignant transformation, and possibly acts through antagonistic pathways.[5 34] Downregulation of DPP-4 has been linked with pro-invasive activities in melanocytes, with a tumor suppressor effect attributed to DPP-4.[35] In melanoma, loss of DPP-4 activity occurs due to aberrant promoter hypermethylation at the RNA level.[35] However, it is unclear whether intake of DPP-4 inhibitors, which inhibit the extracellular activity of the DPP-4 enzyme, can inhibit DPP-4 expression. Indeed, in a RCT of short term sitagliptin treatment (28 day), DPP-4 expression on blood cells *increased* temporarily thereafter returning to baseline level, but not changing substantially long-term.[36] On the other hand, in mouse model of melanoma, sitagliptin administration was found to delay melanoma tumor growth and metastasis.[9] The mechanism of this action was determined to be the increased trafficking of CXCR3+lymphocytes and natural killer cells into the tumor site due to elevation of CXCL10, a chemokine that is a substrate of the DPP-4 enzyme which increases after DPP-4 inhibitor use.[9] In fact, this study also found that DPP-4 inhibitors improved tumoral response to checkpoint blockade through similar lymphocyte trafficking mechanisms.[9] Given that lymphocyte trafficking into the skin is a known effect of DPP-4 inhibitor use (mediating cutaneous side effects such as bullous pemphigoid),[37 38] this could be a potential mechanism behind a reduced melanoma incidence with DPP-4 inhibitor use.

Interestingly, we did not find a change in the risk of nonmelanoma skin cancer with DPP-4 inhibitor use. Indeed, DPP-4 enzyme activity in nonmelanoma skin cancer is variable, with high activity noted in basal cell carcinomas while both high and low activity has been found in squamous cell carcinomas.[4] Even the role of CXCR3 and its ligands is less well understood in nonmelanoma skin cancer.[39] On one hand, immunomodulator drugs such as imiquimod used in nonmelanoma skin cancer are known to recruit CXCR3+ T cells.[40] On the other hand, CXCR3

gene deletion has been shown to lower the incidence of skin tumors in mice, and recruitment of CXCR3+ T cells found to promote keratinocyte proliferation.[41] These variable roles of DPP-4 and CXCR3 on keratinocytes might explain the relatively null association between DPP-4 inhibitors and nonmelanoma skin cancer.

Our study has several strengths. First, we used the CPRD as our data source, a database that is largely representative of the UK population. Furthermore, this database contains information on clinical and laboratory variables which are important confounders and are usually absent in administrative databases. Using this database also allowed us to examine well-validated outcome definitions. Second, we accrued one million person-years of follow-up in both cohorts, with a potential follow-up of 13 years for each cohort, making our study well powered to determine whether DPP-4 inhibitors are associated with skin cancer. Finally, we used a new user, active comparator design which likely minimized confounding and detection bias at the design stage, as well as bias from the inclusion of prevalent users.[42]

Our study also has some limitations. First, exposure misclassification is possible because the CPRD is a general practitioner database and does not record prescriptions written by specialists. However, this is unlikely to be an important source of misclassification since general practitioners almost entirely manage type 2 diabetes in the UK.[43] Importantly, diagnoses made and prescriptions written by specialists are frequently noted down by general practitioners in the database. Second, it was not possible to assess sun exposure at the patient level, an important skin cancer risk factor. Reassuringly, sun exposure is not a consideration when prescribing an antihyperglycemic drug versus another. As such, pattern of sun exposure is unlikely to be differential between users of DPP-4 inhibitors and sulfonylureas. Nonetheless, we included several proxies for variations in sun exposure in the propensity score models. These included the

presence of various photodermatoses which are markers of previous sun exposure. Moreover, we also adjusted for calendar year and region, which serve as proxies for temporal and geographical variations in sun exposure, respectively. Finally, residual confounding is a possibility given the observational nature of this study. However, given that clinical studies on the association between DPP-4 inhibitors and skin cancer has only been published after the study period, any channelling related to this outcome is unlikely.

In summary, DPP-4 inhibitor use was associated with a reduced risk of melanoma but not with the incidence of nonmelanoma skin cancer. Given the high mortality associated with melanoma, and dearth of preventive strategies related to this malignancy, more research should be conducted to confirm our findings.

5.8 ACKNOWLEDGEMENTS

R Pradhan is the recipient of a Doctoral Award from the Fonds de Recherche du Québec – Santé. OHYY holds a Chercheur-Boursier Clinicien Junior 1 award from the Fonds de Recherche du Québec - Santé. R Platt holds the Albert Boehringer I Chair in Pharmacoepidemiology at McGill University. LA holds a Distinguished Research Scholar award from the Fonds de Recherche du Québec - Santé and is the recipient of a William Dawson Scholar Award from McGill University.

5.9 COMPETING INTEREST STATEMENT

R Platt received consulting fees from Biogen, Boehringer Ingelheim, Merck, Nant Pharma, Pfizer, and Reckitt Benckiser for work unrelated to this study. LA received consulting and speaker fees from Janssen, Pfizer, and Roche for work unrelated to this study. Other authors have no conflict of interest to declare.

5.10 CONTRIBUTIONS

All authors conceived and designed the study. LA acquired the data. R Pradhan and LA did the statistical analyses. R Platt provided statistical expertise and OHYY provided clinical expertise. All authors analysed and interpreted the data. R Pradhan wrote the manuscript, and all authors critically revised it. All authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work. LA supervised the study and is the guarantor.

5.11 FUNDING

This study was funded by a Foundation Scheme grant from the Canadian Institutes of Health Research (FDN-143328). The sponsors had no influence on design and conduct of the study;

collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

5.12 REFERENCES

1. Curtis HJ, Dennis JM, Shields BM, et al. Time trends and geographical variation in prescribing of drugs for diabetes in England from 1998 to 2017. *Diabetes Obes Metab* 2018;20(9):2159-68. doi: 10.1111/dom.13346

2. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. *Diabetes care* 2021;44(Suppl 1):S111-S24. doi: 10.2337/dc21-S009

3. Kang SM, Park JH. Pleiotropic Benefits of DPP-4 Inhibitors Beyond Glycemic Control. *Clin Med Insights Endocrinol Diabetes* 2021;14:11795514211051698. doi: 10.1177/11795514211051698 [published Online First: 2021/11/05]

4. Patel PM, Jones VA, Kridin K, et al. The role of Dipeptidyl Peptidase-4 in cutaneous disease. *Exp Dermatol* 2021;30(3):304-18. doi: 10.1111/exd.14228 [published Online First: 2020/11/02]

5. Busek P, Duke-Cohan JS, Sedo A. Does DPP-IV Inhibition Offer New Avenues for Therapeutic Intervention in Malignant Disease? *Cancers (Basel)* 2022;14(9) doi: 10.3390/cancers14092072 [published Online First: 2022/05/15]

6. Wesley UV, Albino AP, Tiwari S, et al. A role for dipeptidyl peptidase IV in suppressing the malignant phenotype of melanocytic cells. *J Exp Med* 1999;190(3):311-22. doi: 10.1084/jem.190.3.311 [published Online First: 1999/08/03]

7. Pethiyagoda CL, Welch DR, Fleming TP. Dipeptidyl peptidase IV (DPPIV) inhibits cellular invasion of melanoma cells. *Clin Exp Metastasis* 2000;18(5):391-400. doi: 10.1023/a:1010930918055 [published Online First: 2001/07/27]

8. Roesch A, Wittschier S, Becker B, et al. Loss of dipeptidyl peptidase IV immunostaining discriminates malignant melanomas from deep penetrating nevi. *Mod Pathol* 2006;19(10):1378-85. doi: 10.1038/modpathol.3800663 [published Online First: 2006/07/11]

9. Barreira da Silva R, Laird ME, Yatim N, et al. Dipeptidylpeptidase 4 inhibition enhances lymphocyte trafficking, improving both naturally occurring tumor immunity and immunotherapy. *Nat Immunol* 2015;16(8):850-8. doi: 10.1038/ni.3201 [published Online First: 2015/06/16]

10. Moehrle MC, Schlagenhauff BE, Klessen C, et al. Aminopeptidase M and dipeptidyl peptidase IV activity in epithelial skin tumors: a histochemical study. *J Cutan Pathol* 1995;22(3):241-7. doi: 10.1111/j.1600-0560.1995.tb00745.x [published Online First: 1995/06/01]

11. Li Z, Lin C, Zhou J, et al. Dipeptidyl peptidase 4-inhibitor treatment was associated with a reduced incidence of neoplasm in patients with type 2 diabetes: a meta-analysis of 115 randomized controlled trials with 121961 participants. *Expert Opin Investig Drugs* 2022;31(9):957-64. doi: 10.1080/13543784.2022.2113056 [published Online First: 2022/08/16]

12. Zhao M, Chen J, Yuan Y, et al. Dipeptidyl peptidase-4 inhibitors and cancer risk in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. *Sci Rep* 2017;7(1):8273. doi: 10.1038/s41598-017-07921-2 [published Online First: 2017/08/16]

13. Dicembrini I, Nreu B, Montereggi C, et al. Risk of cancer in patients treated with dipeptidyl peptidase-4 inhibitors: an extensive meta-analysis of randomized controlled trials. *Acta*

Diabetol 2020;57(6):689-96. doi: 10.1007/s00592-020-01479-8 [published Online First: 2020/01/20]

14. 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
15. 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
16. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. *Pharmacotherapy* 2003;23(5):686-9.
17. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *Br Med J* 1991; 302(6779).
18. 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
19. Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. *Nature Reviews Endocrinology* 2009;5(5):262-69. doi: 10.1038/nrendo.2009.48
20. Home PD, Kahn SE, Jones NP, et al. Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. *Diabetologia* 2010;53(9):1838-45. doi: 10.1007/s00125-010-1804-y [published Online First: 2010/06/10]

21. Hendriks AM, Schrijnders D, Kleefstra N, et al. Sulfonylurea derivatives and cancer, friend or foe? *Eur J Pharmacol* 2019;861:172598. doi: 10.1016/j.ejphar.2019.172598 [published Online First: 2019/08/14]

22. 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 [published Online First: 2017/11/15]

23. Boggon R, van Staa TP, Chapman M, et al. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiology and Drug Safety* 2013;22(2):168-75. doi: 10.1002/pds.3374

24. Dregan A, Moller H, Murray-Thomas T, et al. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. *Cancer Epidemiol* 2012;36(5):425-29. doi: 10.1016/j.canep.2012.05.013

25. Meal A, Leonardi-Bee J, Smith C, et al. Validation of THIN data for non-melanoma skin cancer. *Qual Prim Care* 2008;16(1):49-52.

26. Chiesa Fuxench ZC, Troxel AB, Gelfand JM. Validity of diagnostic codes for identifying cutaneous squamous cell carcinoma in The Health Improvement Network. *Br J Dermatol* 2017;176(5):1363-65. doi: 10.1111/bjd.14957

27. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ (Clinical research ed)* 2019;367:l5657. doi: 10.1136/bmj.l5657

28. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28(25):3083-107. doi: 10.1002/sim.3697 [published Online First: 2009/09/17]

29. Suissa D, Brassard P, Smiechowski B, et al. Number needed to treat is incorrect without proper time-related considerations. *J Clin Epidemiol* 2012;65(1):42-6. doi: 10.1016/j.jclinepi.2011.04.009

30. Robins JM, Hernán MAn, Brumback B. Marginal Structural Models and Causal Inference in Epidemiology. *Epidemiology* 2000;11(5):550-60.

31. Hernán MAn, Brumback B, Robins JM. Marginal Structural Models to Estimate the Causal Effect of Zidovudine on the Survival of HIV-Positive Men. *Epidemiology* 2000;11(5):561-70.

32. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168(6):656-64. doi: 10.1093/aje/kwn164

33. Becker JE, Krumholz HM, Ben-Josef G, et al. Reporting of results in ClinicalTrials.gov and high-impact journals. *Jama* 2014;311(10):1063-5. doi: 10.1001/jama.2013.285634 [published Online First: 2014/03/13]

34. Sulda ML, Abbott CA, Hildebrandt M. DPIV/CD26 and FAP in cancer: a tale of contradictions. *Adv Exp Med Biol* 2006;575:197-206. doi: 10.1007/0-387-32824-6_21 [published Online First: 2006/05/17]

35. McGuinness C, Wesley UV. Dipeptidyl peptidase IV (DPPIV), a candidate tumor suppressor gene in melanomas is silenced by promoter methylation. *Front Biosci* 2008;13:2435-43. doi: 10.2741/2856 [published Online First: 2007/11/06]

36. Price JD, Linder G, Li WP, et al. Effects of short-term sitagliptin treatment on immune parameters in healthy individuals, a randomized placebo-controlled study. *Clin Exp Immunol* 2013;174(1):120-8. doi: 10.1111/cei.12144 [published Online First: 2013/05/29]

37. Shao S, Xu Q, Yu X, et al. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. *Pharmacol Ther* 2020;209:107503. doi: 10.1016/j.pharmthera.2020.107503 [published Online First: 2020/02/18]

38. Mendonça FM, Martín-Gutierrez FJ, Ríos-Martín JJ, et al. Three Cases of Bullous Pemphigoid Associated with Dipeptidyl Peptidase-4 Inhibitors - One due to Linagliptin. *Dermatology* 2016;232(2):249-53. doi: 10.1159/000443330 [published Online First: 2016/01/29]

39. Kuo PT, Zeng Z, Salim N, et al. The Role of CXCR3 and Its Chemokine Ligands in Skin Disease and Cancer. *Front Med (Lausanne)* 2018;5:271. doi: 10.3389/fmed.2018.00271 [published Online First: 2018/10/16]

40. Wenzel J, Uerlich M, Haller O, et al. Enhanced type I interferon signaling and recruitment of chemokine receptor CXCR3-expressing lymphocytes into the skin following treatment with the TLR7-agonist imiquimod. *J Cutan Pathol* 2005;32(4):257-62. doi: 10.1111/j.0303-6987.2005.00297.x [published Online First: 2005/03/17]

41. Winkler AE, Brotman JJ, Pittman ME, et al. CXCR3 enhances a T-cell-dependent epidermal proliferative response and promotes skin tumorigenesis. *Cancer Res* 2011;71(17):5707-16. doi: 10.1158/0008-5472.Can-11-0907 [published Online First: 2011/07/08]

42. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158(9):915-20. doi: 10.1093/aje/kwg231

43. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ open* 2016;6(1):e010210. doi: 10.1136/bmjopen-2015-010210

Table 5.1 Baseline Characteristics of the DPP-4 inhibitor and Sulfonylurea Exposure Groups in Melanoma Outcome Cohort Before and After Propensity Score‡ Weighting

Characteristics	Before weighting			After weighting		
	DPP-4 inhibitors	Sulfonylureas	ASD	DPP-4 inhibitors	Sulfonylureas	ASD
Total	96,739	209,341		96,739	209,341	
Age in years, mean (SD)	60.6 (12.8)	60.4 (13.3)	0.01	60.6 (12.8)	60.2 (12.8)	0.03
Gender, n (%)	55,192 (57.1)	121,277 (57.9)	0.02	55,192 (57.1)	118,692 (56.7)	0.01
Ethnicity, n (%)						
White	60,424 (62.5)	127,109 (60.7)	0.04	60,424 (62.5)	130,528 (62.4)	0.00
South Asian	8,922 (9.2)	17,444 (8.3)	0.03	8,922 (9.2)	19,573 (9.4)	0.00
Black	3,621 (3.7)	9,130 (4.4)	0.03	3,621 (3.7)	7,902 (3.8)	0.00
Mixed	773 (0.8)	1,709 (0.8)	0.00	773 (0.8)	1,689 (0.8)	0.00
Other	999 (1.0)	2,160 (1.0)	0.00	999 (1.0)	2,190 (1.1)	0.00
Unknown	22,000 (22.7)	51,789 (24.7)	0.05	22,000 (22.7)	47,459 (22.7)	0.00
Smoking, n (%)						
Ever	73,119 (75.6)	156,757 (74.9)	0.02	73,119 (75.6)	157,836 (75.4)	0.00
Never	23,444 (24.2)	51,895 (24.8)	0.01	23,444 (24.2)	51,060 (24.4)	0.00
Unknown	176 (0.2)	689 (0.3)	0.03	176 (0.2)	445 (0.2)	0.01
Alcohol dependence, n (%)	7,734 (8.0)	15,819 (7.6)	0.03	7,734 (8.0)	16,803 (8.0)	0.00
Body mass index, n (%)						
≤ 24.9 kg/m²	7,764 (8.0)	28,153 (13.5)	0.01	7,764 (8.0)	16,446 (7.9)	0.01
25.0 - 29.9 kg/m²	26,001 (26.9)	65,686 (31.4)	0.02	26,001 (26.9)	55,168 (26.4)	0.01
≥ 30.0 kg/m²	62,153 (64.3)	111,356 (53.2)	0.23	62,153 (64.3)	135,861 (64.9)	0.01
Unknown	821 (0.9)	4,146 (2.0)	0.10	821 (0.9)	1,866 (0.9)	0.00
HbA1c, n (%)						
≤7.0%	9,480 (9.8)	17,711 (8.5)	0.05	9,480 (9.8)	20,373 (9.7)	0.00
7.1%-8.0%	30,338 (31.4)	50,979 (24.4)	0.16	30,338 (31.4)	62,589 (29.9)	0.03
>8.0%	56,062 (58.0)	128,501 (61.4)	0.07	56,062 (58.0)	124,260 (59.4)	0.03

Unknown	859 (0.9)	12,150 (5.8)	0.28	859 (0.9)	2,119 (1.0)	0.01
Duration of diabetes	6.2 (5.7)	4.5 (5.2)	0.32	6.2 (5.7)	6.2 (5.8)	0.01
Myocardial infarction, n (%)	6,545 (6.8)	14,918 (7.1)	0.01	6,545 (6.8)	14,041 (6.7)	0.00
Peripheral circulatory disorders, n (%)	6,088 (6.3)	12,029 (5.8)	0.02	6,088 (6.3)	12,719 (6.1)	0.01
Stroke, n (%)	4,358 (4.5)	9,952 (4.8)	0.01	4,358 (4.5)	9,367 (4.5)	0.00
Neuropathy, n (%)	17,993 (18.6)	34,042 (16.3)	0.06	17,993 (18.6)	39,044 (18.7)	0.00
Retinopathy, n (%)	24,287 (25.1)	39,177 (18.7)	0.15	24,287 (25.1)	52,220 (24.9)	0.00
Renal diseases, n (%)	14,973 (15.5)	31,114 (14.9)	0.02	14,973 (15.5)	31,297 (15.0)	0.01
Metformin, n (%)	92,246 (95.4)	180,050 (86.0)	0.33	92,246 (95.4)	199,979 (95.5)	0.01
Thiazolidinediones, n (%)	10,341 (10.7)	17,914 (8.6)	0.07	10,341 (10.7)	23,394 (11.2)	0.02
Sodium-glucose cotransporter-2 inhibitors, n (%)	3,544 (3.7)	1,515 (0.7)	0.20	3,544 (3.7)	6,915 (3.3)	0.02
Alpha glucosidase inhibitors, n (%)	267 (0.3)	482 (0.2)	0.05	267 (0.3)	587 (0.3)	0.00
Meglitinides, n (%)	893 (0.9)	1,059 (0.5)	0.01	893 (0.9)	2,064 (1.0)	0.01
Insulin, n (%)	5,566 (5.8)	7,226 (3.5)	0.01	5,566 (5.8)	12,237 (5.9)	0.00
Heart failure, n (%)	3,725 (3.9)	8,417 (4.0)	0.02	3,725 (3.9)	8,051 (3.9)	0.00
Cancer, n (%)	6,848 (7.1)	15,754 (7.5)	0.08	6,848 (7.1)	14,826 (7.1)	0.00
Obstructive sleep apnea, n (%)	4,125 (4.3)	5,858 (2.8)	0.05	4,125 (4.3)	8,993 (4.3)	0.00
Osteoarthritis, n (%)	23,735 (24.5)	46,937 (22.4)	0.00	23,735 (24.5)	50,917 (24.3)	0.01
Chronic obstructive pulmonary disease, n (%)	7,665 (7.9)	16,692 (8.0)	0.06	7,665 (7.9)	16,485 (7.9)	0.00
Depression, n (%)	32,690 (33.8)	65,346 (31.2)	0.06	32,690 (33.8)	71,788 (34.3)	0.01
Dyslipidemia	22,885 (23.7)	44,460 (21.2)	0.05	22,885 (23.7)	49,351 (23.6)	0.00
Gastrointestinal esophageal reflux disease, n (%)	14,900 (15.4)	28,389 (13.6)	0.01	14,900 (15.4)	31,996 (15.3)	0.00
Arrhythmia, n (%)	7,995 (8.3)	16,908 (8.1)	0.11	7,995 (8.3)	17,040 (8.1)	0.00
Hypertension	62,634 (64.8)	124,473 (59.5)	0.00	62,634 (64.8)	134,820 (64.4)	0.01
Hypothyroidism, n (%)	4,044 (4.2)	8,828 (4.2)	0.03	4,044 (4.2)	8,761 (4.2)	0.00
Photodermatoses, n (%)	2,548 (2.6)	4,539 (2.2)	0.11	2,548 (2.6)	5,435 (2.6)	0.00
Antihypertensives, n (%)	75,030 (77.6)	152,660 (72.9)	0.07	75,030 (77.6)	162,083 (77.4)	0.00
Antiarrhythmics, n (%)	18,104 (18.7)	33,801 (16.2)	0.00	18,104 (18.7)	38,919 (18.6)	0.00

Antiplatelet agents, n (%)	33,664 (34.8)	73,067 (34.9)	0.19	33,664 (34.8)	72,224 (34.5)	0.01
Statins, n (%)	80,382 (83.1)	158,173 (75.6)	0.07	80,382 (83.1)	173,517 (82.9)	0.01
Non-steroidal anti-inflammatory drugs, n (%)	78,267 (80.9)	163,768 (78.2)	0.09	78,267 (80.9)	169,410 (80.9)	0.00
Corticosteroids, n (%)	78,245 (80.9)	161,810 (77.3)	0.01	78,245 (80.9)	169,141 (80.8)	0.00
Biologics, n (%)	265 (0.3)	445 (0.2)	0.14	265 (0.3)	608 (0.3)	0.00
Proton-pump inhibitors, n (%)	54,813 (56.7)	103,901 (49.6)	0.15	54,813 (56.7)	118,542 (56.6)	0.00
Phototoxic drugs, n (%)	92,285 (95.4)	192,228 (91.8)	0.01	92,285 (95.4)	199,614 (95.4)	0.00
Immunosuppressants, n (%)	2,350 (2.4)	5,377 (2.6)	0.08	2,350 (2.4)	5,226 (2.5)	0.00
Opioids, n (%)	68,658 (71.0)	140,743 (67.2)	0.16	68,658 (71.0)	148,581 (71.0)	0.00
Colon cancer screening, n (%)	11,557 (12.0)	14,973 (7.2)	0.44	11,557 (12.0)	24,462 (11.7)	0.01
Mammogram, n (%)	6,624 (6.9)	12,864 (6.1)	0.03	6,624 (6.9)	14,414 (6.9)	0.00
Prostate specific antigen, n (%)	7,490 (7.7)	15,612 (7.5)	0.01	7,490 (7.7)	15,982 (7.6)	0.00
Pneumococcal vaccine, n (%)	5,645 (5.8)	13,342 (6.4)	0.72	5,645 (5.8)	12,475 (6.0)	0.01
Influenza vaccine, n (%)	18,968 (19.6)	82,348 (39.3)	0.02	18,968 (19.6)	41,433 (19.8)	0.00
Cohort entry year, n (%)						
2007-2010	12,261 (12.7)	88,323 (42.2)	0.17	12,261 (12.7)	26,654 (12.7)	0.00
2011-2014	28,882 (29.9)	70,581 (33.7)	0.08	28,882 (29.9)	62,758 (30.0)	0.00
2015-2019	55,596 (57.5)	50,437 (24.1)	0.68	55,596 (57.5)	119,929 (57.3)	0.00

Abbreviations: ASD, absolute standardized difference; SD, standard deviation; DPP-4, dipeptidyl peptidase 4.
‡ Additionally adjusted for region, for which the absolute standardized differences ranged between 0.00 to 0.01 after propensity score fine stratification weighting.

Table 5.2 Hazard Ratios for Melanoma Comparing DPP-4 Inhibitors with Sulfonylureas						
Exposure	**No. of patients**	**Events**	**Person-years**	**Weighted incidence rate (95% CI) ***	**Crude HR**	**Weighted HR (95% CI) †**
Primary analysis						
Sulfonylureas	209,341	515	807,734	65.3 (58.9-72.1)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	96,739	119	239,306	49.7 (41.2-59.5)	0.81	0.77 (0.61-0.96)
Time since initiation						
0-2 years						
Sulfonylureas	209,341	100	189,832	50.0 (40.3-61.4)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	96,739	50	81,047	61.7 (45.8-81.3)	1.18	1.24 (0.83-1.86)
2.1-5 years						
Sulfonylureas	171,110	226	371,967	71.0 (62.1-80.8)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	66,433	48	115,603	41.5 (30.6-55.1)	0.68	0.59 (0.41-0.84)
>5 years						
Sulfonylureas	83,658	189	246,193	71.1 (59.4-84.4)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	19,803	21	42,882	49.0 (30.3-74.9)	0.66	0.69 (0.42-1.13)
Cumulative duration of use						
0-2 years						
Sulfonylureas	209,512	176	336,493	52.2 (44.8-60.5)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	96,830	78	132,332	58.9 (46.6-73.5)	1.14	1.14 (0.84-1.54)
2.1-5 years						
Sulfonylureas	114,053	172	194,958	88.2 (75.5-102.4)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	44,177	34	86,893	39.1 (27.1-54.7)	0.55	0.43 (0.29-0.66)
>5 years						

Sulfonylureas	36,575	43	41,008	104.9 (75.9-141.3)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	9559	7	20,145	34.7 (14.0-71.6)	0. 41	0.33 (0.15-0.74)
Individual drugs						
Sulfonylureas	64,218	83	139,697	74.9 (60.4-91.7)	1.00 [Reference]	1.00 [Reference]
Alogliptin	13,804	12	19,959	60.1 (31.1-105.0)	1.00	0.83 (0.43-1.59)
Sulfonylureas	120,639	213	359,962	79.1 (68.8-90.5)	1.00 [Reference]	1.00 [Reference]
Linagliptin	19,746	20	38,358	52.1 (31.8-80.5)	0.88	0.67 (0.40-1.12)
Sulfonylureas	165,686	362	572,340	71.1 (63.9-78.8)	1.00 [Reference]	1.00 [Reference]
Saxagliptin	8380	15	24,258	61.8 (34.6-102.0)	1.01	0.88 (0.51-1.51)
Sulfonylureas	209,373	515	807,932	61.7 (55.9-68.1)	1.00 [Reference]	1.00 [Reference]
Sitagliptin	53,865	69	149,607	46.1 (35.9-58.4)	0.75	0.76 (0.58-0.99)
Sulfonylureas	206,643	511	799,710	65.3 (60.1-70.8)	1.00 [Reference]	1.00 [Reference]
Vildagliptin	3346	7	13,415	52.2 (21.0-107.5)	0.81	0.80 (0.38-1.70)

Abbreviations: HR, Hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase.
* Per 100,000 person-years.
† Weighted using propensity score fine stratification

Table 5.3 Baseline Characteristics of the DPP-4 inhibitor and Sulfonylurea Exposure Groups in Nonmelanoma Skin Cancer Outcome Cohort Before and After Propensity Score‡ Weighting

Characteristics	Before weighting			After weighting		
	DPP-4 inhibitors	Sulfonylureas	ASD	DPP-4 inhibitors	Sulfonylureas	ASD
Total	96,411	208,626		96,411	208,626	
Age in years, mean (SD)	60.5 (12.8)	60.4 (13.3)	0.01	60.5 (12.8)	60.2 (12.8)	0.03
Gender, n (%)	54,990 (57.0)	120,839 (57.9)	0.02	54,990 (57.0)	118,246 (56.7)	0.01
Ethnicity, n (%)						
White	60,188 (62.4)	126,625 (60.7)	0.04	60,188 (62.4)	130,017 (62.3)	0.00
South Asian	8,918 (9.3)	17,437 (8.4)	0.03	8,918 (9.3)	19,561 (9.4)	0.00
Black	3,621 (3.8)	9,130 (4.4)	0.03	3,621 (3.8)	7,897 (3.8)	0.00
Mixed	773 (0.8)	1,709 (0.8)	0.00	773 (0.8)	1,689 (0.8)	0.00
Other	998 (1.0)	2,158 (1.0)	0.00	998 (1.0)	2,188 (1.1)	0.00
Unknown	21,913 (22.7)	51,567 (24.7)	0.05	21,913 (22.7)	47,274 (22.7)	0.00
Smoking, n (%)						
Ever	72,855 (75.6)	156,187 (74.9)	0.02	72,855 (75.6)	157,267 (75.4)	0.00
Never	23,382 (24.3)	51,750 (24.8)	0.01	23,382 (24.3)	50,917 (24.4)	0.00
Unknown	174 (0.2)	689 (0.3)	0.03	174 (0.2)	443 (0.2)	0.01
Alcohol dependence, n (%)	7,717 (8.0)	15,768 (7.6)	0.03	7,717 (8.0)	16,765 (8.0)	0.00
Body mass index, n (%)						
≤ 24.9 kg/m²	7,729 (8.0)	28,026 (13.4)	0.01	7,729 (8.0)	16,380 (7.9)	0.01
25.0 - 29.9 kg/m²	25,911 (26.9)	65,404 (31.4)	0.02	25,911 (26.9)	54,986 (26.4)	0.01
≥ 30.0 kg/m²	61,955 (64.3)	111,053 (53.2)	0.23	61,955 (64.3)	135,403 (64.9)	0.01
Unknown	816 (0.9)	4,143 (2.0)	0.10	816 (0.9)	1,856 (0.9)	0.00
HbA1c, n (%)						
≤7.0%	9,437 (9.8)	17,637 (8.5)	0.05	9,437 (9.8)	20,273 (9.7)	0.00
7.1%-8.0%	30,193 (31.3)	50,752 (24.3)	0.16	30,193 (31.3)	62,292 (29.9)	0.03
>8.0%	55,926 (58.0)	128,121 (61.4)	0.07	55,926 (58.0)	123,950 (59.4)	0.03

Unknown	855 (0.9)	12,116 (5.8)	0.28	855 (0.9)	2,111 (1.0)	0.01
Duration of diabetes in years, mean (SD)	6.2 (5.7)	4.5 (5.2)	0.32	6.2 (5.7)	6.1 (5.8)	0.01
Myocardial infarction, n (%)	6,514 (6.8)	14,842 (7.1)	0.01	6,514 (6.8)	13,990 (6.7)	0.00
Peripheral circulatory disorders, n (%)	6,058 (6.3)	11,951 (5.7)	0.02	6,058 (6.3)	12,664 (6.1)	0.01
Stroke, n (%)	4,334 (4.5)	9,887 (4.7)	0.01	4,334 (4.5)	9,333 (4.5)	0.00
Neuropathy, n (%)	17,917 (18.6)	33,909 (16.3)	0.06	17,917 (18.6)	38,902 (18.7)	0.00
Retinopathy, n (%)	24,194 (25.1)	39,021 (18.7)	0.15	24,194 (25.1)	52,025 (24.9)	0.00
Renal diseases, n (%)	14,868 (15.4)	30,887 (14.8)	0.02	14,868 (15.4)	31,116 (14.9)	0.01
Metformin, n (%)	91,948 (95.4)	179,484 (86.0)	0.33	91,948 (95.4)	199,318 (95.5)	0.01
Thiazolidinediones, n (%)	10,304 (10.7)	17,864 (8.6)	0.07	10,304 (10.7)	23,318 (11.2)	0.02
SGLT2 Inhibitors, n (%)	3,538 (3.7)	1,513 (0.7)	0.20	3,538 (3.7)	6,899 (3.3)	0.02
Alfa glucosidase inhibitors, n (%)	266 (0.3)	481 (0.2)	0.05	266 (0.3)	587 (0.3)	0.00
Meglitinides, n (%)	888 (0.9)	1,056 (0.5)	0.11	888 (0.9)	2,061 (1.0)	0.01
Insulin, n (%)	5,557 (5.8)	7,212 (3.5)	0.11	5,557 (5.8)	12,226 (5.9)	0.00
Heart failure, n (%)	3,703 (3.8)	8,345 (4.0)	0.01	3,703 (3.8)	8,001 (3.8)	0.00
Cancer, n (%)	6,796 (7.1)	15,618 (7.5)	0.02	6,796 (7.1)	14,730 (7.1)	0.00
Obstructive sleep apnea, n (%)	4,111 (4.3)	5,840 (2.8)	0.08	4,111 (4.3)	8,961 (4.3)	0.00
Osteoarthritis, n (%)	23,606 (24.5)	46,705 (22.4)	0.05	23,606 (24.5)	50,647 (24.3)	0.00
Chronic obstructive pulmonary disease, n (%)	7,628 (7.9)	16,609 (8.0)	0.00	7,628 (7.9)	16,407 (7.9)	0.00
Depression, n (%)	32,610 (33.8)	65,141 (31.2)	0.06	32,610 (33.8)	71,601 (34.3)	0.01
Dyslipidemia	22,780 (23.6)	44,289 (21.2)	0.06	22,780 (23.6)	49,128 (23.6)	0.00
Gastrointestinal esophageal reflux disease, n (%)	14,843 (15.4)	28,270 (13.6)	0.05	14,843 (15.4)	31,878 (15.3)	0.00
Arrhythmia, n (%)	7,943 (8.2)	16,781 (8.0)	0.01	7,943 (8.2)	16,937 (8.1)	0.00
Hypertension	62,373 (64.7)	123,976 (59.4)	0.11	62,373 (64.7)	134,269 (64.4)	0.01
Hypothyroidism, n (%)	4,022 (4.2)	8,784 (4.2)	0.00	4,022 (4.2)	8,708 (4.2)	0.00
Photodermatoses, n (%)	2,499 (2.6)	4,442 (2.1)	0.03	2,499 (2.6)	5,328 (2.6)	0.00
Antihypertensives, n (%)	74,734 (77.5)	152,040 (72.9)	0.11	74,734 (77.5)	161,447 (77.4)	0.00
Antiarrhythmics, n (%)	18,005 (18.7)	33,599 (16.1)	0.07	18,005 (18.7)	38,710 (18.6)	0.00

Antiplatelet agents, n (%)	33,481 (34.7)	72,718 (34.9)	0.00	33,481 (34.7)	71,875 (34.5)	0.01
Statins, n (%)	80,095 (83.1)	157,578 (75.5)	0.19	80,095 (83.1)	172,888 (82.9)	0.01
Non-steroidal anti-inflammatory drugs, n (%)	77,985 (80.9)	163,175 (78.2)	0.07	77,985 (80.9)	168,813 (80.9)	0.00
Corticosteroids, n (%)	77,945 (80.9)	161,181 (77.3)	0.09	77,945 (80.9)	168,497 (80.8)	0.00
Biologics, n (%)	264 (0.3)	443 (0.2)	0.01	264 (0.3)	612 (0.3)	0.00
Proton-pump inhibitors, n (%)	54,583 (56.6)	103,451 (49.6)	0.14	54,583 (56.6)	118,044 (56.6)	0.00
Phototoxic drugs, n (%)	91,960 (95.4)	191,534 (91.8)	0.15	91,960 (95.4)	198,907 (95.3)	0.00
Immunosuppressants, n (%)	2,336 (2.4)	5,344 (2.6)	0.01	2,336 (2.4)	5,197 (2.5)	0.00
Opioids, n (%)	68,395 (70.9)	140,203 (67.2)	0.08	68,395 (70.9)	148,029 (71.0)	0.00
Colon cancer screening, n (%)	11,495 (11.9)	14,899 (7.1)	0.16	11,495 (11.9)	24,334 (11.7)	0.01
Mammogram, n (%)	6,606 (6.9)	12,831 (6.2)	0.03	6,606 (6.9)	14,370 (6.9)	0.00
Prostate specific antigen, n (%)	7,435 (7.7)	15,506 (7.4)	0.01	7,435 (7.7)	15,879 (7.6)	0.00
Pneumococcal vaccine, n (%)	5,635 (5.8)	13,306 (6.4)	0.02	5,635 (5.8)	12,450 (6.0)	0.01
Influenza vaccine, n (%)	18,909 (19.6)	81,991 (39.3)	0.44	18,909 (19.6)	41,310 (19.8)	0.00
Cohort entry year, n (%)						
2007-2010	12,234 (12.7)	88,016 (42.2)	0.70	12,234 (12.7)	26,596 (12.8)	0.00
2011-2014	28,785 (29.9)	70,332 (33.7)	0.08	28,785 (29.9)	62,546 (30.0)	0.00
2015-2019	55,392 (57.5)	50,278 (24.1)	0.72	55,392 (57.5)	119,485 (57.3)	0.00

Abbreviations: ASD, absolute standardized difference; SD, standard deviation; DPP-4, dipeptidyl peptidase 4.

‡ Additionally adjusted for region, for which the absolute standardized differences ranged between 0.00 to 0.01 after propensity score fine stratification weighting.

Table 5.4 Hazard Ratios for Nonmelanoma Skin Cancer Comparing DPP-4 Inhibitors with Sulfonylureas

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) *	Crude HR	Weighted HR (95% CI) †
Primary analysis						
Sulfonylureas	208,626	3,643	795,481	426.1 (409.5-443.1)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	96,411	1,059	236,339	448.1 (421.5-475.9)	1.02	1.06 (0.98-1.15)
Time since initiation						
0-2 years						
Sulfonylureas	208,626	737	188,875	378.8 (351.0-408.3)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	96,.411	333	80,647	412.9 (369.8-459.7)	1.06	1.09 (0.93-1.28)
2.1-5 years						
Sulfonylureas	169,749	1620	367,147	402.9 (381.3-425.5)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	65,970	507	114,245	443.8 (406.0-484.2)	1.01	1.10 (0.98-1.24)
>5 years						
Sulfonylureas	82,072	1281	239016	511.1 (478.5-545.3)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	19,431	219	41670	525.6 (458.3-600.0)	0.99	1.04 (0.88-1.22)
Cumulative duration of use						
0-2 years						
Sulfonylureas	210,260	1299	333,747	389.1 (368.2-410.8)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	96,929	504	131,371	383.7 (350.9-418.7)	0.95	0.98 (0.87-1.11)
2.1-5 years						
Sulfonylureas	114185	891	192,180	463.4 (433.5-494.9)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	44225	454	85,595	530.4 (482.7-581.5)	1.12	1.16 (1.02-1.31)
>5 years						

Sulfonylureas	36252	245	39,817	614.6 (540.0-696.6)	1.00 [Reference]	1.00 [Reference]
DPP-4 inhibitors	9413	101	19,440	519.6 (423.2-631.3)	0.85	0.85 (0.68-1.08)
Individual drugs						
Sulfonylureas	64,024	515	138,582	403.9 (369.2-441.0)	1.00 [Reference]	1.00 [Reference]
Alogliptin	13,752	80	19,819	403.6 (320.1-502.4)	1.11	1.02 (0.79-1.33)
Sulfonylureas	120,223	1476	355,686	578.3 (549.6-608.0)	1.00 [Reference]	1.00 [Reference]
Linagliptin	19,643	230	37,827	608.0 (532.0-692.0)	1.50	1.05 (0.89-1.29)
Sulfonylureas	165,100	2498	564,489	459.4 (440.8-478.6)	1.00 [Reference]	1.00 [Reference]
Saxagliptin	8353	115	23,927	480.6 (396.8-576.9)	1.10	1.05 (0.87-1.28)
Sulfonylureas	208,657	3642	795,682	384.0 (369.0-399.4)	1.00 [Reference]	1.00 [Reference]
Sitagliptin	53,716	588	147,806	397.8 (366.3-431.3)	0.90	1.05 (0.96-1.16)
Sulfonylureas	205,962	3604	787,607	411.7 (398.3-425.4)	1.00 [Reference]	1.00 [Reference]
Vildagliptin	3343	68	13,192	515.5 (400.3-653.5)	1.12	1.25 (0.98-1.60)

Abbreviations: HR, Hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase.
* Per 100,000 person-years.
† Weighted using propensity score fine stratification

S5. Dipeptidyl Peptidase-4 Inhibitors and the Risk of Skin Cancer Among Patients with Type 2 Diabetes: Population-Based Cohort Study: Supplementary material

Figure S5.1: Melanoma cohort: study flow chart:

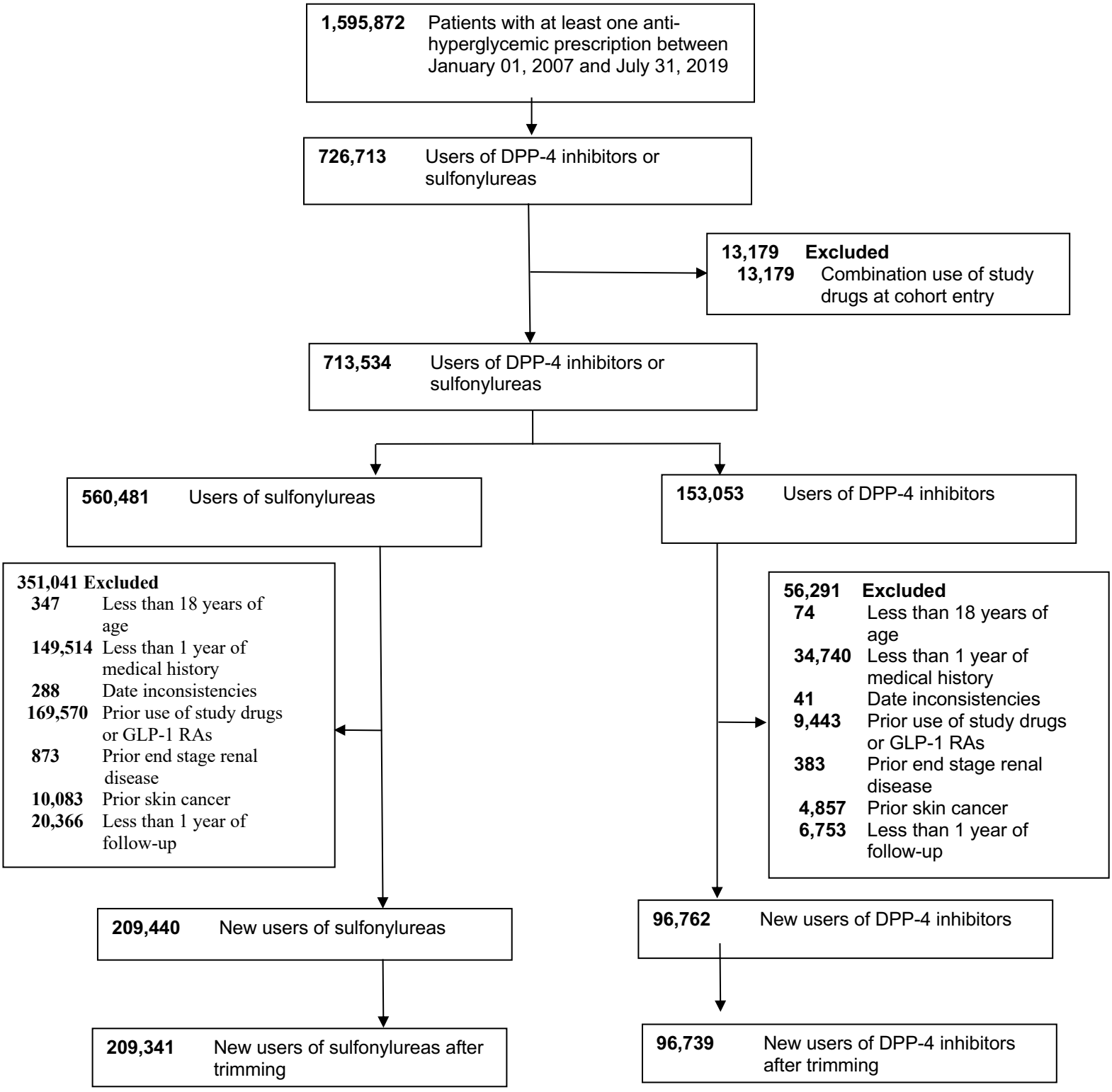


Figure S5.2: Weighted cumulative incidence curves of melanoma in the dipeptidyl peptidase-4 inhibitor vs. sulfonylurea cohort

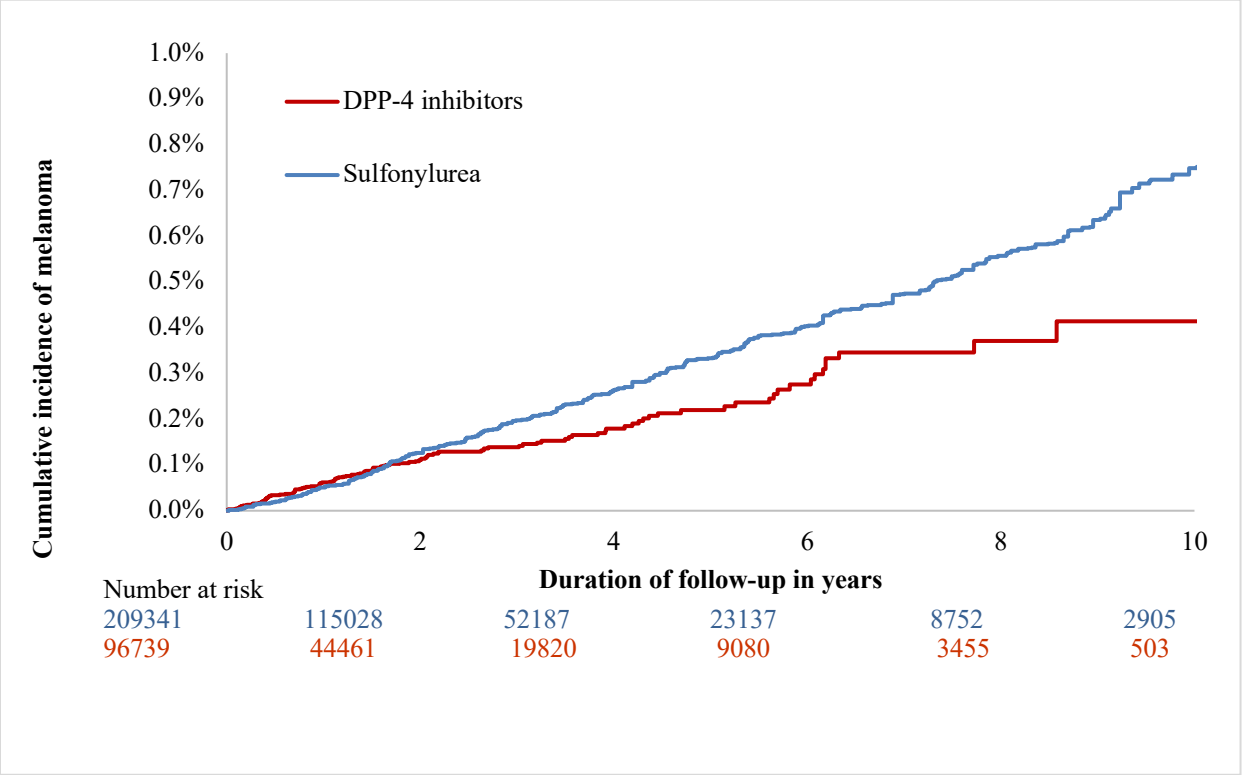


Figure S5.3: Melanoma cohort: effect measure modification analyses

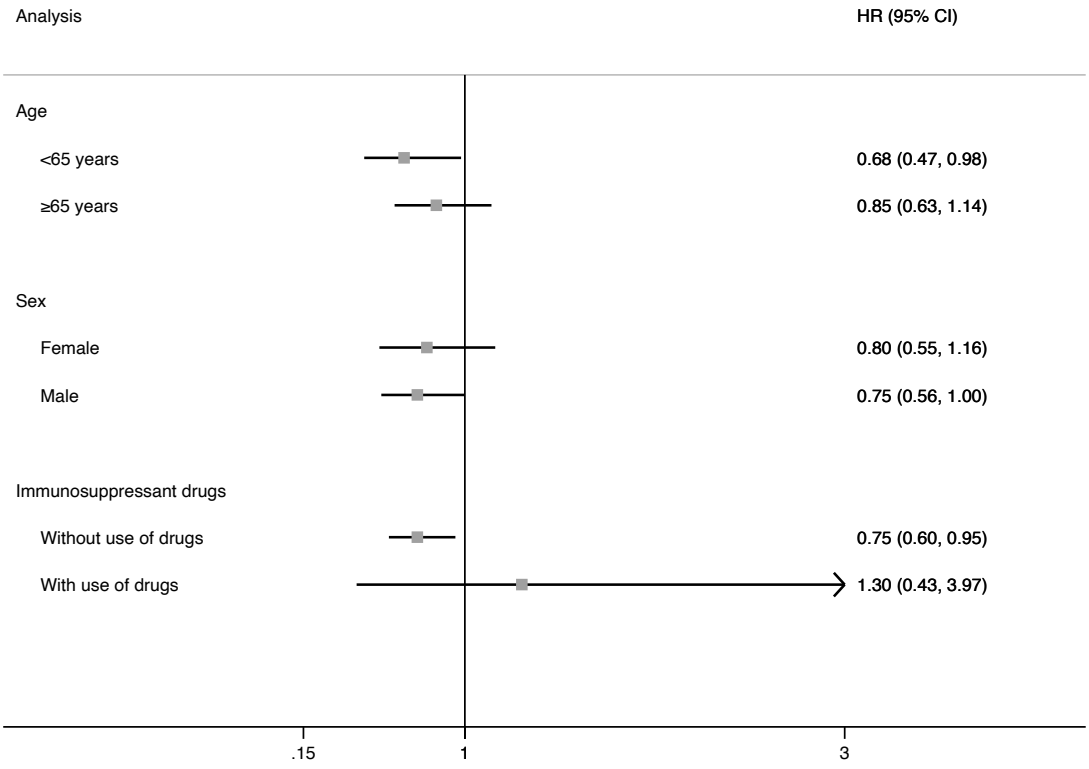


Figure S5.4: Melanoma cohort: sensitivity analyses

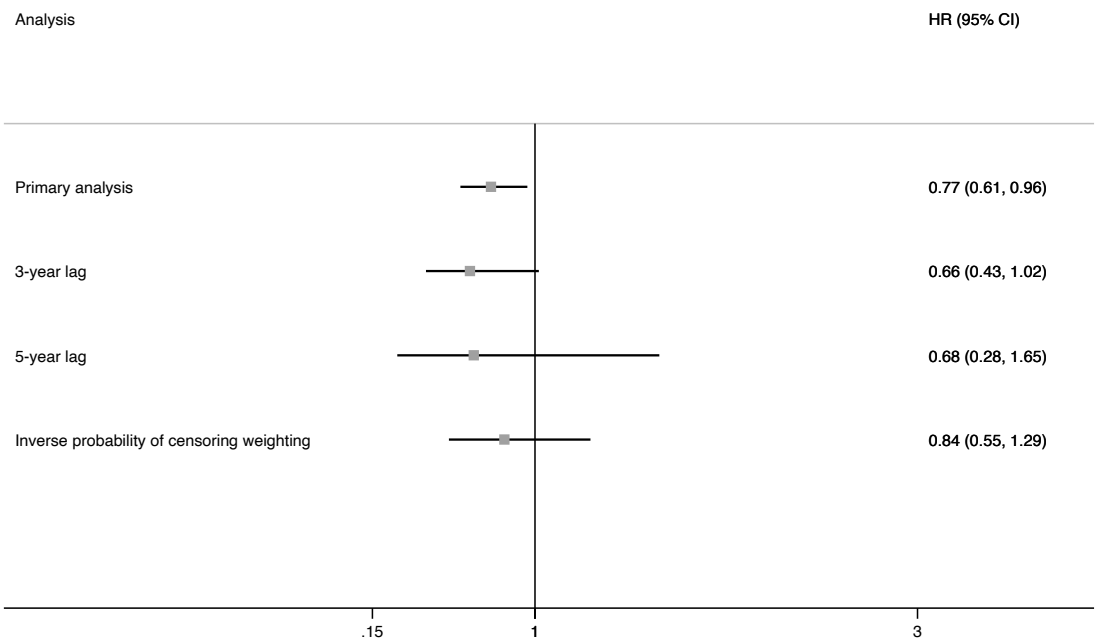


Figure S5.5: Nonmelanoma skin cancer cohort: study flow chart

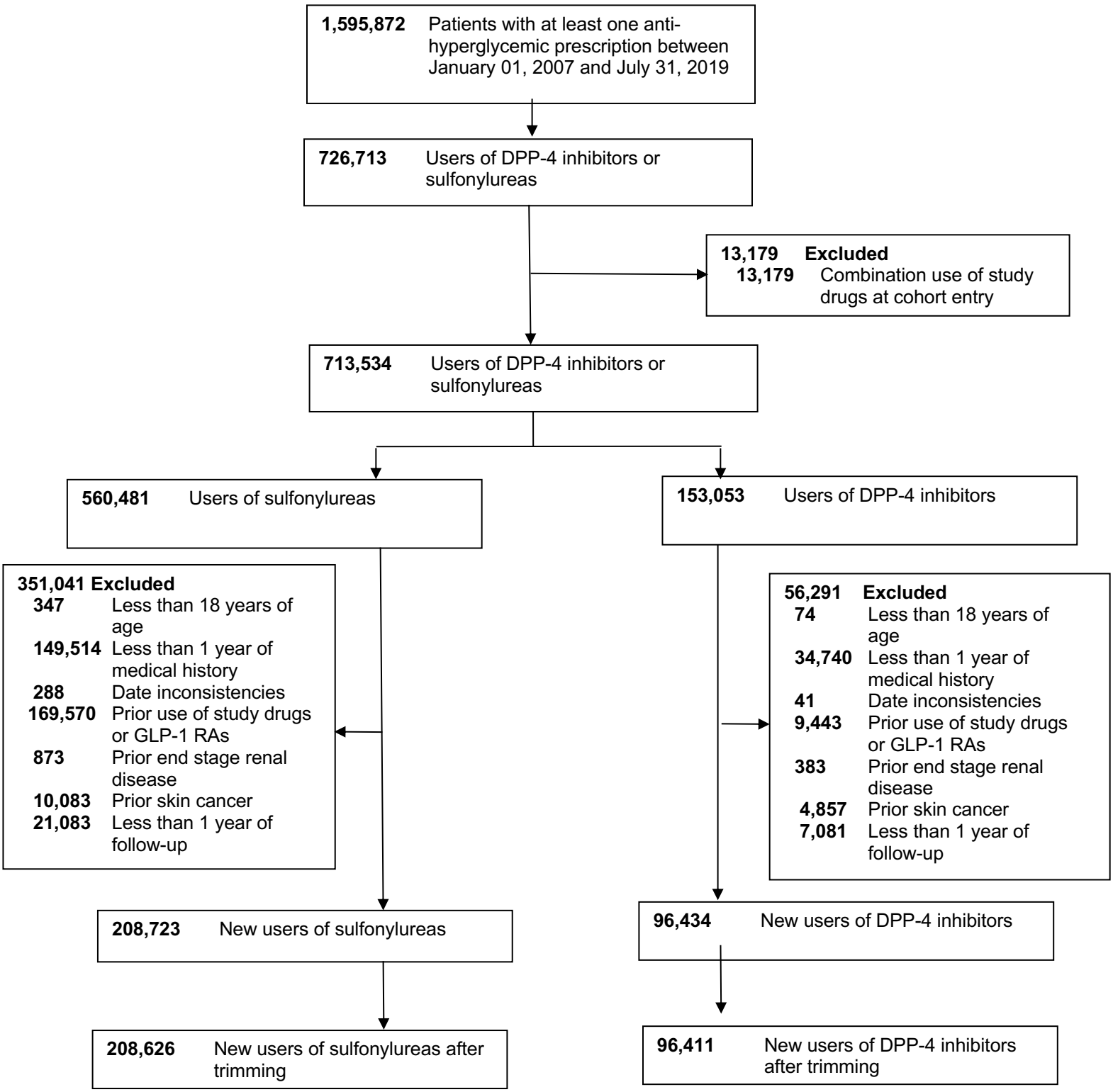


Figure S5.6: Weighted cumulative incidence curves of nonmelanoma skin cancer in the dipeptidyl peptidase-4 inhibitor vs. sulfonylurea cohort

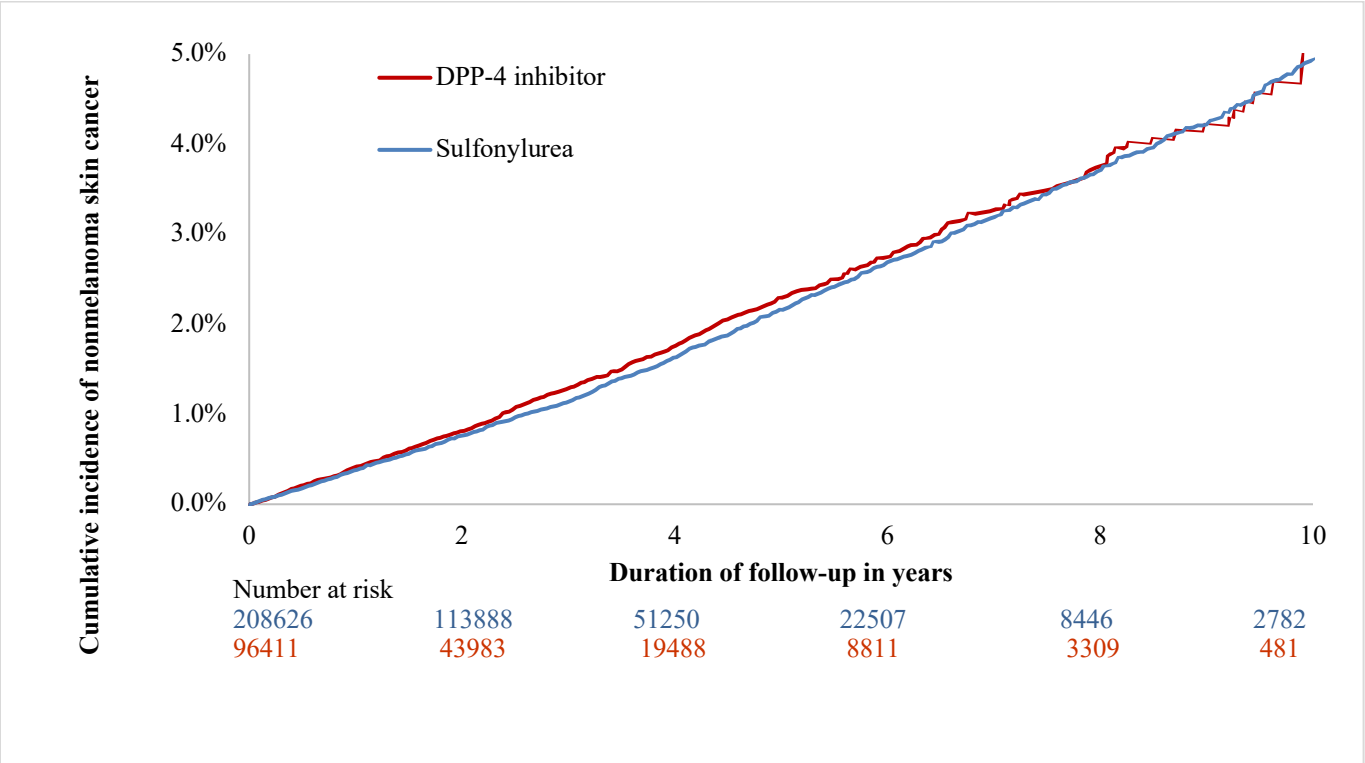


Figure S5.7: Nonmelanoma skin cancer cohort: effect measure modification analyses

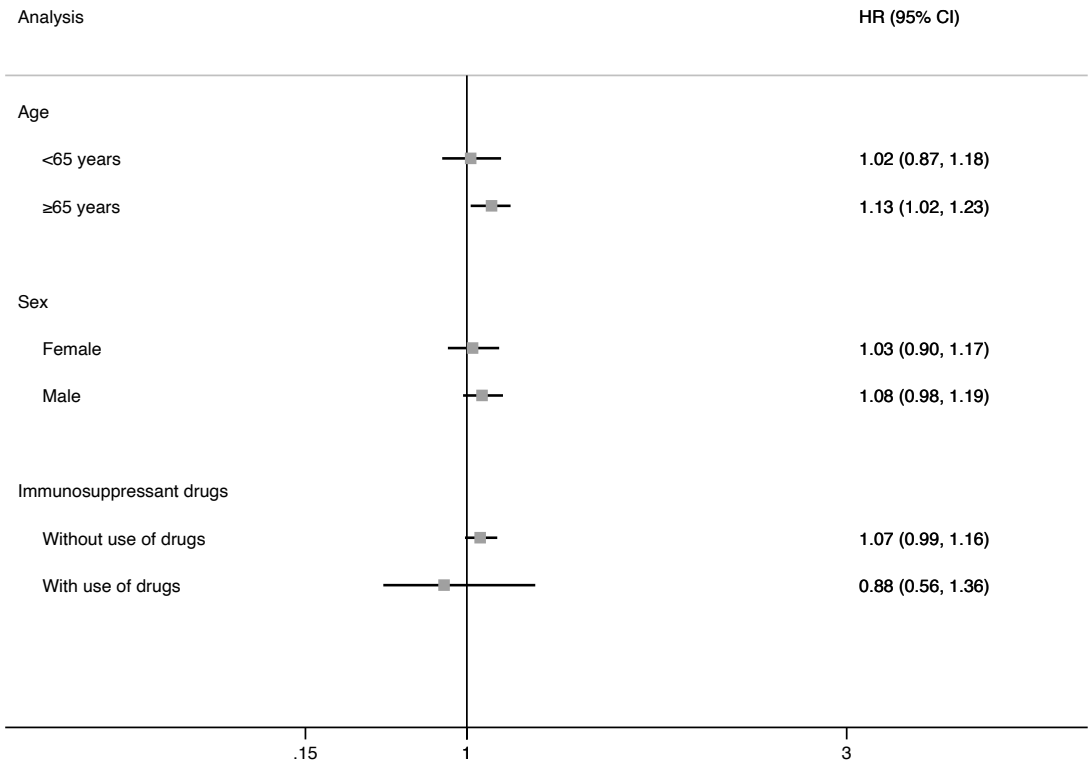
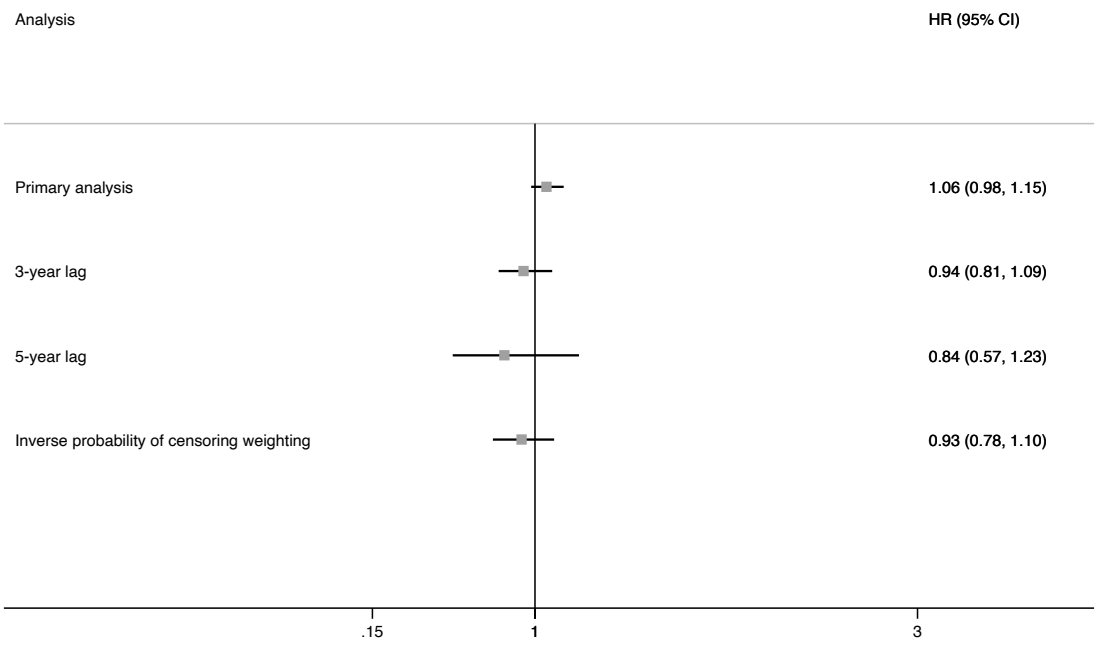


Figure S5.8: Nonmelanoma skin cancer cohort: sensitivity analyses



Chapter 6. Glucagon Like Peptide-1 Receptor Agonist and the Risk of Skin Cancer Among Patients with Type 2 Diabetes: Population-Based Cohort Study

6.1 Preface

In chapter five, when compared with sulfonylureas, we found that DPP-4 inhibitors, a class of incretin-based antihyperglycemic drugs, were associated with a reduced risk of melanoma but not the incidence of nonmelanoma skin cancer among patients with diabetes. This raised the question about the effect of GLP-1 RAs, another class of incretin-based antihyperglycemic drugs, on skin cancer. In particular, concerns regarding the safety of GLP-1 RAs with respect to skin cancer were raised when a large randomized clinical trial of liraglutide, the most used GLP-1 RA, reported an up to 10-fold increase in the risk of melanoma among liraglutide users.[17] However, long-term trials of other GLP-1 RAs such as semaglutide did not report such an increase in risk.[153] Furthermore, the biological rationale of a potential increase in skin cancer risk with GLP-1 RAs remains uncertain. Nevertheless, a substantial increase in melanoma risk would significantly change the risk benefit profile of GLP-1 RAs. Indeed, an increased risk of skin cancer was a regulatory concern during the final approval of liraglutide.[20] [152] [157] No observational study has been conducted to examine the effect of GLP-1 RA use on the risk of skin cancer. Accordingly, in chapter six, using primary care data from the UK, we examined whether GLP-1 RAs are associated with melanoma and nonmelanoma skin cancer, separately, in patients with diabetes. This paper has been submitted to *Diabetes Obesity and Metabolism.*

6.2 Title page

Glucagon Like Peptide-1 Receptor Agonists and the Risk of Skin Cancer Among Patients with Type 2 Diabetes: Population-Based Cohort Study

Richeek Pradhan MD MS,[1,2] Oriana H. Y. Yu MD MSc,[2,3] Robert W. Platt PhD,[1,2] Laurent Azoulay PhD[1,2,4]

[1] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada.

[2] Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Canada.

[3] Division of Endocrinology, Jewish General Hospital, Montreal, Canada.

[4] Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada.

Word count: 3062

Abstract word count: 236

Number of references: 41

Number of tables: 4

Number of figures: 1

Running title: GLP-1 Receptor Agonists and Skin Cancer

Correspondence:

Dr. Laurent Azoulay

Centre for Clinical Epidemiology, Jewish General Hospital, Lady Davis Institute

3755 Cote Sainte-Catherine, H425.1, Montreal, Canada, H3T 1E2

Tel.: (514) 340-8222 ext. 28396

Email: laurent.azoulay@mcgill.ca

Twitter: @LaurentAzoulay0

December 15, 2022

6.3 ABSTRACT

Aims: The objective of this study was to determine whether the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) is associated with an increased risk of melanoma and nonmelanoma skin cancer, separately, compared with the use of sulfonylureas among patients with type 2 diabetes.

Materials and Methods: Using the United Kingdom Clinical Practice Research Datalink (2007-2019), we assembled two new-user active comparator cohorts. In the first cohort assessing melanoma as the outcome, 11,786 new users of GLP-1 RAs were compared with 208,519 new users of sulfonylureas. In the second cohort assessing nonmelanoma skin cancer as the outcome, 11,778 new users of GLP-1 RAs were compared with 207,305 new users of sulfonylureas. Cox proportional hazards models weighted using propensity score fine stratification were fit to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of melanoma and nonmelanoma skin cancer, respectively.

Results: Compared with sulfonylureas, GLP-1 RAs were not associated with an increased risk of either melanoma (42.6 vs. 43.9 per 100,000 person-years, respectively; HR 0.96, 95% CI 0.53-1.75) or nonmelanoma skin cancer (243.9 vs. 244.1 per 100,000 person-years, respectively; HR 0.96, 95% CI 0.75-1.23). There was no evidence of an association between cumulative duration of use with either melanoma or nonmelanoma skin cancer. Consistent results were observed in secondary and sensitivity analyses.

Conclusions: In this population-based cohort study, GLP-1 RAs were not associated with an increased risk of melanoma or nonmelanoma skin cancer, compared with sulfonylureas.

6.4 INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are effective treatments in the management of type 2 diabetes.[1] Compared with other antihyperglycemic agents, these incretin-based drugs have been associated with a lower risk of hypoglycemia and favourable effects on body weight, cardiovascular, and renal outcomes,[2] resulting in their significantly increased use over the years.[3] However, signals from pre- and post-approval randomized controlled trials (RCTs) have raised concerns regarding their safety, such as their potential association with melanoma and nonmelanoma skin cancer.[4]

Specific concerns about an association with skin cancer began with imbalances observed in a large cardiovascular outcome trial of liraglutide, the most commonly used GLP-1 RA.[5,6] In this placebo-controlled trial, the liraglutide group had a higher incidence of both melanoma (hazard ratio [HR] 2.59, 95% confidence interval [CI] 0.92-7.27) and nonmelanoma skin cancer (HR 1.25, 95% CI 0.90-1.75).[5] In fact, in a pre-specified analysis excluding early events in the first year of follow-up to reduce potentially unrelated prevalent cases, the association of liraglutide with melanoma strengthened (HR 10.95, 95% CI 1.41-84.82).[5] However, long-term randomized controlled trials of other GLP-1 RA molecules either did not report an elevated risk (such as SUSTAIN trial of semaglutide, HR 1.41, 95% CI 0.76-2.63),[7] or did not report on skin cancer events.[8-11] In experimental models, GLP-1 RAs stimulate potentially mitogenic signalling pathways in both melanocytes[12,13] and keratinocytes,[14] although it remains uncertain whether this leads to proliferation of or malignant transformation within these cells. Nevertheless, the available evidence on the association between GLP-1 RAs and skin cancer has raised regulatory concerns during the final approval of liraglutide.[4,15,16] To date, however, no observational study has examined this association.

Thus, the objective of this study was to determine whether the use of GLP-1 RAs is associated with an increased risk of melanoma and nonmelanoma skin cancer in a population-based cohort of patients with type 2 diabetes.

6.5 Materials and Methods

6.5.1 Data source

This large population-based cohort study was conducted using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD). The CPRD is a population-based clinical database consisting of medical records for more than 50 million patients from over 2000 general practices in the UK.[17] Diagnoses and procedures are recorded using the Read and SNOMED-CT classications,[17,18] while drug prescriptions are recorded using the UK Prescription Pricing Authority Dictionary.[19] The CPRD also records lifestyle and anthropometric variables (e.g., smoking, body mass index [BMI]), clinical measures (e.g., blood pressure), and laboratory test results (e.g., hemoglobin A1c). These variables have been validated,[18,20,21] and the data and practices are audited regularly to ensure high quality. Finally, the CPRD has been extensively used to conduct studies investigating the effectiveness and safety of antihyperglycemic drugs.[22-26] The study protocol was approved by the Research Data Governance of the CPRD (Protocol number: 22_001715) and the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

6.5.2 Study population

We used an active comparator, new-user design to assemble two cohorts, one for each outcome, melanoma and nonmelanoma skin cancer. These cohorts extended from January 1, 2007 (the year the first GLP-1 RAs entered the UK market) through July 31, 2019, and both consisted of patients starting on either GLP-1 RAs (dulaglutide, exenatide, liraglutide [except the 6 mg/ml formulation indicated for weight loss], lixisenatide, semaglutide) or sulfonylureas (glibenclamide, gliclazide, glimepiride, glipizide, and tolbutamide), with the cohort entry being the date of the first-ever prescription of either drug class during the study period. To be included in the cohorts, all patients were required to be at least 18 years of age and have at least one year of medical history

in the CPRD before cohort entry, and no concomitant use of study drugs at cohort entry. We excluded patients previously diagnosed with any type of skin cancer, patients with a history of use of DPP-4 inhibitors (due to shared mechanism of action of the two classes of incretin-based drugs), and end stage renal disease at any time before cohort entry. Finally, we excluded those with less than one year of follow-up to allow for cancer latency and to exclude potentially prevalent events. Because the follow-up depended on the outcome (melanoma or nonmelanoma skin cancer), implementation of the lag by exclusion of those with less than a year of follow-up resulted in two cohorts, one specific to each outcome of interest.

6.5.3 Follow-up

Patients were followed from one year following the cohort entry until an incident diagnosis of melanoma or nonmelanoma skin cancer, one year after switching to one of the study drugs (i.e., sulfonylurea to an incretin-based drug, an incretin-based drug to a sulfonylurea, or switch between incretin-based drug classes), death, end of registration with the general practice, or the end of the study period (July 31, 2020), whichever occurred first.

6.5.4 Potential Confounders

We considered 50 potential confounders, all measured before or at cohort entry (Tables 1 and 3). We considered a wide range of potential confounders, all measured before or at cohort entry. These included age (modeled using cubic splines with five interior knots to account for a possible non-linear relation with the exposure), sex, lifestyle-related factors (body mass index, alcohol-related disorders, smoking status), cohort entry year, and region (as a proxy for exposure to sunlight). We considered known skin cancer risk factors, including pre-cancerous photodermatoses (serving as markers of ultraviolet exposure), and use of photosensitizing and

immunosuppressive drugs. We also considered diabetes-related variables (hemoglobin A1c, duration of diabetes (calculated as the time between cohort entry and the earliest of a diabetes diagnosis, use of an antihyperglycemic drug, or an HbA1c value of ≥ 6.5%), microvascular [nephropathy, neuropathy, retinopathy] and macrovascular [myocardial infarction, stroke, peripheral arteriopathy] complications, and use of antihyperglycemic drugs ever before cohort entry including metformin, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, sodium-glucose cotransporter-2 inhibitors, and insulin), common comorbidities (heart failure, cancer, obstructive sleep apnea, osteoarthritis, chronic obstructive pulmonary disease, depression, dyslipidemia, gastrointestinal reflux disease, cardiac arrhythmia, hypertension, hypothyroidism) and comedications (antihypertensives, antiarrhythmics, antiplatelet agents, statins, non-steroidal anti-inflammatory drugs, corticosteroids, biologics, proton pump inhibitors) in diabetes, and markers of healthcare-seeking behavior (uptake of cancer screening [fecal occult blood testing or colonoscopy, mammography, prostate-specific antigen testing] and vaccinations [including influenza and pneumococcal vaccinations] in the year before cohort entry).

6.5.5 Primary Analyses

We used propensity score fine stratification weighting for confounding adjustment.[27] We first calculated the predicted probability (propensity score) of receiving GLP-1 RAs versus sulfonylureas using the covariates listed above using multiple logistic regression model. Thereafter, after trimming of the non-overlapping regions of propensity score, we stratified the cohort into 50 strata based on the propensity scores of the GLP-1 RA users. Within each stratum, the GLP-1RA users received a weight of one, and the sulfonylurea users received a weight proportional to the number exposed in the corresponding stratum. This method attempts to balance

the covariate distribution within each stratum and estimates the average treatment effect on the treated, that is, the GLP-1 RA users.

We summarized the covariate distribution within the exposure groups before and after weighting, with a standardized difference of less than 0.10 indicating good covariate balance.[28] We calculated weighted incidence rates of melanoma and nonmelanoma skin cancer with 95% CIs based on the Poisson distribution for each exposure group. The cumulative incidence of the outcome over the follow-up period was plotted using weighted Kaplan-Meier curves. We estimated the weighted HRs with 95% CIs of incident melanoma and nonmelanoma skin cancer using the Cox proportional hazards models, comparing GLP-1 RAs with sulfonylureas.

6.5.6 Secondary analyses

We conducted four secondary analyses. First, we assessed in a time-varying manner whether the association varies based on time since treatment initiation, defined as the period between the first prescription and the time of the risk set. Second, we examined in a time-varying manner whether cumulative duration of use affects the association, calculated by adding the duration of each prescription from drug initiation till the risk set. Third, we assessed whether the association varies by GLP-1 RA type, liraglutide (the most commonly used GLP-1 RA, with which a signal regarding skin cancer was found in the LEADER trial[3,5]), and other GLP-1 RAs. Finally, we considered any potential effect measure modification by age (<65 years vs. ≥ 65 years; up to 40% of melanoma are diagnosed among individuals ≥65 years),[29] sex (given sex differences in dermal DNA damage mechanisms and incidence of skin cancer),[30] and use of immunosuppressive drugs (given the higher incidence of skin cancer among immunosuppressed patients)[31] by including interaction terms between exposures and these variables in the models.

6.5.7 Sensitivity analyses

We conducted two sensitivity analyses. First, due to uncertainties with respect to the optimal length of the cancer latency window, we increased the exposure lag period to three and five years. Second, to address the possibility that the differences between reasons for censoring such as drug switching or death affected the results, we conducted an inverse probability of censoring weighted analysis. This entailed dividing the follow-up into periods of one year and constructing two logistic regression models to predict the propensity for remaining on the study drug or remaining alive based on the distribution of the previously described covariates in the year prior. The product of these weights was used to create a pseudopopulation with equal chances of being censored, and the weights were stabilized using intercept only models as numerators. We conducted all analyses with SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

6.6 Results

6.6.1 Melanoma outcome cohort

This cohort consisted of 11,786 patients initiating GLP-1 RAs and 208,519 initiating sulfonylureas, followed up over a median period of 3.1 years (interquartile range: 1.4-5.7 years) (**Figure S6.1**). During this period, 529 patients were newly-diagnosed with melanoma, generating an incidence rate of 62.7 (95% CI 57.5-68.2) per 100,000 person-years. The GLP-1 RA users tended to be younger, female, white, obese, with a longer duration of diabetes and have prior insulin use. After propensity score fine stratification weighting, the standardized differences in the covariate distribution between the groups were below 0.10, indicating good balance (**Table 6.1**).

Overall, there was no evidence of an association between GLP-1 RA use and an increased risk of melanoma compared with sulfonylurea use, though the confidence intervals were wide (42.6 vs. 43.9 per 100,000 person-years, respectively; HR 0.96, 95% CI 0.53-1.75) (**Table 6.2**). The Kaplan Meier curves for the two groups representing cumulative incidence overlapped throughout the follow-up (**Figure 6A)**. There was no evidence of a duration-response relationship by time since initiation or cumulative duration. Liraglutide (HR: 0.86 95% CI 0.62-1.19) or other drugs (HR: 1.06 95% CI 0.81-1.40) were not associated with an increased risk of melanoma. We did not find effect measure modification in subgroups by age, sex, or use of immunosuppressant agents (**Figure S6.2**).

The **Figure 6.3** summarizes the primary and sensitivity analyses. Overall, the sensitivity analyses remained consistent with the primary analysis results. The point estimates for sensitivity analyses ranged from 1.28 for the intention-to-treat analysis lagged by 3 years to 0.64 for the inverse probability of censoring weighted analysis, and all estimates included the null value.

6.6.2 Nonmelanoma skin cancer outcome cohort

This cohort included 11,778 and 207,305 patients initiating GLP-1 RAs and sulfonylureas, respectively (**Figure 6.4**). Over a median follow-up of 3.1 years (interquartile range 1.4-5.6), 3683 patients were diagnosed with nonmelanoma skin cancer, at a crude incidence rate of 443.9 per 100,000 person-years (95% 429.7-458.4). Imbalances were similar to the melanoma outcome cohort, but covariates were well-balanced after propensity score fine stratification weighting (**Table 6.3**).

GLP-1 RAs were not associated with an increased risk of nonmelanoma skin cancer (243.9 vs. 244.1 per 100,000 person-years, respectively; HR 0.96, 95% CI 0.75-1.23) (**Table 6.4**). The cumulative incidence curves overlapping overall, though a divergence was noted between 4-9 years of use (**Figure 6B**). The HR reduced with increasing time since initiation of the drugs, though the confidence intervals remained wide (0-2 years HR 1.07, 95% CI 0.78-1.47; 2.1-5 years HR 1.05, 95% CI 0.73-1.51; >5 years HR 0.79, 95% CI 0.42-1.47) (**Table 6.4**). However, no consistent pattern was seen in the cumulative duration of use analysis (0-2 years HR 1.46, 95% CI 0.50-4.27; 2.1-5 years HR 0.83, 95% CI 0.53-1.31; >5 years HR 1.16, 95% CI 0.59-2.29). Neither liraglutide nor other molecules were associated with nonmelanoma skin cancers.

There were no subgroup effects for age or sex, but we were unable to examine effect measure modification by immunosuppressant because of no events among patients with prior immunosuppressant use (**Figure S6.5)**. Overall, the sensitivity analyses aligned with the primary analyses with point estimates ranging from 0.92-1.28, and CIs encompassing the null value (**Figure 6.6**).

6.7 DISCUSSION

In this large population-based cohort study, the use of GLP-1 RAs was not associated with an increased risk of either melanoma or nonmelanoma skin cancer. These results remained consistent in secondary and sensitivity analyses. Notably, liraglutide, the drug with which a skin cancer signal had emerged, was also not associated with an increased risk.

Imbalances in skin cancer incidence were initially reported in the large LEADER trial of liraglutide,[6] where there was an increased risk of investigator-reported skin cancer events with liraglutide versus placebo (96/4668 vs. 68/4672, odds ratio [OR] 1.42, 95% CI 1.03-1.94).[15] Although the findings were no longer statistically significant after classifying the adjudicated skin cancer events into the melanoma and nonmelanoma skin cancer subtypes, the imbalance remained, with a higher number of events with liraglutide versus placebo for both melanoma (13/4668 vs. 5/4672, HR 2.59, 95% CI: 0.92-7.27) and nonmelanoma skin cancer (78/4668 vs. 62/4672, HR 1.25, 95% CI 0.90-1.75).[10] Moreover, a sensitivity analysis excluding skin cancer events in the first year after randomization (to reduce the effect of drug-unrelated prevalent cases and differential detection between groups) led to elevated HRs for both melanoma (11/4599 vs. 1/4601, HR 10.95, 95% CI 1.41-84.82) and nonmelanoma skin cancer (61/4599 vs. 48/4601, HR 1.26, 95% CI 0.87-1.84).[10] A higher point estimate for skin cancer (though not granulated into subtypes) was reported in SUSTAIN-6 trial of semaglutide (24/1624 vs. 17/1632, HR 1.41, 95% CI 0.76-2.63),[7] but publications of other long-term randomized controlled trials of GLP-1 RA did not consistently report skin cancer events. However, it is difficult to assess the risk of skin cancer from these trials as they lacked generalizability to the diabetes population at large,[32] had relatively small sample sizes and short median durations of follow-up,[33] as well as has inconsistent reporting of skin cancer events, making the case for well conducted large observational studies. To our

knowledge, this is the first such study examining the association between GLP-1 RAs and skin cancer.

The biological evidence on the association between GLP-1 RAs and skin cancer is limited. Importantly, skin cells leading to melanoma and nonmelanoma skin cancers, melanocytes and keratinocytes respectively, both express the GLP-1 receptor.[7,8] Indeed, an experimental GLP-1 RA called geniposide has been shown to stimulate in melanocytes the phosphoinositol-3-kinase (PI3K)-Akt signaling pathway,[12,13] a pathway known to play a critical role in the malignant transformation of skin cells.[34] However, these findings have not been replicated with the clinically approved GLP-1 RAs. Nor is there any evidence that PI3K-Akt pathway activation by geniposide leads to actual melanocyte proliferation or malignant transformation in vitro or in vivo. In contrast, while liraglutide has been shown to stimulate the PI3K-Akt pathway in keratinocytes, it was found that such activation does not lead to keratinocyte proliferation.[14] Such findings align with the lack of an association between GLP-1 RAs, including liraglutide, and skin cancer evidenced in our study.

This study has several strengths. First, we answered questions directly posed by regulatory agencies in the first large-scale real-world observational study assessing the association between GLP-1 RAs and skin cancer incidence.[4,15,16] Second, this study uses a population-based database representative of the UK population, thus improving over the restricted populations of the cardiovascular outcome trials. Our large sample size also allowed pre-specified subgroups analyses to identify patients who might be at increased risk of skin cancer. Finally, our results remained consistent in sensitivity analyses lengthening the lag period as well as accounting for potential differential censoring, an important factor in the comparison between GLP-1 RAs and sulfonylureas.

Our study also has some limitations. First, given that the CPRD is a primary care database, there might be potential misclassification of outcomes such as skin cancer, which would be typically treated by dermatologists or oncologists, and diagnoses are recorded by the general practitioners on the CPRD retrospectively. However, previous studies examining the concordance of melanoma and nonmelanoma skin cancer with medical review of notes and data from the national cancer registry of the UK have reported a high positive predictive value of the Read diagnoses in UK primary care databases.[35-37] In fact, for nonmelanoma skin cancers, recording in the CPRD may be better than in the national cancer registry.[38,39] Second, potential for exposure misclassification remains given that CPRD is a primary care database. However, given that most patients with diabetes in the UK are managed by general practioners,[40] such misclassification is unlikely to be significant. Third, we were unable to record sun exposure, an important risk factor for skin cancer.[41] However, sun exposure is not directly considered while prescribing antihyperglycemic medications, which makes it unlikely that this risk factor is differentially distributed between the exposure groups. Furthermore, we adjusted for region as a proxy for regional variations in ultraviolet radiation and cohort entry years as proxy for temporal variation in sun exposure. Also, baseline variables such as photodermatoses, representative of prior sun exposure, and other risk factors for skin cancer such as immunosuppressants and phototoxic drugs were well-balanced between the groups even before propensity score weighting, indicating unmeasured confounding might be limited. In contrast, factors such as ethnicity which had relatively large imbalance before weighting were well-balanced after propensity score weighting. Nevertheless, given the observational nature of the study, potential for unmeasured confounding could not be eliminated. Finally, given the UK has a unique single-payer healthcare system and

imposes a uniform token payment for all prescriptions, our results may not be generalizable to other health systems.

In summary, the results of this study suggest that over a median follow-up of over 3 years and a potential follow-up of up to 13 years, the use of GLP-1 RAs was not associated with an increased risk of skin cancer, compared with the use of sulfonylureas, among patients with type 2 diabetes. These findings remained consistent in secondary and sensitivity analyses and should provide reassurance to clinicians and regulatory agencies regarding the safety profile of these commonly used drugs.

6.8 ACKNOWLEDGEMENTS

R Pradhan is the recipient of a Doctoral Award from the Fonds de Recherche du Québec – Santé. OHYY holds a Chercheur-Boursier Clinicien Junior 1 award from the Fonds de Recherche du Québec - Santé. R Platt holds the Albert Boehringer I Chair in Pharmacoepidemiology at McGill University. LA holds a Distinguished Research Scholar award from the Fonds de Recherche du Québec - Santé and is the recipient of a William Dawson Scholar Award from McGill University.

6.9 COMPETING INTEREST STATEMENT

R Platt received consulting fees from Biogen, Boehringer Ingelheim, Merck, Nant Pharma, Pfizer, and Reckitt Benckiser for work unrelated to this study. LA received consulting and speaker fees from Janssen, Pfizer, and Roche for work unrelated to this study. Other authors have no conflict of interest to declare.

6.10 CONTRIBUTIONS

All authors conceived and designed the study. LA acquired the data. R Pradhan and LA did the statistical analyses. R Platt provided statistical expertise and OHYY provided clinical expertise. All authors analysed and interpreted the data. R Pradhan wrote the manuscript, and all authors critically revised it. All authors approved the final version of the manuscript and agree to be accountable for the accuracy of the work. LA supervised the study and is the guarantor.

6.11 FUNDING

This study was funded by a Foundation Scheme grant from the Canadian Institutes of Health Research (FDN-143328). The sponsors had no influence on design and conduct of the study;

collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

6.12 REFERENCE

1. Gupta V. Glucagon-like peptide-1 analogues: An overview. *Indian Journal of Endocrinology and Metabolism.* 2013;17(3):413-421.
2. Islam Z, Akter S, Inoue Y, et al. Prediabetes, Diabetes, and the Risk of All-Cause and Cause-Specific Mortality in a Japanese Working Population: Japan Epidemiology Collaboration on Occupational Health Study. *Diabetes Care.* 2021;44(3):757-764.
3. Curtis HJ, Dennis JM, Shields BM, et al. Time trends and geographical variation in prescribing of drugs for diabetes in England from 1998 to 2017. *Diabetes Obes Metab.* 2018;20(9):2159-2168.
4. Committee for Medicinal Products for Human U. Assessment report: Victoza: EMA/479764/2017. In:2017.
5. Nauck MA, Jensen TJ, Rosenkilde C, Calanna S, Buse JB, Investigators LPCobotLT. Neoplasms Reported With Liraglutide or Placebo in People With Type 2 Diabetes: Results From the LEADER Randomized Trial. *Diabetes Care.* 2018;41(8):1663-1671.
6. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2016;375(4):311-322.
7. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
8. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2017;377(13):1228-1239.
9. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med.* 2015;373(23):2247-2257.

10. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet (London, England).* 2019;394(10193):121-130.

11. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet (London, England).* 2018;392(10157):1519-1529.

12. Wen-Jun L, Hai-Yan W, Wei L, Ke-Yu W, Rui-Ming W. Evidence that geniposide abrogates norepinephrine-induced hypopigmentation by the activation of GLP-1R-dependent c-kit receptor signaling in melanocyte. *J Ethnopharmacol.* 2008;118(1):154-158.

13. Lu W, Zhao Y, Kong Y, et al. Geniposide prevents H2 O2 -induced oxidative damage in melanocytes by activating the PI3K-Akt signalling pathway. *Clin Exp Dermatol.* 2018;43(6):667-674.

14. Nagae K, Uchi H, Morino-Koga S, Tanaka Y, Oda M, Furue M. Glucagon-like peptide-1 analogue liraglutide facilitates wound healing by activating PI3K/Akt pathway in keratinocytes. *Diabetes Res Clin Pract.* 2018;146:155-161.

15. FDA Briefing Document: Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC): Liraglutide-LEADER. In:2017.

16. Food, Drug Administration CfDE, Research. Endocrinologic and Metabolic Advisory Committee Meeting Minutes. In:2017.

17. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol.* 2015;44(3):827-836.

18. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners.* 2010;60(572):e128-136.

19. Dictionary of medicines and devices (dm+d) | NHSBSA.

20. 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.

21. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *British Journal of Clinical Pharmacology.* 2010;69(1):4-14.

22. Azoulay L, Yin H, Filion KB, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. *BMJ (Clinical research ed).* 2012;344:e3645.

23. Hicks BM, Yin H, Yu OHY, Pollak MN, Platt RW, Azoulay L. Glucagon-like peptide-1 analogues and risk of breast cancer in women with type 2 diabetes: population based cohort study using the UK Clinical Practice Research Datalink. *BMJ (Clinical research ed).* 2016;355:i5340.

24. Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ (Clinical research ed).* 2016;352:i1541.

25. Filion KB, Azoulay L, Platt RW, et al. A Multicenter Observational Study of Incretin-based Drugs and Heart Failure. *N Engl J Med.* 2016;374(12):1145-1154.

26. Filion KB, Lix LM, Yu OH, et al. Sodium glucose cotransporter 2 inhibitors and risk of major adverse cardiovascular events: multi-database retrospective cohort study. *Bmj.* 2020;370:m3342.

27. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ (Clinical research ed).* 2019;367:l5657.

28. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine.* 2009;28(25):3083-3107.

29. Garcovich S, Colloca G, Sollena P, et al. Skin Cancer Epidemics in the Elderly as An Emerging Issue in Geriatric Oncology. *Aging Dis.* 2017;8(5):643-661.

30. Welsh MM, Karagas MR, Kuriger JK, et al. Genetic determinants of UV-susceptibility in non-melanoma skin cancer. *PLoS ONE.* 2011;6(7):e20019.

31. Fortina AB, Piaserico S, Caforio ALP, et al. Immunosuppressive level and other risk factors for basal cell carcinoma and squamous cell carcinoma in heart transplant recipients. *Arch Dermatol.* 2004;140(9):1079-1085.

32. Wittbrodt ET, Eudicone JM, Bell KF, Enhoffer DM, Latham K, Green JB. Generalizability of glucagon-like peptide-1 receptor agonist cardiovascular outcome trials enrollment criteria to the US type 2 diabetes population. *The American Journal of Managed Care.* 2018;24(8 Suppl):S146-S155.

33. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care.* 2018;41(1):14-31.

34. Chamcheu JC, Roy T, Uddin MB, et al. Role and Therapeutic Targeting of the PI3K/Akt/mTOR Signaling Pathway in Skin Cancer: A Review of Current Status and Future Trends on Natural and Synthetic Agents Therapy. *Cells.* 2019;8(8).

35. 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):308-313.

36. Meal A, Leonardi-Bee J, Smith C, Hubbard R, Bath-Hextall F. Validation of THIN data for non-melanoma skin cancer. *Qual Prim Care.* 2008;16(1):49-52.

37. Chiesa Fuxench ZC, Troxel AB, Gelfand JM. Validity of diagnostic codes for identifying cutaneous squamous cell carcinoma in The Health Improvement Network. *Br J Dermatol.* 2017;176(5):1363-1365.

38. Boggon R, van Staa TP, Chapman M, Gallagher AM, Hammad TA, Richards MA. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiology and Drug Safety.* 2013;22(2):168-175.

39. Dregan A, Moller H, Murray-Thomas T, Gulliford MC. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. *Cancer Epidemiol.* 2012;36(5):425-429.

40. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ open.* 2016;6(1):e010210.

41. Gordon R. Skin cancer: an overview of epidemiology and risk factors. Paper presented at: Seminars in oncology nursing2013.

FIGURE LEGENDS

Figure 6

Figure 6A: Weighted cumulative incidence curves of melanoma in the glucagon like peptide-1 receptor agonist vs. sulfonylurea cohort

Figure 6B: Weighted cumulative incidence curves of nonmelanoma skin cancer in the glucagon like peptide-1 receptor agonist vs. sulfonylurea cohort

Figure 6A. Weighted cumulative incidence curves of melanoma in the glucagon like peptide-1 receptor agonist vs. sulfonylurea cohort

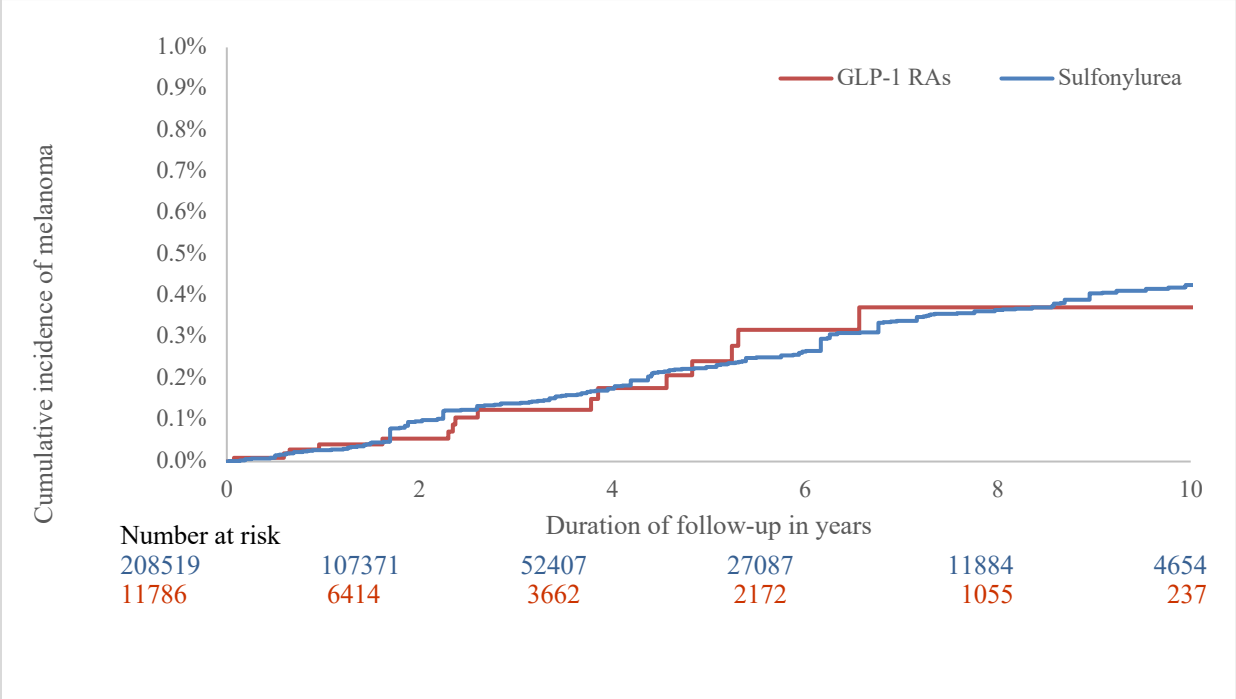


Figure 6B. Weighted cumulative incidence curves of nonmelanoma skin cancer in the glucagon like peptide-1 receptor agonist vs. sulfonylurea cohort

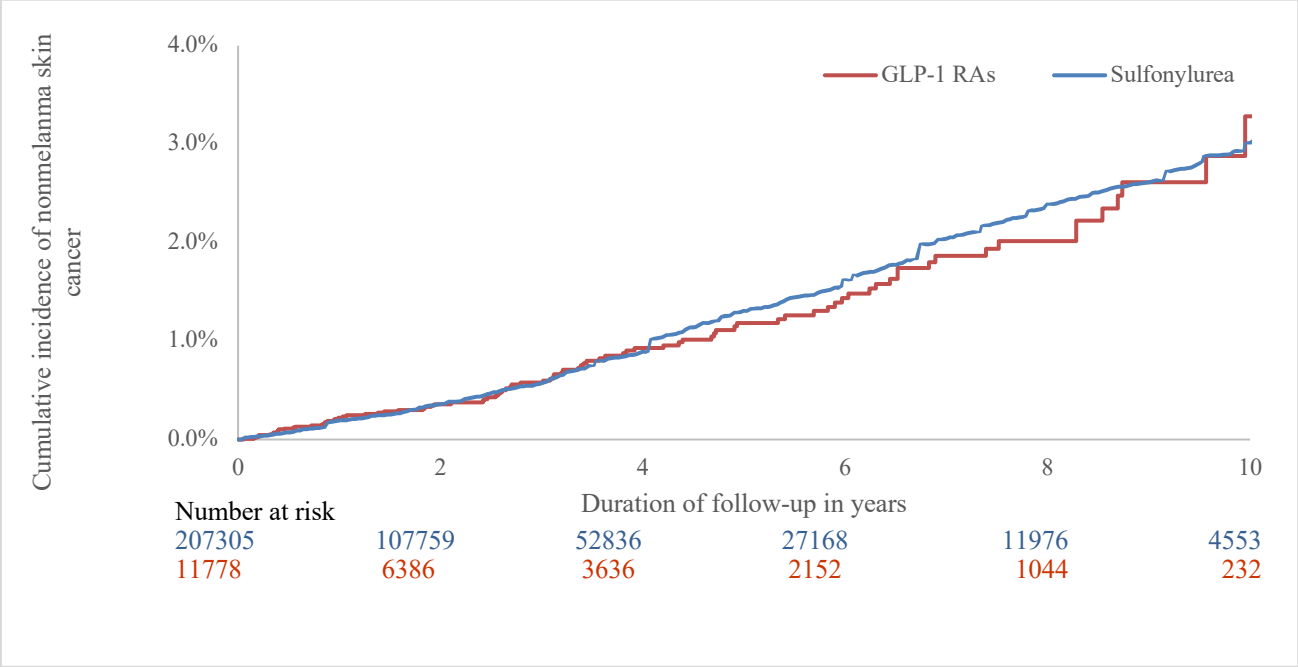


Table 6.1 Baseline Characteristics of the GLP1-1 receptor agonists and Sulfonylurea Exposure Groups in Melanoma Outcome Cohort Before and After Propensity Score‡ Weighting

Characteristics	Before weighting			After weighting		
	GLP-1 RA	Sulfonylureas	ASD	GLP-1 RA	Sulfonylureas	ASD
Total	11786	208519		11786	208519	
Age in years, Mean (Standard Deviation)	52.1 (11.7)	60.3 (13.2)	0.66	52.1 (11.7)	51.3 (11.9)	0.07
Male, n (%)	5,586 (47.4)	120,930 (58.0)	0.21	5,586 (47.4)	94,708 (45.4)	0.04
Ethnicity, n (%)						
White	7,798 (66.2)	126,667 (60.8)	0.11	7,798 (66.2)	137,010 (65.7)	0.01
South Asian	623 (5.3)	17,393 (8.3)	0.12	623 (5.3)	10,982 (5.3)	0.00
Black	417 (3.5)	9,112 (4.4)	0.04	417 (3.5)	7,364 (3.5)	0.00
Mixed	113 (1.0)	1,706 (0.8)	0.01	113 (1.0)	2,220 (1.1)	0.01
Other	75 (0.6)	2,148 (1.0)	0.04	75 (0.6)	1,315 (0.6)	0.00
Unknown	2,760 (23.4)	51,493 (24.7)	0.03	2,760 (23.4)	49,628 (23.8)	0.01
Smoking, n (%)						
Ever	8,811 (74.8)	156,257 (74.9)	0.00	8,811 (74.8)	156,410 (75.0)	0.01
Never	2,929 (24.9)	51,574 (24.7)	0.00	2,929 (24.9)	51,257 (24.6)	0.01
Unknown	46 (0.4)	688 (0.3)	0.01	46 (0.4)	852 (0.4)	0.00
Alcohol dependence, n (%)	828 (7.0)	15,810 (7.6)	0.01	828 (7.0)	14,658 (7.0)	0.00
Body mass index, n (%)						
≤ 24.9 kg/m²	86 (0.7)	27,435 (13.2)	0.00	86 (0.7)	2,048 (1.0)	0.03
25.0 - 29.9 kg/m²	593 (5.0)	65,577 (31.5)	0.00	593 (5.0)	10,080 (4.8)	0.01
≥ 30.0 kg/m²	11,009 (93.4)	111,361 (53.4)	1.02	11,009 (93.4)	194,745 (93.4)	0.00
Unknown	98 (0.8)	4,146 (2.0)	0.10	98 (0.8)	1,646 (0.8)	0.00
HbA1c, n (%)						
≤7.0%	1,787 (15.2)	17,664 (8.5)	0.21	1,787 (15.2)	35,753 (17.2)	0.05
7.1%-8.0%	2,240 (19.0)	50,741 (24.3)	0.13	2,240 (19.0)	38,610 (18.5)	0.01

>8.0%	7,452 (63.2)	128,009 (61.4)	0.04	7,452 (63.2)	128,272 (61.5)	0.04
Unknown	307 (2.6)	12,105 (5.8)	0.16	307 (2.6)	5,884 (2.8)	0.01
Duration of diabetes	7.6 (7.7)	4.5 (5.2)	0.47	7.6 (7.7)	7.1 (7.2)	0.07
Myocardial infarction, n (%)	765 (6.5)	14,810 (7.1)	0.02	765 (6.5)	12,973 (6.2)	0.01
Peripheral circulatory disorders, n (%)	821 (7.0)	11,963 (5.7)	0.05	821 (7.0)	13,784 (6.6)	0.01
Stroke, n (%)	359 (3.1)	9,804 (4.7)	0.09	359 (3.1)	5,968 (2.9)	0.01
Neuropathy, n (%)	2,600 (22.1)	33,925 (16.3)	0.15	2,600 (22.1)	41,858 (20.1)	0.05
Retinopathy, n (%)	3,627 (30.8)	39,053 (18.7)	0.28	3,627 (30.8)	56,739 (27.2)	0.08
Renal diseases, n (%)	1,226 (10.4)	30,718 (14.7)	0.13	1,226 (10.4)	20,413 (9.8)	0.02
Metformin, n (%)	10,864 (92.2)	179,574 (86.1)	0.20	10,864 (92.2)	192,652 (92.4)	0.01
Thiazolidinediones, n (%)	2,122 (18.0)	17,908 (8.6)	0.28	2,122 (18.0)	38,804 (18.6)	0.02
Sodium-glucose cotransporter-2 inhibitors, n (%)	1,326 (11.3)	1,515 (0.7)	0.45	1,326 (11.3)	22,652 (10.9)	0.01
Alfa glucosidase inhibitors, n (%)	127 (1.1)	482 (0.2)	0.14	127 (1.1)	2,249 (1.1)	0.00
Meglitinides, n (%)	253 (2.2)	1,060 (0.5)	0.94	253 (2.2)	4,467 (2.1)	0.00
Insulin, n (%)	4,458 (37.8)	7,229 (3.5)	0.94	4,458 (37.8)	75,403 (36.2)	0.03
Heart failure, n (%)	382 (3.2)	8,305 (4.0)	0.04	382 (3.2)	6,460 (3.1)	0.01
Cancer, n (%)	458 (3.9)	15,592 (7.5)	0.16	458 (3.9)	7,866 (3.8)	0.01
Obstructive sleep apnea, n (%)	1,349 (11.5)	5,858 (2.8)	0.34	1,349 (11.5)	24,104 (11.6)	0.00
Osteoarthritis, n (%)	2,500 (21.2)	46,649 (22.4)	0.03	2,500 (21.2)	42,473 (20.4)	0.02
Chronic obstructive pulmonary disease, n (%)	815 (6.9)	16,629 (8.0)	0.04	815 (6.9)	13,779 (6.6)	0.01
Depression, n (%)	5,686 (48.2)	65,222 (31.3)	0.35	5,686 (48.2)	103,204 (49.5)	0.03
Dyslipidemia	2,581 (21.9)	44,362 (21.3)	0.02	2,581 (21.9)	42,410 (20.3)	0.04
Gastrointestinal esophageal reflux disease, n (%)	1,805 (15.3)	28,281 (13.6)	0.05	1,805 (15.3)	32,186 (15.4)	0.00
Arrhythmia, n (%)	706 (6.0)	16,691 (8.0)	0.08	706 (6.0)	12,232 (5.9)	0.01
Hypertension	7,352 (62.4)	123,972 (59.5)	0.06	7,352 (62.4)	127,570 (61.2)	0.02

Hypothyroidism, n (%)	646 (5.5)	8,788 (4.2)	0.06	646 (5.5)	10,837 (5.2)	0.01
Photodermatoses, n (%)	167 (1.4)	4,493 (2.2)	0.06	167 (1.4)	2,755 (1.3)	0.01
Antihypertensives, n (%)	9,219 (78.2)	151,960 (72.9)	0.12	9,219 (78.2)	159,972 (76.7)	0.04
Antiarrhythmics, n (%)	2,236 (19.0)	33,648 (16.1)	0.07	2,236 (19.0)	39,456 (18.9)	0.00
Antiplatelet agents, n (%)	3,872 (32.9)	72,623 (34.8)	0.04	3,872 (32.9)	65,446 (31.4)	0.03
Statins, n (%)	8,930 (75.8)	157,691 (75.6)	0.00	8,930 (75.8)	153,413 (73.6)	0.05
Non-steroidal anti-inflammatory drugs, n (%)	9,585 (81.3)	163,128 (78.2)	0.08	9,585 (81.3)	169,768 (81.4)	0.00
Corticosteroids, n (%)	9,868 (83.7)	161,159 (77.3)	0.16	9,868 (83.7)	174,959 (83.9)	0.00
Biologics, n (%)	25 (0.2)	440 (0.2)	0.00	25 (0.2)	491 (0.2)	0.01
Proton-pump inhibitors, n (%)	6,697 (56.8)	103,500 (49.6)	0.14	6,697 (56.8)	118,331 (56.8)	0.00
Phototoxic drugs, n (%)	11,083 (94.0)	191,484 (91.8)	0.09	11,083 (94.0)	195,139 (93.6)	0.02
Immunosuppressants, n (%)	316 (2.7)	5,369 (2.6)	0.01	316 (2.7)	5,800 (2.8)	0.01
Opioids, n (%)	8,961 (76.0)	140,228 (67.3)	0.2	8,961 (76.0)	158,206 (75.9)	0.00
Colon cancer screening, n (%)	882 (7.5)	14,966 (7.2)	0.01	882 (7.5)	15,083 (7.2)	0.01
Mammogram, n (%)	899 (7.6)	12,862 (6.2)	0.06	899 (7.6)	16,187 (7.8)	0.00
Prostate specific antigen, n (%)	491 (4.2)	15,530 (7.5)	0.14	491 (4.2)	7,939 (3.8)	0.02
Pneumococcal vaccine, n (%)	707 (6.0)	13,319 (6.4)	0.02	707 (6.0)	12,344 (5.9)	0.00
Influenza vaccine, n (%)	3,389 (28.8)	81,849 (39.3)	0.22	3,389 (28.8)	57,489 (27.6)	0.03
Cohort entry year, n (%)						
2007-2010	2,755 (23.4)	87,753 (42.1)	0.41	2,755 (23.4)	45,967 (22.0)	0.03
2011-2014	3,554 (30.2)	70,375 (33.8)	0.08	3,554 (30.2)	63,038 (30.2)	0.00
2015-2019	5,477 (46.5)	50,391 (24.2)	0.48	5,477 (46.5)	99,514 (47.7)	0.03

Abbreviations: ASD, absolute standardized difference; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists.
‡ Additionally adjusted for region, for which the absolute standardized differences ranged between 0.00 to 0.02 after propensity score fine stratification weighting.

Table 6.2 Hazard Ratios for Melanoma Comparing GLP-1 RAs with Sulfonylureas

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) [§]	Crude HR	Weighted HR (95% CI) [†]
Primary analysis						
Sulfonylureas	208,519	513	805,808	43.9 (38.8-49.6)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	11,786	16	37,506	42.6 (24.4-69.3)	0.69	0.97 (0.54-1.73)
Time since initiation						
0-2 years						
Sulfonylureas	208,519	99	189,168	27.2 (20.1-36.1)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	11,786	S[¶]	10,070	39.7 (10.8-101.7)	0.76	1.46 (0.50-4.27)
2.1-5 years						
Sulfonylureas	166,237	213	361,644	54.4 (46.7-63.2)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	8601	7	17,222	40.6 (16.3-83.7)	0.69	0.75 (0.28-2.07)
>5 years						
Sulfonylureas	76,658	175	225,018	44.0 (35.3-54.2)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	3657	S[¶]	10,237	48.8 (15.9-114.0)	0.64	1.10 (0.40-3.04)
Cumulative duration of use						
0-2 years						
Sulfonylureas	208,903	118	365,887	32.2 (26.6-38.5)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	11,808	9	25,537	35.2 (16.1-66.9)	0.69	1.11 (0.55-2.26)
2.1-5 years						
Sulfonylureas	110,047	145	198,910	73.1 (61.7-86.0)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	3910	S[¶]	10,116	39.5 (10.8-10.1)	0.54	0.57 (0.20-1.63)
>5 years						

Sulfonylureas	35,044	44	47,164	92.9 (67.4-124.8)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	838	S[¶]	1873	160.1 (33.0-468.0)	1.81	1.91 (0.51-7.18)
Individual drugs						
Sulfonylureas	202,459	489	784,238	50.0 (44.5-56.0)	1.00 [Reference]	1.00 [Reference]
Liraglutide	5549	11	18,337	60.0 (30.0-107.3)	1.00	1.17 (0.62-2.22)
Sulfonylureas	205,888	502	797,292	50.2 (44.7-56.2)	1.00 [Reference]	1.00 [Reference]
Other GLP-1 RAs	6640	S[¶]	20,351	24.6 (8.0-57.3)	0.39	0.49 (0.20-1.21)

Abbreviations: CI, confidence interval; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists; HR, hazard ratio.
[§] Per 100,000 person-years.
[†] The models were weighted using propensity score fine stratification.
[¶] Suppressed: Numbers fewer than five are not displayed, as per confidentiality policies of the Clinical Practice Research Datalink.

Table 6.3 Baseline Characteristics of the GLP1-1 receptor agonists and Sulfonylurea Exposure Groups in Nonmelanoma Skin Cancer Outcome Cohort Before and After Propensity Score‡ Weighting

Characteristics	Before weighting			After weighting		
	GLP-1 RA	Sulfonylureas	ASD	GLP-1 RA	Sulfonylureas	ASD
Total	11778	207305		11778	207305	
Age in years, Mean (Standard Deviation)	52.1 (11.7)	60.2 (13.2)	0.65	52.1 (11.7)	51.3 (11.9)	0.07
Gender, n (%)	5,582 (47.4)	120,214 (58.0)	0.21	5,582 (47.4)	94,106 (45.4)	0.04
Ethnicity, n (%)						
White	7,790 (66.1)	126,068 (60.8)	0.11	7,790 (66.1)	136,703 (65.9)	0.00
South Asian	623 (5.3)	17,374 (8.4)	0.12	623 (5.3)	10,746 (5.2)	0.00
Black	418 (3.6)	9,106 (4.4)	0.04	418 (3.6)	7,096 (3.4)	0.01
Mixed	113 (1.0)	1,706 (0.8)	0.01	113 (1.0)	2,136 (1.0)	0.01
Other	75 (0.6)	2,137 (1.0)	0.04	75 (0.6)	1,383 (0.7)	0.00
Unknown	2,759 (23.4)	50,914 (24.6)	0.03	2,759 (23.4)	49,241 (23.8)	0.01
Smoking, n (%)						
Ever	8,808 (74.8)	155,359 (74.9)	0.00	8,808 (74.8)	155,646 (75.1)	0.01
Never	2,924 (24.8)	51,261 (24.7)	0.00	2,924 (24.8)	50,793 (24.5)	0.01
Unknown	46 (0.4)	685 (0.3)	0.01	46 (0.4)	865 (0.4)	0.00
Alcohol dependence, n (%)	829 (7.0)	15,723 (7.6)	0.01	829 (7.0)	14,419 (7.0)	0.00
Body mass index, n (%)						
≤ 24.9 kg/m²	148 (1.3)	16,956 (8.2)	0.00	148 (1.3)	2,602 (1.3)	0.00
25.0 - 29.9 kg/m²	2,821 (24.0)	31,267 (15.1)	0.23	2,821 (24.0)	49,327 (23.8)	0.00
≥ 30.0 kg/m²	8,788 (74.6)	152,703 (73.7)	0.02	8,788 (74.6)	154,782 (74.7)	0.00
Unknown	21 (0.2)	6,379 (3.1)	0.00	21 (0.2)	594 (0.3)	0.02
HbA1c, n (%)						
≤7.0%	374 (3.2)	4,257 (2.1)	0.07	374 (3.2)	7,347 (3.5)	0.02
7.1%-8.0%	559 (4.8)	12,811 (6.2)	0.06	559 (4.8)	9,449 (4.6)	0.01
>8.0%	8,828 (75.0)	154,631 (74.6)	0.01	2,017 (17.1)	34,859 (16.8)	0.01

Unknown	2,017 (17.1)	35,606 (17.2)	0.00	8,828 (75.0)	155,650 (75.1)	0.00
Duration of diabetes	7.5 (7.7)	4.4 (5.1)	0.48	7.5 (7.7)	7 (7.1)	0.06
Myocardial infarction, n (%)	765 (6.5)	14,654 (7.1)	0.02	765 (6.5)	12,825 (6.2)	0.01
Peripheral circulatory disorders, n (%)	820 (7.0)	11,834 (5.7)	0.05	820 (7.0)	13,688 (6.6)	0.01
Stroke, n (%)	360 (3.1)	9,676 (4.7)	0.08	360 (3.1)	5,854 (2.8)	0.01
Neuropathy, n (%)	2,598 (22.1)	33,755 (16.3)	0.15	2,598 (22.1)	42,424 (20.5)	0.04
Retinopathy, n (%)	3,624 (30.8)	38,818 (18.7)	0.28	3,624 (30.8)	57,378 (27.7)	0.07
Renal diseases, n (%)	1,220 (10.4)	30,295 (14.6)	0.13	1,220 (10.4)	20,087 (9.7)	0.02
Metformin, n (%)	10,856 (92.2)	178,755 (86.2)	0.19	10,856 (92.2)	191,303 (92.3)	0.00
Thiazolidinediones, n (%)	2,119 (18.0)	17,856 (8.6)	0.28	2,119 (18.0)	39,196 (18.9)	0.02
Sodium-glucose cotransporter-2 inhibitors, n (%)	1,328 (11.3)	1,513 (0.7)	0.46	1,328 (11.3)	22,342 (10.8)	0.02
Alfa glucosidase inhibitors, n (%)	127 (1.1)	481 (0.2)	0.14	127 (1.1)	2,150 (1.0)	0.00
Meglitinides, n (%)	253 (2.2)	1,054 (0.5)	0.94	253 (2.2)	4,578 (2.2)	0.00
Insulin, n (%)	4,455 (37.8)	7,214 (3.5)	0.94	4,455 (37.8)	74,844 (36.1)	0.04
Heart failure, n (%)	383 (3.3)	8,154 (3.9)	0.04	383 (3.3)	6,314 (3.1)	0.01
Cancer, n (%)	458 (3.9)	15,358 (7.4)	0.15	458 (3.9)	7,738 (3.7)	0.01
Obstructive sleep apnea, n (%)	1,352 (11.5)	5,840 (2.8)	0.34	1,352 (11.5)	23,916 (11.5)	0.00
Osteoarthritis, n (%)	2,497 (21.2)	46,268 (22.3)	0.03	2,497 (21.2)	42,273 (20.4)	0.02
Chronic obstructive pulmonary disease, n (%)	815 (6.9)	16,467 (7.9)	0.04	815 (6.9)	13,723 (6.6)	0.01
Depression, n (%)	5,684 (48.3)	64,918 (31.3)	0.35	5,684 (48.3)	102,757 (49.6)	0.03
Dyslipidemia	2,578 (21.9)	44,091 (21.3)	0.02	2,578 (21.9)	42,488 (20.5)	0.03
Gastrointestinal esophageal reflux disease, n (%)	1,802 (15.3)	28,086 (13.6)	0.05	1,802 (15.3)	31,739 (15.3)	0.00
Arrhythmia, n (%)	704 (6.0)	16,453 (7.9)	0.08	704 (6.0)	12,237 (5.9)	0.00
Hypertension	7,342 (62.3)	123,167 (59.4)	0.06	7,342 (62.3)	126,929 (61.2)	0.02
Hypothyroidism, n (%)	646 (5.5)	8,706 (4.2)	0.06	646 (5.5)	10,818 (5.2)	0.01
Photodermatoses, n (%)	167 (1.4)	4,366 (2.1)	0.05	167 (1.4)	2,823 (1.4)	0.01

Antihypertensives, n (%)	9,210 (78.2)	150,938 (72.8)	0.13	9,210 (78.2)	159,442 (76.9)	0.03
Antiarrhythmics, n (%)	2,235 (19.0)	33,386 (16.1)	0.08	2,235 (19.0)	39,326 (19.0)	0.00
Antiplatelet agents, n (%)	3,866 (32.8)	72,333 (34.9)	0.04	3,866 (32.8)	64,460 (31.1)	0.04
Statins, n (%)	8,920 (75.7)	156,763 (75.6)	0.00	8,920 (75.7)	152,851 (73.7)	0.05
Non-steroidal anti-inflammatory drugs, n (%)	9,577 (81.3)	162,333 (78.3)	0.07	9,577 (81.3)	168,829 (81.4)	0.00
Corticosteroids, n (%)	9,861 (83.7)	160,144 (77.3)	0.16	9,861 (83.7)	174,244 (84.1)	0.01
Biologics, n (%)	25 (0.2)	435 (0.2)	0.00	25 (0.2)	473 (0.2)	0.00
Proton-pump inhibitors, n (%)	6,689 (56.8)	102,775 (49.6)	0.14	6,689 (56.8)	117,586 (56.7)	0.00
Phototoxic drugs, n (%)	11,075 (94.0)	190,339 (91.8)	0.09	11,075 (94.0)	194,369 (93.8)	0.01
Immunosuppressants, n (%)	314 (2.7)	5,329 (2.6)	0.01	314 (2.7)	5,644 (2.7)	0.00
Opioids, n (%)	8,958 (76.1)	139,338 (67.2)	0.20	8,958 (76.1)	157,843 (76.1)	0.00
Colon cancer screening, n (%)	882 (7.5)	14,882 (7.2)	0.01	882 (7.5)	14,766 (7.1)	0.01
Mammogram, n (%)	897 (7.6)	12,821 (6.2)	0.06	897 (7.6)	15,675 (7.6)	0.00
Prostate specific antigen, n (%)	491 (4.2)	15,359 (7.4)	0.14	491 (4.2)	7,779 (3.8)	0.02
Pneumococcal vaccine, n (%)	705 (6.0)	13,264 (6.4)	0.02	705 (6.0)	12,288 (5.9)	0.00
Influenza vaccine, n (%)	3,384 (28.7)	81,181 (39.2)	0.22	3,384 (28.7)	57,167 (27.6)	0.03
Cohort entry year, n (%)						
2007-2010	2,750 (23.4)	87,156 (42.0)	0.41	2,750 (23.4)	44,659 (21.5)	0.04
2011-2014	3,554 (30.2)	69,994 (33.8)	0.08	3,554 (30.2)	63,320 (30.5)	0.01
2015-2019	5,474 (46.5)	50,155 (24.2)	0.48	5,474 (46.5)	99,326 (47.9)	0.03

Abbreviations: ASD, absolute standardized difference; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists.

‡ Additionally adjusted for region, for which the absolute standardized differences ranged between 0.00 to 0.02 after propensity score fine stratification weighting.

Table 6.4 Hazard Ratios for Nonmelanoma Skin Cancer Comparing GLP-1 RAs with Sulfonylureas

Exposure	No. of patients	Events	Person-years	Weighted incidence rate (95% CI) [§]	Crude HR	Weighted HR (95% CI) [†]
Primary analysis						
Sulfonylureas	207,305	3592	792,392	244.1 (231.7-257.0)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	11,778	91	37,305	243.9 (196.4-299.5)	0.54	0.96 (0.75-1.24)
Time since initiation						
0-2 years						
Sulfonylureas	207,305	722	187,788	187.1 (167.5-208.5)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	11,778	22	10,052	218.9 (137.2-331.4)	0.76	1.46 (0.50-4.27)
2.1-5 years						
Sulfonylureas	167,168	1544	362,177	202.8 (187.4-219.1)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	8576	37	17,145	215.8 (152.0-297.5)	0.51	1.05 (0.73-1.51)
>5 years						
Sulfonylureas	76,437	1118	223,885	400.2 (372.9-429.0)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	3634	32	10,137	315.7 (215.9-445.6)	0.64	0.79 (0.42-1.47)
Cumulative duration of use						
0-2 years						
Sulfonylureas	208,982	732	377,501	194.0 (180.2-208.6)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	11,832	54	25,407	212.5 (159.7-.277.3)	0.53	1.07 (0.78-1.47)
2.1-5 years						
Sulfonylureas	109,871	554	176,137	314.5 (288.9-341.9)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	3919	28	10,047	278.7 (185.2-402.8)	0.58	0.83 (0.53-1.31)
>5 years						

Sulfonylureas	34,672	160	38,771	412.7 (351.2-481.8)	1.00 [Reference]	1.00 [Reference]
GLP-1 RAs	833	9	1857	484.7 (221.6-.920.1)	0.79	1.16 (0.59-2.29)
Individual drugs						
Sulfonylureas	198,986	3257	763,656	246.4 (233.8-259.4)	1.00 [Reference]	1.00 [Reference]
Liraglutide	5540	39	18,235	213.9 (152.1-292.4)	0.51	0.86 (0.62-1.19)
Sulfonylureas	205,228	3507	786,110	247.3 (234.9-260.2)	1.00 [Reference]	1.00 [Reference]
Other GLP-1 RAs	6632	55	20,230	271.9 (204.8-353.9)	0.61	1.06 (0.81-1.40)

Abbreviations: CI, confidence interval; GLP-1 RAs, Glucagon-like peptide-1 receptor agonists; HR, hazard ratio.
[§] Per 100,000 person-years.
[†] The models were weighted using propensity score fine stratification.

S6. Glucagon Like Peptide-1 Receptor Agonists and the Risk of Skin Cancer Among Patients with Type 2 Diabetes: Population-Based Cohort Study: Supplementary material

Figure S6.1 Melanoma cohort: study flow chart

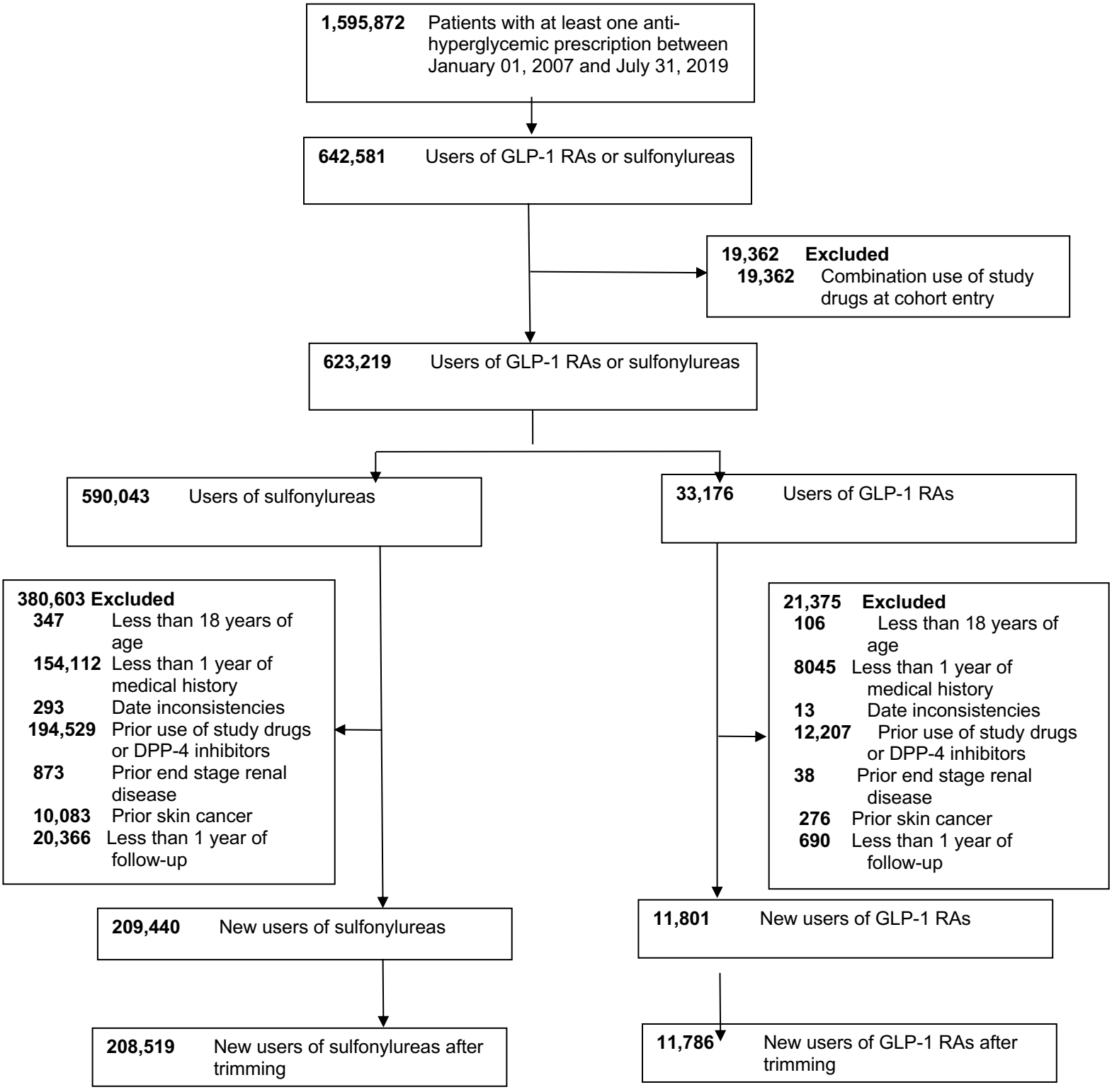
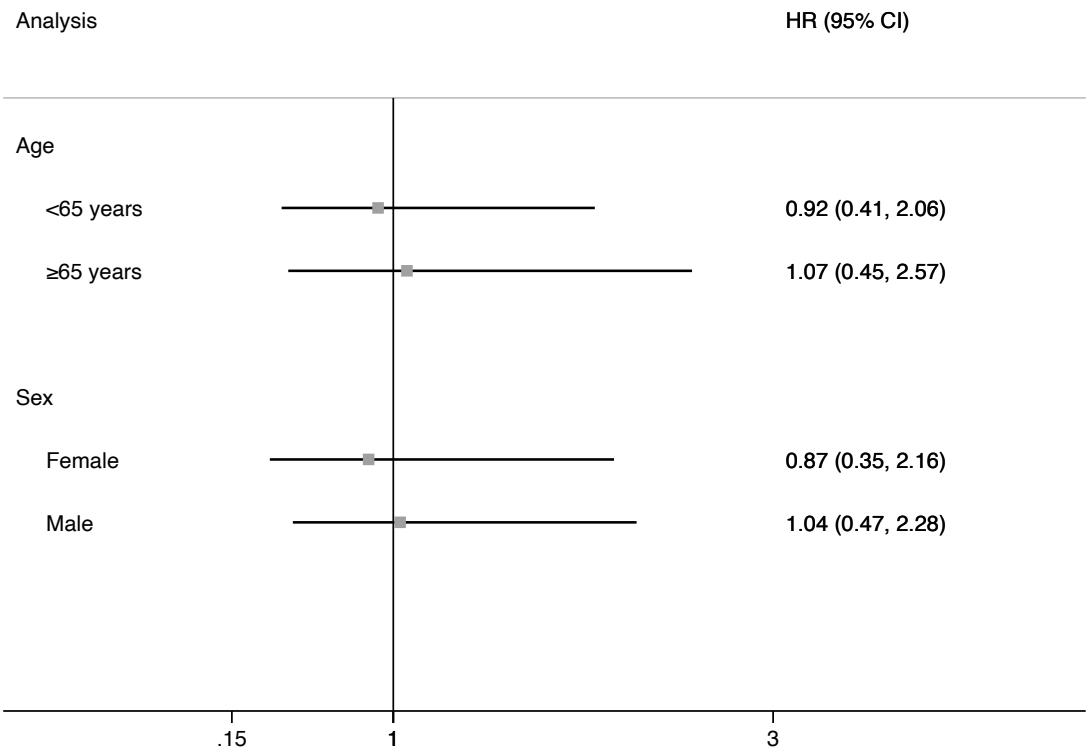


Figure S6.2 Melanoma cohort: effect measure modification



(There were no events for immunosuppressant use in the GLP-1 RA group, so effect modification analysis did not yield valid estimates.)

Figure S6.3 Melanoma cohort: sensitivity analyses

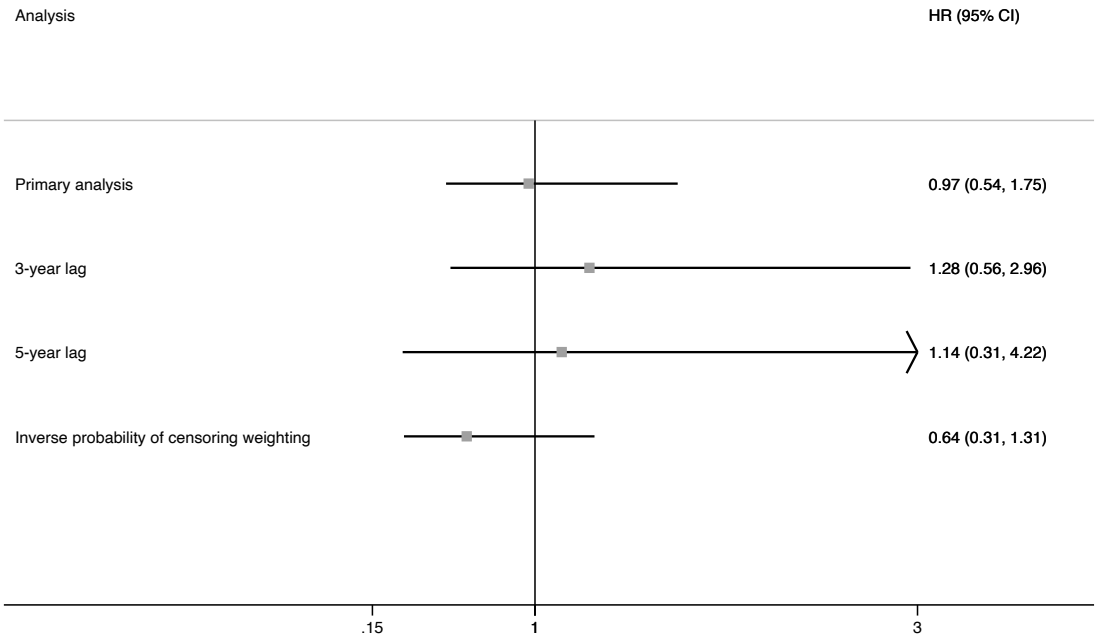


Figure S6.4 Nonmelanoma skin cancer cohort: study flow chart

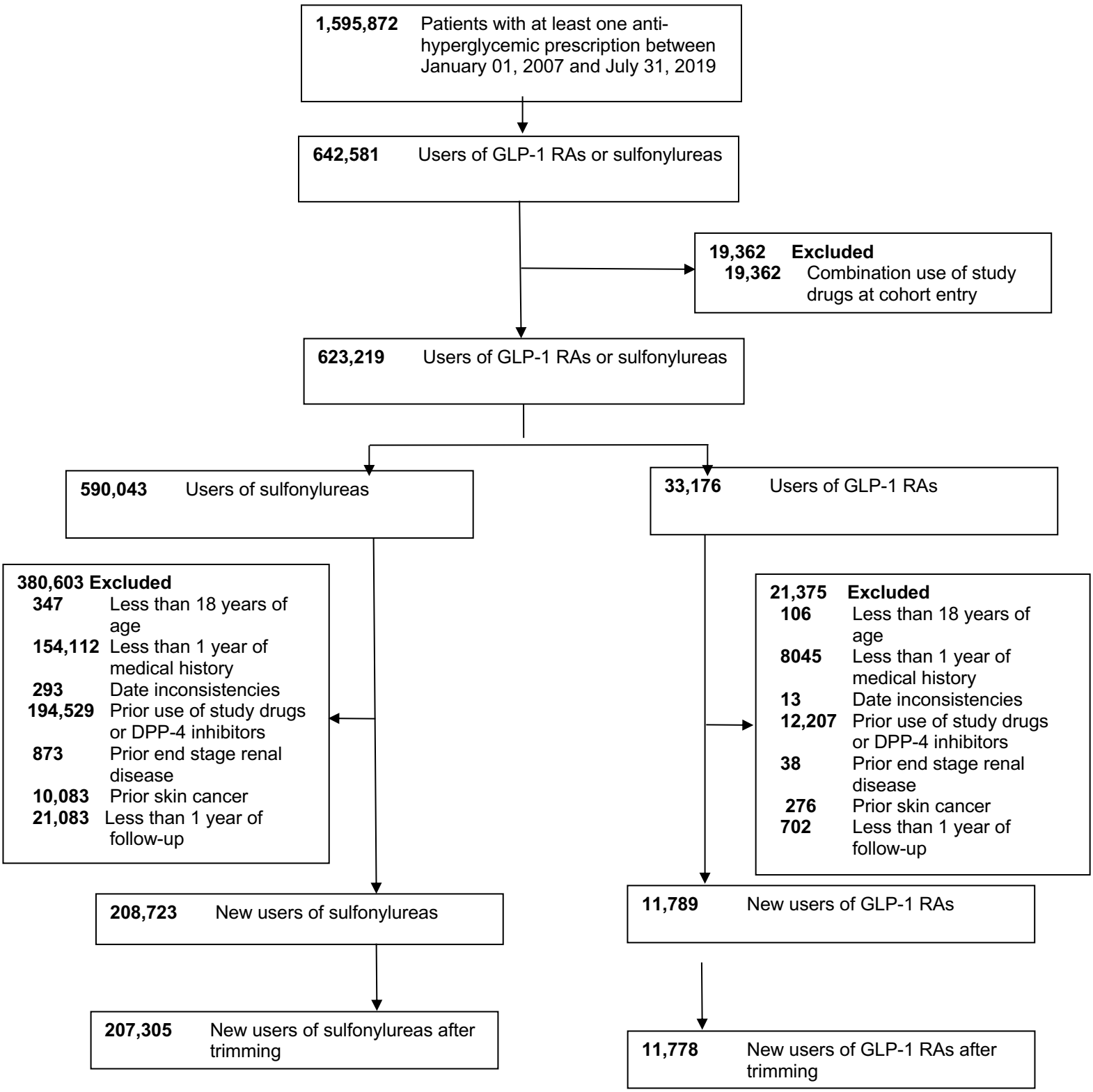


Figure S6.5 Nonmelanoma skin cancer cohort: effect measure modification

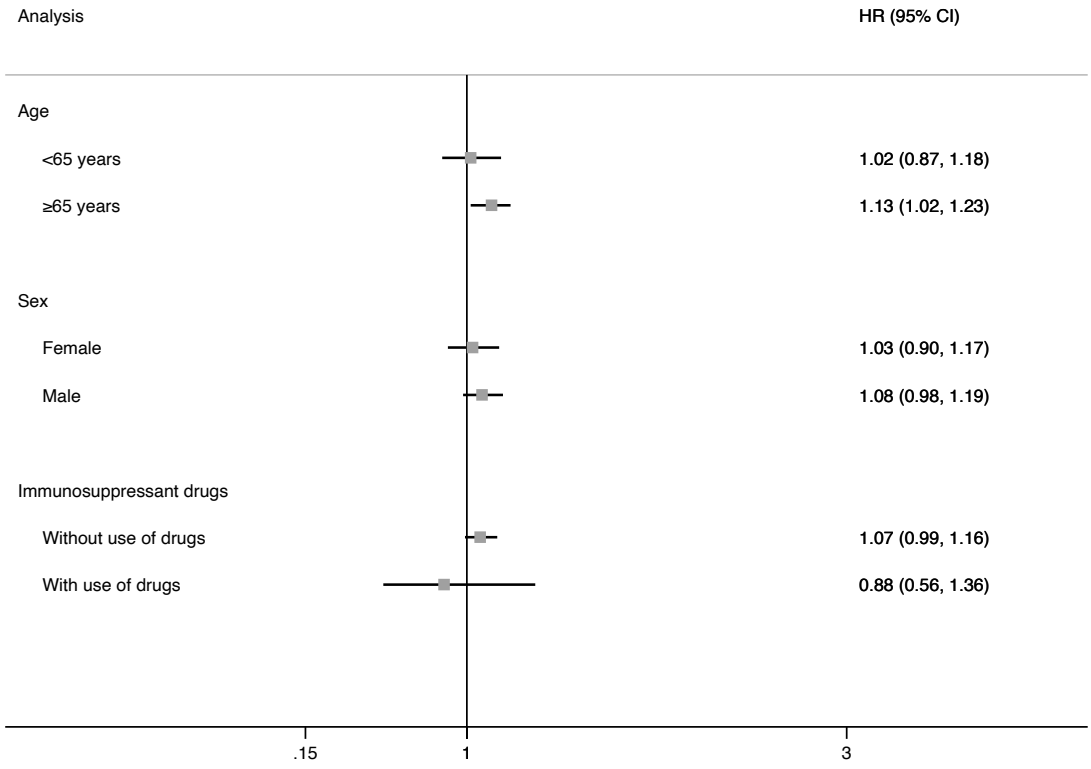
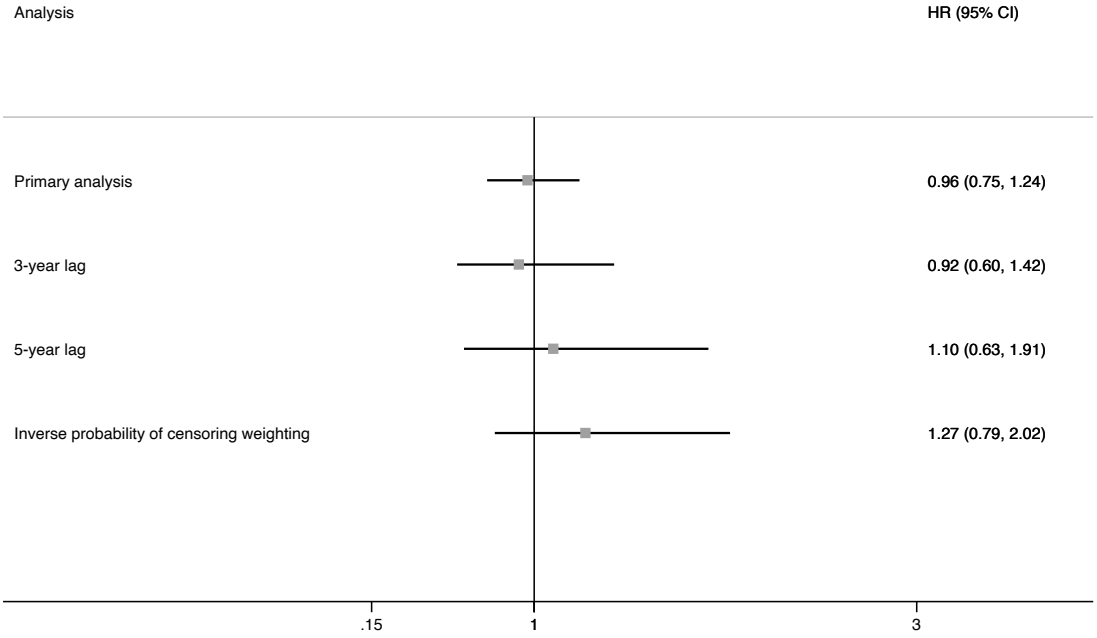


Figure S6.6 Nonmelanoma skin cancer cohort: sensitivity analyses



Chapter 7. Discussion

7.1 Summary of findings

This thesis was designed to investigate the diabetes-cancer association in a population-based cohort with a long-term follow-up, as well as examine the association between incretin-based drugs and skin cancer.

One large clinical trial of the incretin-based drugs such as liraglutide have been reported of up to 10-fold increase in the risk of melanoma,[17] raising concern of the regulatory authorities.[20 152 157] Indeed, both molecules concerning incretin-based drugs, including the DPP-4 and GLP-1 proteins, are deeply involved in pathways affecting carcinogenesis in the skin. [24-27] Given that clinical trials examining such an association would be prohibitively expensive, we conducted observational studies that could shed light on the association.[207] Simultaneously, given the literature on the association between diabetes and cancer, particularly skin cancer, suffers from methodologically inadequacies,[15] we also investigate the diabetes-cancer association in a population-based cohort with a long-term follow-up.

The first manuscript in this thesis investigated the burden of cancer overall and site-specific cancers among patients with and without type 2 diabetes. After a median follow-up of 6 years and a potential follow-up of 30 years, patients with type 2 diabetes had an 19% higher incidence of cancer overall compared with patients without type 2 diabetes. The strongest associations seen were for pancreatic, liver and biliary tree, and uterine cancers. Inverse associations were seen in testes, prostate, and nonmelanoma skin cancers. When stratified based on follow-up, associations with many site-specific cancers were strongest in the first two years of diabetes diagnosis, indicating detection bias may have been an important component in the

diabetes-cancer association. The association was strongest among those who entered the cohort after 2010 (IRR: 1.25, 95% CI: 1.23-1.28), compared with previous decades (2000 to 2009 IRR: 1.18, 95% CI: 1.16-1.20; before 2000 IRR: 1.16, 95% CI: 1.13-1.19). Patients with type 2 diabetes were more likely to have multiple cancers than patients without type 2 diabetes (IRR 1.05, 95% CI 1.04-1.07).

The second manuscript was designed to examine the association between DPP-4 inhibitor use and the incidence of skin cancer, compared with the use of sulfonylureas. We used the UK CPRD to assemble two new-user active comparator cohorts for each skin cancer outcome between 2007-2019. Using propensity score fine stratification weighted Cox proportional hazards and adjusting for 50 covariates, we found that DPP-4 inhibitor use was associated 23% decreased risk of melanoma compared with sulfonylureas (HR 0.77, 95% CI 0.61-0.96) after a median follow-up of 2.60 years. The risk reduction was highest only after 2 years of use, with the number needed to treat at 5 years was 880 patients. Risk were similar in all subgroups and sensitivity analyses results were similar to the primary results. However, the incidence of nonmelanoma skin cancer was comparable between DPP-4 inhibitor use and sulfonylureas use (HR 1.06, 95% CI 0.98-1.15) after a median follow-up of 2.59 years.

Lastly, the third manuscript in this thesis was designed to determine whether GLP-1 RAs are associated with an increased risk of skin cancer, compared with sulfonylureas. Again, based on the outcome, two new-user active comparator cohorts were constructed between 2007-2019. Propensity score fine stratification weighted Cox proportional hazards model showed that GLP-1 RA use was not associated with an increased risk of either melanoma (HR 0.96, 95% CI 0.53-1.75) or nonmelanoma skin cancer (HR 0.96, 95% CI 0.75-1.23). The cumulative incidence

curves overlapped for both outcomes. Results were similar for liraglutide, the molecule for which the signal for skin cancer was reported in a large randomized controlled trial.[17] Overall, these findings were reassuring.

7.2 Public health and clinical implications of assessing cancer burden in diabetes

Our findings of a higher burden of cancers overall and determination of higher, similar, or lower burdens of specific cancers in patients with type 2 diabetes has public health implications distinct from the causal research in the literature on the topic.[126] Whether or not a particular cancer is causally linked with diabetes, cooccurrence of diabetes and cancer diagnoses has profound implications for a patient's life, their medical teams, increasing chances of drug interactions, costs pertaining to both physical and mental health, as well as hard outcomes such as mortality.[130 132 208-210] Indeed, even with relatively well-managed cancers and with which a robust causal link with diabetes is not established, prognosis is worse among patients who also have diabetes.[133] The public health consequences are demonstrated by the fact that, between 2001 and 2018, cancer mortality actually increased among patients with diabetes compared with those without diabetes for those cancers with which a causal link is not firmly established.[8] Thus, special focus from public health strategists is warranted to better manage and educate patients/physicians for cancers that we found had a higher burden in, but no causal link with, diabetes.

Our findings that there is an increase in cancer burdens in recent years compared with earlier decades is novel and needs confirmation in future research. This finding was driven by pancreatic, lung, and prostate cancers. A strengthening association between diabetes and cancer over time may simply represent decreasing mortality among patients with diabetes, creating

more opportunities for carcinogenesis.[211-213] However, search for other risk factors, including antihyperglycemic drugs that may be associated with such cancers is needed. Interestingly, both pancreatic and lung cancer have been linked with antihyperglycemic medications, incretin-based drugs[214] and certain pharmaceutical formulations of insulin,[215] and thus closer examination of such drug-cancer associations need to be undertaken.

Our finding that multiple cancers is more common among patients with diabetes than those without diabetes, is also novel. This finding may have several interpretations: indeed, if diabetes increases the risk of cancers generally then it is expected that multiple cancers are more common in such patients. However, these findings should be interpreted in light of several non-causal considerations: first, genetic conditions that predispose to multiple cancers may also increase the risk of diabetes. Second, just as detection bias explains at least part of the higher incidence of first cancer in diabetes, it can explain a higher count of multiple cancers.[216-218] However, patients who already had one cancer may undergo a similar degree of scrutiny, whether with or without diabetes, and thus possibility of detection bias explaining this finding may be lower than the analysis on first cancers. Notably, patients with type 2 diabetes are likelier to have a higher mortality, and thus shorter follow up. A higher count of cancer despite this is a cause for concern, suggesting that clinicians should keep a look out for second cancers among diabetes patients who were diagnosed with a first cancer.

7.3 Risk benefit profile of incretin-based drugs

The finding that DPP-4 inhibitors are associated with a lower risk of melanoma is novel and important. However, this needs to be contextualized within a broader clinical perspective. As observed in the results of objective 1,[204] the burden of melanoma in type 2 diabetes is not higher

than in patients without diabetes. Thus, given that the absolute risk of melanoma in the population is not high,[204] it is unlikely that the findings will shift the risk benefit profile of DPP-4 inhibitor use in diabetes substantially. This is particularly because DPP-4 inhibitors do not reduce the risk of cardiorenal diseases,[43] which, together, continue to be greater contributors to mortality in diabetes than cancer,[8] whereas other drugs such as GLP-1 RAs and SGLT-2 inhibitors do so.[43] Nevertheless, if individual diabetes patients are deemed to be at high risk of melanoma,[219] clinicians may consider DPP-4 inhibitors for chemoprevention, if findings of this thesis are validated in future research. Our findings that DPP-4 inhibitors were not consistently associated with a higher risk of nonmelanoma skin cancers is reassuring.

In contrast, although GLP-1 RAs are associated with benefits with respect to cardiovascular outcomes and kidney diseases, they have been associated with an increased risk of several cancers in observational studies, including pancreatic cancer, cholangiocarcinoma, and thyroid cancer. The finding in a large randomized controlled trial of liraglutide, a commonly used GLP-1 RA, that the users of the drug had up to 10-fold increased risk of melanoma is a significant one and could substantially alter the risk benefit ratio of these drugs.[17] In this context, our finding that GLP-1 RAs were not associated with an increased risk of melanoma should reassure patients, physicians, and regulators alike, and provides a basis for their continued prescribing to even those patients who are perceived to be at a high risk of melanoma. Similarly, the finding that GLP-1 RAs were not associated with a higher risk of nonmelanoma skin cancers is also reassuring, given the finding of our objective 1, that nonmelanoma skin cancers, though negatively associated with diabetes, are still the commonest form of cancer in diabetes.[204]

7.4 Strengths and limitations

This thesis has several strengths. First, to our knowledge, objective 1 examined the trends in incidence of cancer among patients with type 2 diabetes compared with the non-diabetic population over a 30-year period, making it, to our knowledge, the largest study on the topic to date.[16] Second, objectives 2 and 3 were the first studies conducted examining incretin-based drugs and skin cancer as a standalone outcome, thus answering key regulatory questions.[20 152 157] In the process, they provide essential information to better characterize the risk benefit profile of the most commonly used second-to-third line agents in type 2 diabetes.[18] Third, by using an active comparator, new user design, and propensity score methods, we tried to minimize bias due to prevalent users while answering a clinically relevant question.[184] Finally, we used CPRD as the data source for all studies, a database that has been extensively validated, with special reference to both diabetes and cancer research.[169-175] Moreover, it is largely representative of the population of the UK,[164 166] a country with universal healthcare coverage, a fact which should minimize differences in access to medications due to socioeconomic reasons, a major confounding-related concern while comparing older drugs such as sulfonylurea and newer drugs such as incretin-based drugs.[220]

Several limitations of this thesis also merit discussion. First, the CPRD contains records of written and not filled prescriptions or information on whether the patient took the medications as instructed or not. However, given that all prescriptions, regardless of drug class, require a uniform, nominal payment, a large difference between written and filled prescription is not expected. Our intention-to-treat exposure definition did not consider non-adherence and treatment termination. Finally, the prescriptions are written by general practitioners and not specialists. However, since the routine outpatient care of diabetes patients largely is undertaken

by general practitioners, we do not expect substantial misclassification.[221] Second, we did not link the CPRD data with cancer registry data. Consequently, some outcome misclassification is possible. However, CPRD has been validated with respect to cancer diagnoses, with studies reporting a concordance with cancer registry data.[181] Moreover, previous studies have shown that the recording of skin cancer in CPRD is more complete than in cancer registries.[172 181] Thus, any misclassification should be minimal and non-differential. Third, we did not link with hospital data. Hence, any diagnoses or prescriptions exclusively recorded in hospital data were not available, which can result in immeasurable time bias due to potential inequalities in person time recorded.[222] However, given prescriptions of all study drugs of interest are likely to be started and continued in outpatient settings, and cancer diagnoses are also chronic disease diagnoses, misclassification due to unaccounted hospital time is unlikely to be substantial. Fourth, we were unable to account for sun exposure in objectives 2 and 3, which is an important risk factor for the outcome. However, we did include region and calendar time in the propensity score models, which can be considered as proxies for regional and calendar time variations in sun exposure. Furthermore, we adjusted for variables such as body mass index, that may be considered a proxy of physical activity,[223] an important determinant of sun exposure. Notably, antihyperglycemic treatments are not decided upon by sun exposure, which indicates any channeling based on this factor is unlikely.[36 43] Finally, given the observational nature of the studies, residual confounding from unmeasured or unknown variables is possible despite use of propensity score methods.

7.5 Future directions

There are several questions that emerge out of the findings of this thesis. First, future well-designed observational studies should examine whether the new associations we reported between diabetes and site-specific cancers, including testicular cancer and nonmelanoma skin

cancer, are causal. Second, multiple studies conducting data-driven cluster analysis have now reproduced the presence of distinct subgroups in diabetes which vary phenotypically and with respect to prognosis.[224-226] It would be important to see whether the burden of cancer overall and specific cancers vary between these subgroups. Third, to my knowledge, ours are the first studies examining the association between incretin-based drugs and skin cancer. These findings need to be reproduced in other settings and health systems using appropriate methodologies. Though it is difficult to plan and execute sufficiently powered randomized controlled trials to examine the association between incretin-based drugs and skin cancer, it would be important to examine whether our findings are replicated by systematically reviewing accumulating clinical trial data as more incretin-based drugs trials are conducted, with better adjudication and granulation of skin cancer events. Fourth, given the uncertainties in the basic science literature on the role of DPP-4 in skin cancer,[148 149] more preclinical research needs to be conducted to understand the role of loss of DPP-4 expression as opposed to pharmacological inhibition of DPP-4 in development of skin cancer, in light of our findings.

7.6 Conclusions

This thesis made several novel contributions to the existing literature. We found that the burden of cancer overall was higher in patients with diabetes compared with those without diabetes, over a follow-up of 30 years. We examined the burden of several site-specific cancers, finding novel negative associations between diabetes and nonmelanoma skin cancer and testicular cancer. We also report that the burden of cancer among patients with diabetes has increased in recent decades, mainly due to strengthening associations with pancreatic, lung, and prostate cancers. The incidence of multiple cancer was higher among patients with diabetes than without. Further research needs to be conducted to examine whether this link is causal. In an

observational study examining the association between DPP-4 inhibitor use and skin cancer, we found that DPP-4 inhibitor use was associated with a 23% risk of melanoma, and no consistent difference in the incidence of nonmelanoma skin cancer, compared with sulfonylurea users. These findings need to be confirmed in future observational studies in other settings, while more evidence needs to be accumulated on the biological basis of a decreased melanoma risk with pharmacological DPP-4 inhibition. Finally, we found that the risk of neither melanoma nor nonmelanoma skin cancer were higher among users of GLP-1 RAs compared with sulfonylurea users, which is a reassuring finding given the increasing use of these drugs. Taken together, the evidence generated in this thesis may help public health practitioners, physicians, and patients plan better cancer care in diabetes, and make more informed decisions regarding the risks and benefits of incretin-based drugs in diabetes patients.

Chapter 8. References

1. International Diabetes F. Diabetes Atlas, 9th edition 2019.

2. World Health Organization: Key facts on diabetes.

3. Statistics C. Health Fact Sheets: Diabetes, 2017.

4. Canada D. Economic tsunami: the cost of diabetes in Canada. 2009. 2009

5. Kahn BB. Type 2 diabetes: when insulin secretion fails to compensate for insulin resistance. *Cell* 1998;92(5):593-96. doi: 10.1016/s0092-8674(00)81125-3

6. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. *Diabetologia* 2003;46(1):3-19. doi: 10.1007/s00125-002-1009-0

7. Schlienger J-L. [Type 2 diabetes complications]. *Presse medicale (Paris, France : 1983)* 2013;42(5):839-48. doi: 10.1016/j.lpm.2013.02.313

8. 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. *Lancet Diabetes Endocrinol* 2021;9(3):165-73. doi: 10.1016/S2213-8587(20)30431-9

9. Islam Z, Akter S, Inoue Y, et al. Prediabetes, Diabetes, and the Risk of All-Cause and Cause-Specific Mortality in a Japanese Working Population: Japan Epidemiology Collaboration on Occupational Health Study. *Diabetes Care* 2021;44(3):757-64. doi: 10.2337/dc20-1213

10. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *CA Cancer J Clin* 2010;60(4):207-21. doi: 10.3322/caac.20078

11. Mardilovich K, Pankratz SL, Shaw LM. Expression and function of the insulin receptor substrate proteins in cancer. *Cell Commun Signal* 2009;7:14. doi: 10.1186/1478-811X-7-14

12. Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: an update. *Nat Rev Cancer* 2012;12(3):159-69. doi: 10.1038/nrc3215

13. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009;324(5930):1029-33. doi: 10.1126/science.1160809

14. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev* 2009;18(10):2569-78. doi: 10.1158/1055-9965.Epi-09-0372 [published Online First: 2009/09/17]

15. Tsilidis KK, Kasimis JC, Lopez DS, et al. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. *BMJ (Clinical research ed)* 2015;350:g7607. doi: 10.1136/bmj.g7607

16. 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

17. Nauck MA, Jensen TJ, Rosenkilde C, et al. Neoplasms Reported With Liraglutide or Placebo in People With Type 2 Diabetes: Results From the LEADER Randomized Trial. *Diabetes Care* 2018;41(8):1663-71. doi: 10.2337/dc17-1825

18. Curtis HJ, Dennis JM, Shields BM, et al. Time trends and geographical variation in prescribing of drugs for diabetes in England from 1998 to 2017. *Diabetes Obes Metab* 2018;20(9):2159-68. doi: 10.1111/dom.13346

19. American Diabetes A. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020;43(Suppl 1):S98-S110. doi: 10.2337/dc20-S009

20. Committee for Medicinal Products for Human U. Assessment report: Victoza: EMA/479764/2017, 2017.

21. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2016;375(4):311-22. doi: 10.1056/NEJMoa1603827

22. Li Z, Lin C, Zhou J, et al. Dipeptidyl peptidase 4-inhibitor treatment was associated with a reduced incidence of neoplasm in patients with type 2 diabetes: a meta-analysis of 115 randomized controlled trials with 121961 participants. *Expert Opin Investig Drugs* 2022;31(9):957-64. doi: 10.1080/13543784.2022.2113056 [published Online First: 2022/08/16]

23. Cefalu WT, Kaul S, Gerstein HC, et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care* 2018;41(1):14-31. doi: 10.2337/dci17-0057

24. Kacar A, Arikok AT, Kokenek Unal TD, et al. Stromal expression of CD34, α-smooth muscle actin and CD26/DPPIV in squamous cell carcinoma of the skin: a comparative immunohistochemical study. *Pathol Oncol Res* 2012;18(1):25-31. doi: 10.1007/s12253-011-9412-9

25. Pethiyagoda CL, Welch DR, Fleming TP. Dipeptidyl peptidase IV (DPPIV) inhibits cellular invasion of melanoma cells. *Clin Exp Metastasis* 2000;18(5):391-400.

26. Nagae K, Uchi H, Morino-Koga S, et al. Glucagon-like peptide-1 analogue liraglutide facilitates wound healing by activating PI3K/Akt pathway in keratinocytes. *Diabetes Res Clin Pract* 2018;146:155-61. doi: 10.1016/j.diabres.2018.10.013

27. Wen-Jun L, Hai-Yan W, Wei L, et al. Evidence that geniposide abrogates norepinephrine-induced hypopigmentation by the activation of GLP-1R-dependent c-kit receptor signaling in melanocyte. *J Ethnopharmacol* 2008;118(1):154-58. doi: 10.1016/j.jep.2008.03.021

28. Skin Cancer | Skin Cancer Facts | Common Skin Cancer Types.

29. Organization WH. Diabetes Fact Sheet.

30. Federation ID. IDF diabetes Atlas.

31. Tinajero MG, Malik VS. An Update on the Epidemiology of Type 2 Diabetes: A Global Perspective. *Endocrinol Metab Clin North Am* 2021;50(3):337-55. doi: 10.1016/j.ecl.2021.05.013 [published Online First: 2021/08/18]

32. Federation ID. IDF Diabetes Atlas — 7th Edition.

33. 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: 2017/12/09]

34. Organization WH. The top 10 causes of death.

35. Saeedi P, Salpea P, Karuranga S, et al. Mortality attributable to diabetes in 20-79 years old adults, 2019 estimates: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract* 2020;162:108086. doi: 10.1016/j.diabres.2020.108086 [published Online First: 2020/02/19]

36. Loscalzo J, Fauci AS, Kasper DL, et al. Harrison's Principles of Internal Medicine, Twenty-First Edition (Vol.1 & Vol.2): McGraw-Hill Education 2022.

37. 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: 2020/09/03]

38. Cerf ME. Beta cell dysfunction and insulin resistance. *Front Endocrinol (Lausanne)* 2013;4:37. doi: 10.3389/fendo.2013.00037 [published Online First: 2013/04/02]

39. Porte D, Jr., Kahn SE. beta-cell dysfunction and failure in type 2 diabetes: potential mechanisms. *Diabetes* 2001;50 Suppl 1:S160-3. doi: 10.2337/diabetes.50.2007.s160 [published Online First: 2001/03/29]

40. Goyal R, Jialal I. Diabetes mellitus type 2. 2018

41. Schwartz SS, Epstein S, Corkey BE, et al. The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell-Centric Classification Schema. *Diabetes Care* 2016;39(2):179-86. doi: 10.2337/dc15-1585 [published Online First: 2016/01/23]

42. Committee ADAPP. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2022. *Diabetes Care* 2021;45(Supplement_1):S17-S38. doi: 10.2337/dc22-S002

43. Association AD. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. *Clinical Diabetes* 2022;40(1):10-38. doi: 10.2337/cd22-as01

44. 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 [published Online First: 2010/07/01]

45. Association AD. Get to Know Your Diabetes Care Team.

46. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2018;41(12):2669-701. doi: 10.2337/dci18-0033

47. Magkos F, Hjorth MF, Astrup A. Diet and exercise in the prevention and treatment of type 2 diabetes mellitus. *Nat Rev Endocrinol* 2020;16(10):545-55. doi: 10.1038/s41574-020-0381-5 [published Online First: 2020/07/22]

48. Sami W, Ansari T, Butt NS, et al. Effect of diet on type 2 diabetes mellitus: A review. *Int J Health Sci (Qassim)* 2017;11(2):65-71. [published Online First: 2017/05/26]

49. Association AD. Physical Activity/Exercise and Diabetes Mellitus. *Diabetes Care* 2003;26(suppl_1):s73-s77. doi: 10.2337/diacare.26.2007.S73

50. Young-Hyman D, de Groot M, Hill-Briggs F, et al. Psychosocial Care for People With Diabetes: A Position Statement of the American Diabetes Association. *Diabetes Care* 2016;39(12):2126-40. doi: 10.2337/dc16-2053 [published Online First: 2016/11/24]

51. Brunton L, Knollmann B. Goodman and Gilman's the Pharmacological Basis of Therapeutics, 14th Edition: McGraw-Hill Education 2022.

52. Quianzon CC, Cheikh IE. History of current non-insulin medications for diabetes mellitus. *J Community Hosp Intern Med Perspect* 2012;2(3) doi: 10.3402/jchimp.v2i3.19081 [published Online First: 2012/01/01]

53. 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. [published Online First: 1998/09/22]

54. Lazarus B, Wu A, Shin J-I, et al. Association of Metformin Use With Risk of Lactic Acidosis Across the Range of Kidney Function: A Community-Based Cohort Study. *JAMA Internal Medicine* 2018;178(7):903-10. doi: 10.1001/jamainternmed.2018.0292

55. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2010;2010(4):Cd002967. doi: 10.1002/14651858.CD002967.pub4 [published Online First: 2010/04/16]

56. Wilkinson S, Douglas I, Stirnadel-Farrant H, et al. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000-2017. *BMJ open* 2018;8(7):e022768. doi: 10.1136/bmjopen-2018-022768

57. Fang M, Wang D, Coresh J, et al. Trends in Diabetes Treatment and Control in U.S. Adults, 1999-2018. *N Engl J Med* 2021;384(23):2219-28. doi: 10.1056/NEJMsa2032271 [published Online First: 2021/06/10]

58. Mohan V, Saboo B, Khader J, et al. Position of Sulfonylureas in the Current ERA: Review of National and International Guidelines. *Clin Med Insights Endocrinol Diabetes* 2022;15:11795514221074663. doi: 10.1177/11795514221074663 [published Online First: 2022/02/22]

59. Rosengren A, Jing X, Eliasson L, et al. Why treatment fails in type 2 diabetes. *PLoS Med* 2008;5(10):e215. doi: 10.1371/journal.pmed.0050215 [published Online First: 2008/10/31]

60. Azoulay L, Suissa S. Sulfonylureas and the Risks of Cardiovascular Events and Death: A Methodological Meta-Regression Analysis of the Observational Studies. *Diabetes Care* 2017;40(5):706-14. doi: 10.2337/dc16-1943

61. Black C, Donnelly P, McIntyre L, et al. Meglitinide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007;2007(2):Cd004654. doi: 10.1002/14651858.CD004654.pub2 [published Online First: 2007/04/20]

62. Van de Laar FA, Lucassen PL, Akkermans RP, et al. Alpha-glucosidase inhibitors for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005;2005(2):Cd003639. doi: 10.1002/14651858.CD003639.pub2 [published Online First: 2005/04/23]

63. Eggleton JS, Jialal I. Thiazolidinediones. StatPearls [Internet]: StatPearls Publishing 2021.

64. Chiquette E, Ramirez G, DeFronzo R. A Meta-analysis Comparing the Effect of Thiazolidinediones on Cardiovascular Risk Factors. *Archives of Internal Medicine* 2004;164(19):2097-104. doi: 10.1001/archinte.164.19.2097

65. Kung J, Henry RR. Thiazolidinedione safety. *Expert opinion on drug safety* 2012;11(4):565-79.

66. Rizos CV, Elisaf MS, Mikhailidis DP, et al. How safe is the use of thiazolidinediones in clinical practice? *Expert Opin Drug Saf* 2009;8(1):15-32. doi: 10.1517/14740330802597821 [published Online First: 2009/02/25]

67. Nissen SE, Wolski K. Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes. *New England Journal of Medicine* 2007;356(24):2457-71. doi: 10.1056/NEJMoa072761

68. Stone JC, Furuya-Kanamori L, Barendregt JJ, et al. Was there really any evidence that rosiglitazone increased the risk of myocardial infarction or death from cardiovascular causes? *Pharmacoepidemiol Drug Saf* 2015;24(3):223-7. doi: 10.1002/pds.3736 [published Online First: 2014/12/18]

69. Tuccori M, Filion KB, Yin H, et al. Pioglitazone use and risk of bladder cancer: population based cohort study. *BMJ (Clinical research ed)* 2016;352:i1541. doi: 10.1136/bmj.i1541

70. Wilding J, Fernando K, Milne N, et al. SGLT2 inhibitors in type 2 diabetes management: key evidence and implications for clinical practice. *Diabetes Therapy* 2018;9(5):1757-73.

71. Scheen AJ. An update on the safety of SGLT2 inhibitors. *Expert opinion on drug safety* 2019;18(4):295-311.

72. Fralick M, Kim SC, Schneeweiss S, et al. Risk of amputation with canagliflozin across categories of age and cardiovascular risk in three US nationwide databases: cohort study. *bmj* 2020;370

73. Braunwald E. Gliflozins in the Management of Cardiovascular Disease. *New England Journal of Medicine* 2022;386(21):2024-34. doi: 10.1056/NEJMra2115011

74. Kristensen SL, Rørth R, Jhund PS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet Diabetes & Endocrinology* 2019;7(10):776-85. doi: 10.1016/S2213-8587(19)30249-9

75. Ingelfinger JR, Rosen CJ. Clinical Credence — SGLT2 Inhibitors, Diabetes, and Chronic Kidney Disease. *New England Journal of Medicine* 2019;380(24):2371-73. doi: 10.1056/NEJMe1904740

76. Deacon CF, Ahrén B. Physiology of incretins in health and disease. *Rev Diabet Stud* 2011;8(3):293-306. doi: 10.1900/rds.2011.8.293 [published Online First: 2012/01/21]

77. Creutzfeldt W. The incretin concept today. *Diabetologia* 1979;16(2):75-85. doi: 10.1007/bf01225454 [published Online First: 1979/02/01]

78. Nauck MA, Homberger E, Siegel EG, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab* 1986;63(2):492-8. doi: 10.1210/jcem-63-2-492 [published Online First: 1986/08/01]

79. Deacon CF, Johnsen AH, Holst JJ. Degradation of glucagon-like peptide-1 by human plasma in vitro yields an N-terminally truncated peptide that is a major endogenous metabolite in vivo. *J Clin Endocrinol Metab* 1995;80(3):952-7. doi: 10.1210/jcem.80.3.7883856 [published Online First: 1995/03/01]

80. Nauck M, Stöckmann F, Ebert R, et al. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1986;29(1):46-52. doi: 10.1007/bf02427280 [published Online First: 1986/01/01]

81. Marín-Peñalver JJ, Martín-Timón I, Sevillano-Collantes C, et al. Update on the treatment of type 2 diabetes mellitus. *World J Diabetes* 2016;7(17):354-95. doi: 10.4239/wjd.v7.i17.354

82. Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. *Nat Rev Endocrinol* 2009;5(5):262-69. doi: 10.1038/nrendo.2009.48

83. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *Bmj* 2021;372:m4573. doi: 10.1136/bmj.m4573 [published Online First: 2021/01/15]

84. Mannucci E, Monami M. Cardiovascular Safety of Incretin-Based Therapies in Type 2 Diabetes: Systematic Review of Integrated Analyses and Randomized Controlled Trials. *Advances in Therapy* 2017;34(1):1-40. doi: 10.1007/s12325-016-0432-4

85. Gilbert MP, Pratley RE. Efficacy and safety of incretin-based therapies in patients with type 2 diabetes mellitus. *Am J Med* 2009;122(6 Suppl):S11-24. doi: 10.1016/j.amjmed.2009.03.013

86. White WB, Cannon CP, Heller SR, et al. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. *New England Journal of Medicine* 2013;369(14):1327-35. doi: 10.1056/NEJMoa1305889

87. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *New England Journal of Medicine* 2013;369(14):1317-26. doi: 10.1056/NEJMoa1307684

88. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine* 2015;373(3):232-42. doi: 10.1056/NEJMoa1501352

89. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk The CARMELINA Randomized Clinical Trial. *JAMA* 2019;321(1):69-79. doi: 10.1001/jama.2018.18269

90. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients with Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA* 2019;322(12):1155-66. doi: 10.1001/jama.2019.19012

91. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine* 2016;375(4):311-22. doi: 10.1056/NEJMoa1603827

92. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *New England Journal of Medicine* 2015;373(23):2247-57. doi: 10.1056/NEJMoa1509225

93. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine* 2016;375(19):1834-44. doi: 10.1056/NEJMoa1607141

94. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine* 2017;377(13):1228-39. doi: 10.1056/NEJMoa1612917

95. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet (London, England)* 2018;392(10157):1519-29. doi: 10.1016/S0140-6736(18)32261-X

96. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet (London, England)* 2019;394(10193):121-30. doi: 10.1016/S0140-6736(19)31149-3

97. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *New England Journal of Medicine* 2019;381(9):841-51. doi: 10.1056/NEJMoa1901118

98. Subrahmanyan NA, Koshy RM, Jacob K, et al. Efficacy and cardiovascular safety of DPP-4 inhibitors. *Current Drug Safety* 2021;16(2):154-64.

99. Yang F, Dong Y, Li B, et al. Pancreatic safety of DPP-4 inhibitors in type 2 diabetes millitus: A protocol for systematic review and network meta-analysis. *Medicine* 2022;101(17):e29154-e54.

100. Shao S, Xu Q, Yu X, et al. Dipeptidyl peptidase 4 inhibitors and their potential immune modulatory functions. *Pharmacol Ther* 2020;209:107503. doi: 10.1016/j.pharmthera.2020.107503 [published Online First: 2020/02/18]

101. Douros A, Rouette J, Yin H, et al. Dipeptidyl Peptidase 4 Inhibitors and the Risk of Bullous Pemphigoid Among Patients With Type 2 Diabetes. *Diabetes Care* 2019;42(8):1496-503. doi: 10.2337/dc19-0409

102. Lee H, Chung HJ, Pawar A, et al. Evaluation of Risk of Bullous Pemphigoid With Initiation of Dipeptidyl Peptidase-4 Inhibitor vs Second-generation Sulfonylurea. *JAMA Dermatol* 2020;156(10):1107-14. doi: 10.1001/jamadermatol.2020.2158 [published Online First: 2020/07/23]

103. Abrahami D, Douros A, Yin H, et al. Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study. *BMJ (Clinical research ed)* 2018;360:k872. doi: 10.1136/bmj.k872

104. Bishnoi R, Hong YR, Shah C, et al. Dipeptidyl peptidase 4 inhibitors as novel agents in improving survival in diabetic patients with colorectal cancer and lung cancer: A Surveillance Epidemiology and Endpoint Research Medicare study. *Cancer medicine* 2019;8(8):3918-27.

105. Barreira da Silva R, Laird ME, Yatim N, et al. Dipeptidylpeptidase 4 inhibition enhances lymphocyte trafficking, improving both naturally occurring tumor immunity and

immunotherapy. *Nat Immunol* 2015;16(8):850-8. doi: 10.1038/ni.3201 [published Online First: 2015/06/16]

106. Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. *Nature Reviews Endocrinology* 2009;5(5):262-69. doi: 10.1038/nrendo.2009.48

107. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs Context* 2015;4:212283. doi: 10.7573/dic.212283 [published Online First: 2015/07/28]

108. Gupta V. Glucagon-like peptide-1 analogues: An overview. *Indian J Endocrinol Metab* 2013;17(3):413-21. doi: 10.4103/2230-8210.111625 [published Online First: 2013/07/23]

109. Hinnen D. Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. *Diabetes Spectrum* 2017;30(3):202-10. doi: 10.2337/ds16-0026

110. Kim HS, Jung CH. Oral Semaglutide, the First Ingestible Glucagon-Like Peptide-1 Receptor Agonist: Could It Be a Magic Bullet for Type 2 Diabetes? *Int J Mol Sci* 2021;22(18) doi: 10.3390/ijms22189936 [published Online First: 2021/09/29]

111. Abrahami D, Douros A, Yin H, et al. Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study. *BMJ (Clinical research ed)* 2018;363:k4880. doi: 10.1136/bmj.k4880

112. Pradhan R, Patorno E, Tesfaye H, et al. Glucagon-Like Peptide-1 Receptor Agonists and Risk of Anaphylactic Reaction Among Patients With Type 2 Diabetes: Multisite Population-Based Cohort Study. *Am J Epidemiol* 2022 doi: 10.1093/aje/kwac021 [published Online First: 2022/02/10]

113. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. *Nature reviews Endocrinology* 2012;8(12):728-42. doi: 10.1038/nrendo.2012.140

114. Hegele RA, Maltman GM. Insulin's centenary: the birth of an idea. *Lancet Diabetes Endocrinol* 2020;8(12):971-77. doi: 10.1016/s2213-8587(20)30337-5 [published Online First: 2020/11/02]

115. Sims EK, Carr ALJ, Oram RA, et al. 100 years of insulin: celebrating the past, present and future of diabetes therapy. *Nat Med* 2021;27(7):1154-64. doi: 10.1038/s41591-021-01418-2 [published Online First: 2021/07/17]

116. 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 [published Online First: 2009/11/13]

117. Home P. Insulin Therapy and Cancer. *Diabetes Care* 2013;36(Supplement_2):S240-S44. doi: 10.2337/dcS13-2002

118. Apovian CM, Okemah J, O'Neil PM. Body weight considerations in the management of type 2 diabetes. *Advances in therapy* 2019;36(1):44-58.

119. Wu JW, Filion KB, Azoulay L, et al. Effect of long-acting insulin analogs on the risk of cancer: a systematic review of observational studies. *Diabetes care* 2016;39(3):486-94.

120. Heinzerling L, Raile K, Rochlitz H, et al. Insulin allergy: clinical manifestations and management strategies. *Allergy* 2008;63(2):148-55.

121. Gregg EW, Cheng YJ, Srinivasan M, et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. *Lancet* 2018;391(10138):2430-40. doi: 10.1016/s0140-6736(18)30314-3 [published Online First: 2018/05/23]

122. Harding JL, Shaw JE, Peeters A, et al. Age-Specific Trends From 2000-2011 in All-Cause and Cause-Specific Mortality in Type 1 and Type 2 Diabetes: A Cohort Study of More

Than One Million People. *Diabetes Care* 2016;39(6):1018-26. doi: 10.2337/dc15-2308 [published Online First: 2016/05/22]

123. Zhang H, Pelzer AM, Kiang DT, et al. Down-regulation of type I insulin-like growth factor receptor increases sensitivity of breast cancer cells to insulin. *Cancer research* 2007;67(1):391-97.

124. Johnson J, Carstensen B, Witte D, et al. Diabetes and cancer (1): evaluating the temporal relationship between type 2 diabetes and cancer incidence. *Diabetologia* 2012;55(6):1607-18.

125. Klil-Drori AJ, Azoulay L, Pollak MN. Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? *Nat Rev Clin Oncol* 2017;14(2):85-99. doi: 10.1038/nrclinonc.2016.120

126. Fox MP, Murray EJ, Lesko CR, et al. On the Need to Revitalize Descriptive Epidemiology. *Am J Epidemiol* 2022;191(7):1174-79. doi: 10.1093/aje/kwac056 [published Online First: 2022/03/25]

127. Tseng H-W, Shiue Y-L, Tsai K-W, et al. Risk of skin cancer in patients with diabetes mellitus: A nationwide retrospective cohort study in Taiwan. *Medicine* 2016;95(26):e4070. doi: 10.1097/MD.0000000000004070

128. Qi L, Qi X, Xiong H, et al. Type 2 diabetes mellitus and risk of malignant melanoma: a systematic review and meta-analysis of cohort studies. *Iran J Public Health* 2014;43(7):857-66.

129. Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. *World J Diabetes* 2017;8(4):120-29. doi: 10.4239/wjd.v8.i4.120

130. Worndl E, Fung K, Fischer HD, et al. Preventable Diabetic Complications After a Cancer Diagnosis in Patients With Diabetes: A Population-Based Cohort Study. *JNCI cancer spectrum* 2018;2(1):pky008. doi: 10.1093/jncics/pky008

131. Clinical Challenges in Caring for Patients With Diabetes and Cancer | Diabetes Spectrum.

132. Milluzzo A, Vigneri P, Martorana F, et al. Type 2 diabetes and cancer: problems and suggestions for best patient management. *Exploration of Medicine* 2020;1(4):184-204. doi: 10.37349/emed.2020.00013

133. Ederaine SA, Dominguez JL, Harvey JA, et al. Survival and glycemic control in patients with co-existing squamous cell carcinoma and diabetes mellitus. *Future Science OA* 2021:FSO683. doi: 10.2144/fsoa-2020-0150

134. Joshua AM. Melanoma prevention: are we doing enough? A Canadian perspective. *Curr Oncol* 2012;19(6):e462-e67. doi: 10.3747/co.19.1222

135. Canadian Cancer S. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics. 2012

136. Miller AJ, Mihm MC. Melanoma. *N Engl J Med* 2006;355(1):51-65. doi: 10.1056/NEJMra052166

137. Nehal KS, Bichakjian CK. Update on Keratinocyte Carcinomas. *N Engl J Med* 2018;379(4):363-74. doi: 10.1056/NEJMra1708701

138. Canada PHAo. Non Melanoma Skin Cancer. *aem* 2009

139. Dempsey W, Mukherjee B. Reflecting on "A Statistician in Medicine" in 2020. *Stat Med* 2021;40(1):42-48. doi: 10.1002/sim.8830 [published Online First: 2020/12/29]

140. Basal & Squamous Cell Skin Cancer Statistics.

141. Barton V, Armeson K, Hampras S, et al. Nonmelanoma skin cancer and risk of all-cause and cancer-related mortality: a systematic review. *Arch Dermatol Res* 2017;309(4):243-51. doi: 10.1007/s00403-017-1724-5

142. The Economic Burden of Skin Cancer in Canada:Current and Projected

143. Urban K, Mehrmal S, Uppal P, et al. The global burden of skin cancer: A longitudinal analysis from the Global Burden of Disease Study, 1990-2017. *JAAD Int* 2021;2:98-108. doi: 10.1016/j.jdin.2020.10.013 [published Online First: 2021/08/20]

144. Leiter LA, Teoh H, Mosenzon O, et al. Frequency of cancer events with saxagliptin in the SAVOR-TIMI 53 trial. *Diabetes Obes Metab* 2016;18(2):186-90. doi: 10.1111/dom.12582

145. Zhao M, Chen J, Yuan Y, et al. Dipeptidyl peptidase-4 inhibitors and cancer risk in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. *Scientific Reports* 2017;7(1):8273. doi: 10.1038/s41598-017-07921-2

146. Dicembrini I, Nreu B, Montereggi C, et al. Risk of cancer in patients treated with dipeptidyl peptidase-4 inhibitors: an extensive meta-analysis of randomized controlled trials. *Acta Diabetol* 2020;57(6):689-96. doi: 10.1007/s00592-020-01479-8 [published Online First: 2020/01/20]

147. Tang E, Ravaud P, Riveros C, et al. Comparison of serious adverse events posted at ClinicalTrials.gov and published in corresponding journal articles. *BMC Med* 2015;13:189. doi: 10.1186/s12916-015-0430-4

148. Busek P, Duke-Cohan JS, Sedo A. Does DPP-IV Inhibition Offer New Avenues for Therapeutic Intervention in Malignant Disease? *Cancers (Basel)* 2022;14(9) doi: 10.3390/cancers14092072 [published Online First: 2022/05/15]

149. Sulda ML, Abbott CA, Hildebrandt M. DPIV/CD26 and FAP in cancer: a tale of contradictions. *Adv Exp Med Biol* 2006;575:197-206. doi: 10.1007/0-387-32824-6_21 [published Online First: 2006/05/17]

150. Price JD, Linder G, Li WP, et al. Effects of short-term sitagliptin treatment on immune parameters in healthy individuals, a randomized placebo-controlled study. *Clin Exp Immunol* 2013;174(1):120-8. doi: 10.1111/cei.12144 [published Online First: 2013/05/29]

151. Winkler AE, Brotman JJ, Pittman ME, et al. CXCR3 enhances a T-cell-dependent epidermal proliferative response and promotes skin tumorigenesis. *Cancer Res* 2011;71(17):5707-16. doi: 10.1158/0008-5472.Can-11-0907 [published Online First: 2011/07/08]

152. FDA Briefing Document: Endocrinologic and Metabolic Drugs Advisory Committee Meeting (EMDAC): Liraglutide-LEADER, 2017.

153. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med* 2016;375(19):1834-44. doi: 10.1056/NEJMoa1607141

154. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med* 2017;377(13):1228-39. doi: 10.1056/NEJMoa1612917

155. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med* 2015;373(23):2247-57. doi: 10.1056/NEJMoa1509225

156. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet (London, England)* 2019;394(10193):121-30. doi: 10.1016/S0140-6736(19)31149-3

157. Food, Drug Administration CfDE, Research. Endocrinologic and Metabolic Advisory Committee Meeting Minutes, 2017.

158. Lu W, Zhao Y, Kong Y, et al. Geniposide prevents H2 O2 -induced oxidative damage in melanocytes by activating the PI3K-Akt signalling pathway. *Clin Exp Dermatol* 2018;43(6):667-74. doi: 10.1111/ced.13409

159. Chamcheu JC, Roy T, Uddin MB, et al. Role and Therapeutic Targeting of the PI3K/Akt/mTOR Signaling Pathway in Skin Cancer: A Review of Current Status and Future Trends on Natural and Synthetic Agents Therapy. *Cells* 2019;8(8) doi: 10.3390/cells8080803

160. Seo E, Lim JS, Jun J-B, et al. Exendin-4 in combination with adipose-derived stem cells promotes angiogenesis and improves diabetic wound healing. *Journal of Translational Medicine* 2017;15(1):35. doi: 10.1186/s12967-017-1145-4

161. Johnson KE, Wilgus TA. Multiple roles for VEGF in non-melanoma skin cancer: angiogenesis and beyond. *Journal of Skin Cancer* 2012;2012:483439. doi: 10.1155/2012/483439

162. Rajabi P, Neshat A, Mokhtari M, et al. The role of VEGF in melanoma progression. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences* 2012;17(6):534-39.

163. Shapiro J. The NHS: the story so far (1948-2010). *Clin Med (Lond)* 2010;10(4):336-8. doi: 10.7861/clinmedicine.10-4-336 [published Online First: 2010/09/21]

164. 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

165. Gillam SJ, Siriwardena AN, Steel N. Pay-for-performance in the United Kingdom: impact of the quality and outcomes framework: a systematic review. *Ann Fam Med* 2012;10(5):461-8. doi: 10.1370/afm.1377 [published Online First: 2012/09/12]

166. 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

167. Chisholm J. The Read clinical classification. *Bmj* 1990;300(6732):1092. doi: 10.1136/bmj.300.6732.1092 [published Online First: 1990/04/28]

168. NHS Digital. SNOMED CT [Available from: https://digital.nhs.uk/services/terminology-and-classifications/snomed-ct#national-requirements-for-snomed-ct.

169. 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

170. Boggon R, van Staa TP, Chapman M, et al. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiology and drug safety* 2013;22(2):168-75. doi: 10.1002/pds.3374

171. Williams R, van Staa T-P, 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) doi: 10.1136/bmjopen-2017-020827

172. Dregan A, Moller H, Murray-Thomas T, et al. Validity of cancer diagnosis in a primary care database compared with linked cancer registrations in England. Population-based cohort study. *Cancer Epidemiol* 2012;36(5):425-29. doi: 10.1016/j.canep.2012.05.013

173. Persson R, Vasilakis-Scaramozza C, Hagberg KW, et al. CPRD Aurum database: Assessment of data quality and completeness of three important comorbidities. *Pharmacoepidemiol Drug Saf* 2020;29(11):1456-64. doi: 10.1002/pds.5135 [published Online First: 2020/09/29]

174. de Burgos-Lunar C, Salinero-Fort MA, Cárdenas-Valladolid J, et al. Validation of diabetes mellitus and hypertension diagnosis in computerized medical records in primary health care. *BMC Med Res Methodol* 2011;11:146. doi: 10.1186/1471-2288-11-146 [published Online First: 2011/11/01]

175. Tate AR, Dungey S, Glew S, et al. Quality of recording of diabetes in the UK: how does the GP's method of coding clinical data affect incidence estimates? Cross-sectional study using the CPRD database. *BMJ Open* 2017;7(1):e012905. doi: 10.1136/bmjopen-2016-012905 [published Online First: 2017/01/27]

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

177. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. *The British Journal of General Practice: The Journal of the Royal College of General Practitioners* 2010;60(572):e128-36. doi: 10.3399/bjgp10X483562

178. 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 [published Online First: 2017/11/15]

179. Meal A, Leonardi-Bee J, Smith C, et al. Validation of THIN data for non-melanoma skin cancer. *Qual Prim Care* 2008;16(1):49-52.

180. Chiesa Fuxench ZC, Troxel AB, Gelfand JM. Validity of diagnostic codes for identifying cutaneous squamous cell carcinoma in The Health Improvement Network. *Br J Dermatol* 2017;176(5):1363-65. doi: 10.1111/bjd.14957

181. Boggon R, van Staa TP, Chapman M, et al. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiology and Drug Safety* 2013;22(2):168-75. doi: 10.1002/pds.3374

182. Rothman KJ, Greenland S, Lash T. Modern Epidemiology. 3 ed. Philadelphia: Lippincott Williams & Wilkins.

183. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *Am J Epidemiol* 2003;158(9):915-20. doi: 10.1093/aje/kwg231

184. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep* 2015;2(4):221-28. doi: 10.1007/s40471-015-0053-5

185. Pottegård A, Friis S, Stürmer T, et al. Considerations for Pharmacoepidemiological Studies of Drug-Cancer Associations. *Basic Clin Pharmacol Toxicol* 2018;122(5):451-59. doi: 10.1111/bcpt.12946 [published Online First: 2017/12/22]

186. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2020;29(9):1101-10. doi: 10.1002/pds.5083 [published Online First: 2020/08/13]

187. Datta-Nemdharry P, Thomson A, Beynon J. Opportunities and Challenges in Developing a Cohort of Patients with Type 2 Diabetes Mellitus Using Electronic Primary Care Data. *PLoS ONE* 2016;11(11):e0162236. doi: 10.1371/journal.pone.0162236 [published Online First: 2016/11/20]

188. Lévesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *Bmj* 2010;340:b5087. doi: 10.1136/bmj.b5087 [published Online First: 2010/03/17]

189. Smith JD, Mills E, Carlisle SE. Treatment of pediatric type 2 diabetes. *Annals of Pharmacotherapy* 2016;50(9):768-77.

190. Schneeweiss S, Rassen JA, Brown JS, et al. Graphical depiction of longitudinal study designs in health care databases. *Ann Intern Med* 2019;170(6):398-406.

191. Schneeweiss S, Patorno E. Conducting Real-world Evidence Studies on the Clinical Outcomes of Diabetes Treatments. *Endocrine Reviews* 2021;42(5):658-90. doi: 10.1210/endrev/bnab007

192. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *The American Statistician* 1985;39(1):33-38.

193. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70(1):41-55.

194. Rubin DB. Estimating causal effects from large data sets using propensity scores. *Ann Intern Med* 1997;127(8_Part_2):757-63.

195. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011;46(3):399-424. doi: 10.1080/00273171.2011.568786 [published Online First: 2011/08/06]

196. Desai RJR, K. J.: Bateman, B. T.: Hernandez-Diaz, S.: Huybrechts, K. F. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. *Epidemiology* 2017;28(2):249-57. doi: 10.1097/ede.0000000000000595 [published Online First: 2016/12/07]

197. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ (Clinical research ed)* 2019;367:l5657. doi: 10.1136/bmj.l5657

198. Infante-Rivard C, Cusson A. Reflection on modern methods: selection bias-a review of recent developments. *Int J Epidemiol* 2018;47(5):1714-22. doi: 10.1093/ije/dyy138 [published Online First: 2018/07/10]

199. Nohr EA, Liew Z. How to investigate and adjust for selection bias in cohort studies. *Acta Obstet Gynecol Scand* 2018;97(4):407-16. doi: 10.1111/aogs.13319 [published Online First: 2018/02/08]

200. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics* 2000;56(3):779-88. doi: 10.1111/j.0006-341x.2000.00779.x [published Online First: 2000/09/14]

201. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550-60. doi: 10.1097/00001648-200009000-00011 [published Online First: 2000/08/24]

202. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology (Cambridge, Mass)* 2000;11(5):561-70.

203. Weuve J, Tchetgen Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology (Cambridge, Mass)* 2012;23(1):119-28. doi: 10.1097/EDE.0b013e318230e861

204. Pradhan R, Yu O, Platt RW, et al. Long-Term patterns of cancer incidence among patients with and without type 2 diabetes in the United Kingdom. *Diabetes Res Clin Pract* 2022;185:109229. doi: 10.1016/j.diabres.2022.109229 [published Online First: 2022/02/07]

205. McGuinness C, Wesley UV. Dipeptidyl peptidase IV (DPPIV), a candidate tumor suppressor gene in melanomas is silenced by promoter methylation. *Front Biosci* 2008;13:2435-43. doi: 10.2741/2856 [published Online First: 2007/11/06]

206. Patel PM, Jones VA, Kridin K, et al. The role of Dipeptidyl Peptidase-4 in cutaneous disease. *Exp Dermatol* 2021;30(3):304-18. doi: 10.1111/exd.14228 [published Online First: 2020/11/02]

207. Caparrotta TM, Dear JW, Colhoun HM, et al. Pharmacoepidemiology: Using randomised control trials and observational studies in clinical decision-making. *Br J Clin Pharmacol* 2019;85(9):1907-24. doi: 10.1111/bcp.14024 [published Online First: 2019/06/18]

208. Shahid RK, Ahmed S, Le D, et al. Diabetes and Cancer: Risk, Challenges, Management and Outcomes. *Cancers* 2021;13(22):5735.

209. 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 [published Online First: 2007/01/19]

210. 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

211. White MC, Holman DM, Boehm JE, et al. Age and cancer risk: a potentially modifiable relationship. *Am J Prev Med* 2014;46(3 Suppl 1):S7-15. doi: 10.1016/j.amepre.2013.10.029 [published Online First: 2014/02/12]

212. Campisi J. Aging, cellular senescence, and cancer. *Annu Rev Physiol* 2013;75:685-705. doi: 10.1146/annurev-physiol-030212-183653 [published Online First: 2012/11/13]

213. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* 2011;62:141-55. doi: 10.1146/annurev-med-042909-093756 [published Online First: 2010/11/26]

214. Butler PC, Elashoff M, Elashoff R, et al. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? *Diabetes care* 2013;36(7):2118-25.

215. Mitri J, Pittas AG. Inhaled insulin—what went wrong. *Nature Clinical Practice Endocrinology & Metabolism* 2009;5(1):24-25.

216. De Bruijn KMJ, Ruiter R, de Keyser CE, et al. Detection bias may be the main cause of increased cancer incidence among diabetics: results from the Rotterdam Study. *Eur J Cancer* 2014;50(14):2449-55. doi: 10.1016/j.ejca.2014.06.019

217. de Jong RGPJ, Burden AM, de Kort S, et al. Impact of detection bias on the risk of gastrointestinal cancer and its subsites in type 2 diabetes mellitus. *Eur J Cancer* 2017;79:61-71. doi: 10.1016/j.ejca.2017.03.039

218. Lega IC, Wilton AS, Austin PC, et al. The temporal relationship between diabetes and cancer: A population-based study. *Cancer* 2016;122(17):2731-38. doi: 10.1002/cncr.30095

219. Carr S, Smith C, Wernberg J. Epidemiology and risk factors of melanoma. *Surgical Clinics* 2020;100(1):1-12.

220. Eberly LA, Yang L, Essien UR, et al. Racial, Ethnic, and Socioeconomic Inequities in Glucagon-Like Peptide-1 Receptor Agonist Use Among Patients With Diabetes in the US. *JAMA Health Forum* 2021;2(12):e214182. doi: 10.1001/jamahealthforum.2021.4182 [published Online First: 2022/08/18]

221. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ open* 2016;6(1):e010210. doi: 10.1136/bmjopen-2015-010210

222. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. *Am J Epidemiol* 2008;168(3):329-35. doi: 10.1093/aje/kwn135 [published Online First: 2008/06/03]

223. Cárdenas Fuentes G, Bawaked RA, Martínez González MÁ, et al. Association of physical activity with body mass index, waist circumference and incidence of obesity in older

adults. *European Journal of Public Health* 2018;28(5):944-50. doi: 10.1093/eurpub/cky030

224. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018;6(5):361-69. doi: 10.1016/s2213-8587(18)30051-2 [published Online First: 2018/03/06]

225. Ahlqvist E, Tuomi T, Groop L. Clusters provide a better holistic view of type 2 diabetes than simple clinical features. *Lancet Diabetes Endocrinol* 2019;7(9):668-69. doi: 10.1016/s2213-8587(19)30257-8 [published Online First: 2019/08/24]

226. Flannick J. Data-driven type 2 diabetes patient clusters predict metabolic surgery outcomes. *Lancet Diabetes Endocrinol* 2022;10(3):150-51. doi: 10.1016/s2213-8587(22)00034-1 [published Online First: 2022/02/13]