REVIEW

Exploring genetic loci of type 2 diabetes and cancer: a review

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Abstract

Diabetes and cancer are two heterogenous diseases which are rapidly increasing in prevalence globally. A link between these two non-communicable diseases was first identified over 100 years ago; however, recent epidemiological studies and advances in genomic research have provided greater insight into the association between diabetes and cancer. Epidemiological studies have suggested that individuals with diabetes have an increased risk of several types of cancer (including liver, pancreas, colorectal, breast, and endometrial) and an increased risk of cancer mortality. However, this increased risk is not observed in all cancers, for example, there is a reduced risk of prostate cancer in individuals with diabetes. It has also been observed that cancer patients have an increased risk of developing diabetes, highlighting that the relationship between these diseases is not straightforward. Evidence of a shared genetic aetiology along with numerous lifestyle and clinical factors have made it challenging to establish if the relationship between the two diseases is causal or a result of confounding factors. This review takes a pan-cancer approach to highlight the complexities of the interactions between type 2 diabetes and cancer development, indicating where advances in genomic research have enabled a greater insight into these two diseases.

Introduction

Diabetes is a complex metabolic disease characterised by hyperglycaemia as a result of abnormal insulin function (Cho *et al.* 2018, Cole & Florez 2020). Circulating glucose levels are regulated by glucagon and insulin which work together in a negative feedback loop to increase and decrease glucose levels, respectively. In people without diabetes, glucose levels are maintained at 4–7 mmol/L prior to eating and rise to no more than 9 mmol/L 2 hours after consuming a meal (https://www.nhs.uk/conditions/high-blood-sugar-hyperglycaemia/), whilst those with diabetes commonly present glucose levels above the expected range of 7 mmol/L (hyperglycaemia) and are often unable to regulate glucose without clinical intervention. If left untreated, prolonged hyperglycaemia can increase the risk of chronic diabetic complications, including retinopathy, neuropathy, nephropathy, cardiovascular disease, and cancer (Nguyen *et al.* 2012, Chilelli *et al.* 2013, Baena-Díez *et al.* 2016). An association between diabetes and cancer was first described over 100 years ago with an observed positive correlation in male death rates (Claremont 1916). Although unable to determine causality at this time, in 1893, King and Newsholme determined that the increase in cancer death rates coincided with more accurate diagnosis and certification of death (King & Newsholme 1893), whilst Claremont (1916) observed the correlation over 20 years later and found the uniformity of the increase unlikely to be a result of improved diagnosis alone. Further studies in the early 1900s went on to question whether

individuals with diabetes were more at risk of developing cancer or whether individuals with cancer developed symptoms that could be characterised as diabetes (Wilson & Maher 1932).

More recent observational epidemiological studies have demonstrated that individuals with type 2 diabetes (T2D) have a higher lifetime risk of several types of cancer, including liver, pancreas, colorectal, breast, and endometrial (Giovannucci *et al.* 2010, Duan *et al.* 2014, Ryu *et al.* 2014, Vincent & Yaghootkar 2020, Hu *et al.* 2021, Pearson-Stuttard *et al.* 2021). Individuals with prediabetes/metabolic syndrome are also associated with an increased risk of several common cancers, suggesting that the development of diabetes is not conditional to the development of cancer (Esposito *et al.* 2012). In addition, it has been repeatedly shown that cancer patients with pre-existing diabetes have increased mortality rates than cancer patients without diabetes (Carstensen *et al.* 2014). However, it is difficult to dissociate whether this observed increase in mortality is due to the reduced life expectancy of both diseases or whether the interactions between cancer and diabetes contribute to the increased risk of mortality. Focussing on the shared genetic aetiology between T2D and cancer, this review aims to provide an

overview of the complex genetic relationship shared by these heterogenous diseases (Fig. 1). Diabetes encompasses several different forms, and the most common types are type 1 diabetes, T2D and gestational diabetes (Solis-Herrera *et al.* 2018). However, due to the differing aetiology of diabetes, this review will solely focus on the genetic overlap between T2D and cancer.

Genetic variation

The biological drivers of many complex diseases remained largely unclear until the development of genome-wide association studies (GWAS) in 2005. GWAS have demonstrated that late-onset diseases such as T2D and cancer are more commonly comprised of multiple low-impact variants rather than single-gene causation (Barroso & McCarthy 2019). Multiple genetic loci have been identified which increase the risk of both diabetes and cancer; however, the degree to which these explain the overlap in the occurrence of these diseases is currently poorly understood. Advances in genomic analysis technologies and the generation of increasingly well-powered and curated datasets have provided an opportunity to look more closely at the association between diabetes and cancer (Sud *et al.* 2017, Barroso & McCarthy 2019). Genetic variation within the protein coding gene *TCF7L2* is a well-evidenced example in which genetic variants and risk alleles independently predispose an individual to both T2D and cancer. The *TCF7L2* gene encodes a transcription factor which acts as a nuclear receptor for β-catenin and subsequently mediates canonical Wnt signalling (Smith 2007, Adams & Vella 2018). Wnt signalling is an essential pathway for regulating cellular function, embryonic development and stem cell renewal (Flanagan *et al.* 2018). However, the role of Wnt signalling in carcinogenesis has also been well characterised most prominently in colorectal cancer (Zhan *et al.* 2017). Wnt signalling is essential for regulating homeostasis within intestinal tissue and alterations to the Wnt pathway resulting from genetic alterations have been shown to disrupt intestinal–crypt villus architecture and therefore cellular homeostasis (Korinek *et al.* 1998, Flanagan *et al.* 2018). Mutations impacting the signalling of canonical pathways have also been associated with cancer treatment resistance. In order to combat treatment resistance, studies of transcription factor TCF4 (encoded by *TCF7L2*) have demonstrated TCF4 as a potential metabolic target to sensitise treatment-resistant cells (Kendziorra *et al.* 2011, Osher & Macaulay 2019). Mutations
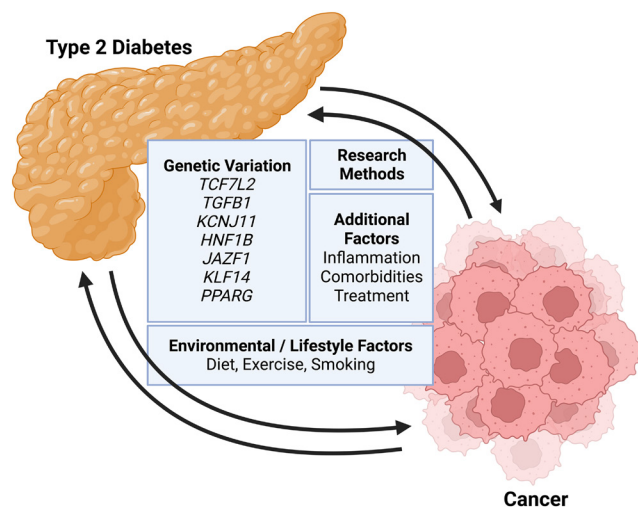

Figure 1
Review overview. This diagram depicts the multiple factors impacting the complex relationship between type 2 diabetes (T2D) and cancer. Focusing on the genetic overlap, this review covers seven genes which provide a plausible explanation for the interactions between T2D and cancer. It is important to note that this relationship is not limited to genetics and strongly influenced by environmental/lifestyle factors, treatments, comorbidities, and metabolic alterations such as inflammation. The review also discusses a range of research methods from observational epidemiological studies to Mendelian randomisation. Advancing genomic technologies and *in silico* methods are enabling a greater insight into the interactions between T2D and cancer (data from Leedy *et al.* 2022).

in *TCF7L2* have also been shown in breast, hepatocellular, and aggressive prostate cancer, supporting the role of Wnt signalling in tumourigenesis.

Variation on the *TCF7L2* locus has also been associated with T2D, leading to a predisposition to the disease, most notably in the T allele at rs7903146. The diabetes-associated T allele has been observed to impair glucose tolerance through glucagon and insulin secretion (Shah *et al.* 2016). In addition, Shim *et al.* (2016) and Sainz *et al.* (2012) replicated an association between T2D risk alleles within the *TCF7L2* gene and a higher risk of colorectal cancer, supporting an association between the two diseases. Despite this supporting evidence, other studies have been unable to replicate strong associations and highlight inconsistencies when investigating other cancers such as breast cancer (Hou *et al.* 2012, Zhao *et al.* 2016). This suggests that despite the *TCF7L2* gene demonstrating an association with an increased susceptibility to T2D and cancer development, shared causality is more difficult to determine.

Transforming growth factor-beta (TGFB) signalling also has shown an important role in the association between diabetes and cancer. The gene *TGFB1* has a regulatory role in TGFB signalling through activation of the SMAD pathway (Polfus *et al.* 2021). Inhibition of TGFB signalling has been shown to promote pancreatic β cell replication in an adaptive response to insulin demand (Polfus *et al.* 2021). Dhawan *et al.* (2016) demonstrated that TGFB signalling induces *INK4a* expression. INK4a proteins are important for cellular senescence and apoptosis; therefore, the increased *INK4a* expression results in the decline of β cells and has thus been associated with T2D. The therapeutic inhibition of TGFB signalling could reduce the production of INK4a proteins specifically p16^{INK4a} and subsequently increase β cell replication as shown in murine models (Dhawan *et al.* 2016). p16^{INK4a} is a protein used in the regulation of the cell cycle and demonstrates altered expression in cancer (Romagosa *et al.* 2011), providing a potential mechanism linking both diabetes and cancer. A greater understanding of the interaction of these genetic and epigenetic pathways could inform the identification of novel therapeutic targets for both diseases (Dhawan *et al.* 2016).

Moving away from signalling pathways, another gene commonly associated with diabetes and cancer is *KCNJ11*. Pancreatic β cells mediate insulin secretion through ATP-sensitive potassium channels. These channels comprise of four potassium ion channel tetramers (Kir6.2), which work together to form the pore of the potassium channel (Haghvirdizadeh *et al.* 2015). The Kir6.2 tetramers are

encoded by the *KCNJ11* gene, which has been linked to an increased susceptibility of T2D through the disruption of insulin secretion pathways. Although the exact mechanism remains unclear, it is suggested that single-nucleotide polymorphisms (SNPs) within the *KCNJ11* gene influence the structure and function of Kir6.2. Therefore, SNPs within this gene would disrupt insulin secretion through the ATP potassium channel and subsequently disrupt the glucose metabolism, β cell homeostasis and give rise to hyperinsulinaemia over time (McTaggart *et al.* 2010). It has also been shown that the SNPs within *KCNJ11* which increase susceptibility to diabetes also increase colorectal cancer risk, which could suggest that hyperinsulinaemia plays a role in colorectal carcinogenesis (Giovannucci *et al.* 2010, Cheng *et al.* 2011).

Whilst there is evidence of a shared genetic aetiology between diabetes and many forms of cancer, there are exceptions to this in which T2D appears to ameliorate the risk of certain types of cancer and reduce cancer mortality. Epidemiological studies have observed that individuals with diabetes demonstrated a reduced risk of prostate cancer when compared to those without diabetes (Kasper *et al.* 2009, Tsilidis *et al.* 2015). Whilst this relationship is multifactorial, the *HNF1B* and *JAZF1* genes have been associated with an increased risk of diabetes and decreased risk of prostate cancer. One study utilised luciferase reporter assays to demonstrate that SNPs altered the binding of microRNAs and subsequently suggested that the binding of these microRNAs regulates *HNF1B* gene expression and therefore T2D susceptibility (Goda *et al.* 2015). Examining the relationship through two large cohorts (the Cancer Prevention Study II Nutrition Cohort and the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial), one study indicated that *HNF1B* variants are directly associated with both diabetes and prostate cancer. However, it was clear that the variants investigated do not mediate the relationship between the two diseases (Stevens *et al.* 2010). Evidence surrounding this gene in the risk of different types of cancer is conflicting, as the overexpression of *HNF1B* has also been associated with clear cell epithelial ovarian cancer. However, the effect varies dependent on the cancer subtype, highlighting that this relationship is not straightforward (Shen *et al.* 2013). Similar conflicting evidence also occurs in prostate cancer; a GWAS of European ancestry demonstrated that one SNP within intron 2 of the *JAZF1* gene provided an association with prostate cancer (Prokunina-Olsson *et al.* 2010). Whilst a genetic relationship has been noted between T2D and prostate cancer, other studies have associated the reduction in cancer risk with alterations in insulin, insulin-like

growth factor 1, and testosterone levels in individuals with diabetes. However, reduced detection of prostate cancer in individuals with diabetes must not be overlooked. Obese males with diabetes generally demonstrate lower prostate-specific antigen levels than individuals without diabetes. This is likely to reduce the detection and diagnosis of prostate cancer, which may also contribute to the reduced incidence of prostate cancer demonstrated in people with diabetes (Wu *et al.* 2011, Preston *et al.* 2014).

In contrast to *HNF1B, JAZF1* also mediates metabolic stress and p53 stress pathways, including the metabolic process of T2D via interactions with nuclear receptors and protein kinases similar to *TCF7L2* (Kobiita *et al.* 2020). SNPs within *JAZF1* have been strongly associated with T2D through multiple mechanisms, including obesity, which epidemiological studies have shown to be the most important risk factor for T2D impacting insulin resistance and disease progression (Wu *et al.* 2014). Studies have shown that overexpression of *JAZF1* reduces the expression of acetyl–coenzyme A carboxylase, fatty acid synthetase, and sterol regulatory element–binding protein 1 messenger RNA, all of which are essential for maintaining cellular homeostasis (Li *et al.* 2011). Li *et al.* (2011) also demonstrated that the overexpression of *Jazf1* in a murine cell line reduced lipogenesis and increased lipolysis, which subsequently impacts the glucose metabolism and could play a role in the association with T2D (Li *et al.* 2011). Similarly linked with obesity through a build-up in adipose tissue, genetic variants in close proximity to the *KLF14* gene have been associated with metabolic disease and increased cancer risk, providing another example of genetic variation impacting both diabetes and cancer (Yang & Civelek 2020).

Further investigation of the relationship with adipose tissue and obesity identified that *PPARG* is associated with adipogenesis and the development of insulin resistance

commonly found in T2D (Schwenk *et al.* 2013). *PPARG* encodes the peroxisome proliferator-activated receptor subfamily of nuclear receptors. The overexpression of *PPARG* has been demonstrated in multiple cancers, including colon, breast, and pancreas; however, the biological role of *PPARG* is deemed controversial. *PPARG* has demonstrated anticancer effects through the promotion of cancer cell differentiation, cell-cycle arrest, and apoptosis, suggesting a tumour-suppressive role (Tang *et al.* 2011). *PPARG* has also demonstrated tumour-promoting properties through the stimulation of angiogenesis (Eibl 2008). This unclear evidence suggests that the role of *PPARG* and many other genetic variants is context dependent (Vincent & Yaghootkar 2020). This conflicting association provides a final example of the vast variation of genes shared by T2D and cancer. Genetic variants not only provide a plausible explanation for the complex associations between diabetes and cancer but also provide an opportunity for novel therapeutics. *PPARG* for example has also been utilised for its therapeutic properties as the binding of fatty acids, fatty acid derivatives, and ligands such as thiazolidinediones activates *PPARG* demonstrating a role in insulin sensitivity and provides a therapeutic target. A novel thiazolidinedione (LPSF/SF-13) has shown a good affinity for *PPARG,* further supporting its potential therapeutic role (De Melo Rêgo *et al.* 2014). In order to utilise the potential therapeutic role of genetic variants, there is a requirement for a greater understanding of causality.

Mendelian randomisation

In recent studies, Mendelian randomisation (MR) has provided a technique to investigate causality and confounding (Fig. 2). Large-scale studies have begun to
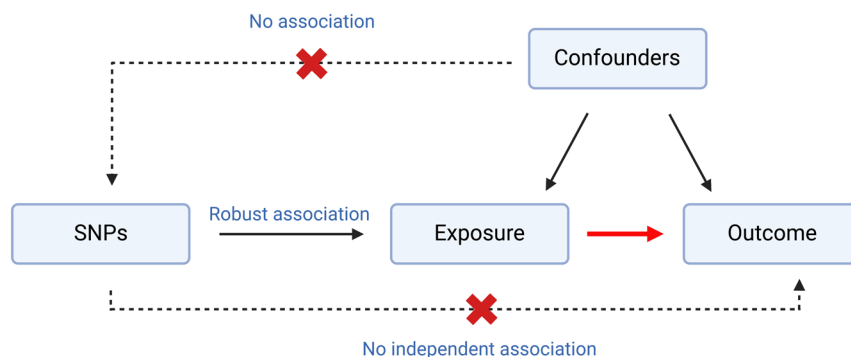

Figure 2
Summary schematic of Mendelian randomisation (MR). Single-nucleotide polymorphisms (SNPs) are selected as an instrumental variable to look at the causal relationship between an exposure and an outcome indicated by the red arrow. The method of MR relies on three assumptions indicated by the blue text. Assumption 1: There must be a robust association between the chosen SNPs and exposure variable. Assumption 2: The chosen SNPs must be independent of any confounding factors. Assumption 3: There must be no independent association between the SNPs and outcome variable. Any violation of these assumptions invalidates the study and can limit the method of MR (data from Gala & Tomlinson 2020).

investigate the role that specific glycaemic traits (including fasting glucose, 2-hour glucose, and HbA1c) may have in the development of cancer, using MR approaches (Murphy *et al.* 2022). The role these traits have in the development of cancer have the potential to give insight into how T2D influences cancer due to the disruption of traits primarily involved in T2D development. MR is an analysis tool that uses genetic variants to establish causal relationships from observational data (Davies *et al.* 2018). The analysis is based on Mendel's law of inheritance and instrumental variable estimation methods (Sanderson *et al.* 2022). Recent approaches using two-sample MR found no significant genetic evidence supporting the increased risk of cancer as a result of diabetes (Goto *et al.* 2020, Yuan *et al.* 2020). Although overall cancer risk differed from retrospective epidemiological studies, Yuan *et al.* (2022) demonstrated 6 of 22 site-specific cancers risks were influenced by diabetes, four sites of which demonstrated an increased cancer risk whilst two sites demonstrated a decreased cancer risk (Yuan *et al.* 2020). The study demonstrated little evidence supporting a causal association between fasting glucose and cancer. However, genetically predicted fasting insulin levels were positively associated with some site-specific cancers included in the study, suggesting that insulin resistance in early diabetes may contribute to cancer risk (Yuan *et al.* 2020).

Murphy *et al.* (2022) also identified an association between fasting insulin and carcinogenesis in the largest MR analysis of glycaemic traits and colorectal cancer to date. The study determined the causal effect of glycaemic traits on colorectal cancer risk including 48,214 cases and 64,159 controls and provided evidence that higher fasting insulin levels increased colorectal cancer risk (Murphy *et al.* 2022). Murphy *et al.* (2022) demonstrated no evidence in support for other glycaemic traits including fasting glucose or 2-hour glucose, which suggests that increased insulin levels are likely to be the primary driver of positive associations between T2D and colorectal cancer in this study. These results support a causal effect of higher fasting insulin levels, which creates an avenue for novel therapeutics and supports further investigation into the use of insulin as a clinical marker. These findings also suggest that interventions to decrease insulin levels may inhibit tumourigenesis (Murphy *et al.* 2022). Overall, MR studies demonstrate the necessity for large, highly powered datasets which are required to investigate the complex relationship between glucose metabolism and tumourigenesis. However, there are limitations to MR (Fig. 2), and it is important to note the many other factors influencing the relationship between diabetes and cancer which cannot be explored using this method.

Additional influences

There are multiple factors to consider in addition to genetics, including metabolic alterations, inflammation, and treatment of T2D. It is beyond the scope of this review to discuss the numerous factors which contribute to the complex relationship between diabetes and cancer in detail. However, it is important to highlight that these factors may also be contributing or confounding to this relationship. For example, obesity is considered to be one of the most significant confounders of T2D. Increased volume of adipose tissue can increase the secretions of adipokines such as leptin and inflammatory molecules such as macrophages which accumulate in the adipose tissue and can stimulate a downstream inflammatory response such as the release of proinflammatory cytokines, tumour necrosis factor alpha, and interleukin-6 (Weisberg *et al.* 2003, Olli *et al.* 2013, Spielman *et al.* 2014). Whilst inflammation is often used as a protective response, overstimulation can contribute to disease initiation and progression of cancer and diabetes. Comorbidities such as obesity and cardiovascular complications can also have significant implications in treatment choice. Lega *et al.* (2018) highlighted that individuals with diabetes often receive less aggressive cancer treatment, which is likely due to their diabetic comorbidities. This could lead to a poorer cancer prognosis and increased cancer progression in individuals with diabetes.

There is also significant evidence of a treatment overlap between diabetes and cancer through metformin. Metformin is currently the first-line treatment for patients with T2D (Foretz *et al.* 2019). The impressive safety profile of metformin and pharmacological benefits demonstrated in individuals with diabetes has led to investigations into the use of metformin as a cancer therapeutic (Liu *et al.* 2016). *In vitro* and *in vivo* studies have demonstrated decreased malignant cell proliferation and increased apoptosis in lung cancer and prostate cancer when treated with metformin (Mallik & Chowdhury 2018), whilst improved patient outcomes have also been observed in many other cancers including endometrial, hepatocellular, and ovarian (Mallik & Chowdhury 2018). However, controversy shrouds the preclinical success as studies have utilised doses 10–1000-fold greater than peak human *in vivo* plasma levels, making the success of metformin

as a cancer therapeutic uncertain (Dowling *et al.* 2012, Lord *et al.* 2018). Advancing systematic bioinformatic approaches are also providing an opportunity for drug discovery and drug repurposing using genomic data. When investigating potential drug targets for T2D, Imamura *et al.* (2016) discussed T2D-susceptibility genes such as *KIF11* to be involved in cancer treatment as inhibitors of the *KIF11* gene product have been developed as chemotherapeutic agents, further supporting a novel opportunity for therapeutics using genetic information.

Whilst discussing the multitude of factors impacting both diabetes and cancer, it is evident that overall improvements in lifestyle such as diet and exercise can aid in the prevention of T2D and the subsequent disease complications. Further clinical trials into metformin and other treatments indicate the potential adaptability of existing therapeutics and support overlapping biological mechanisms between these two diseases. Whilst discussing the shared genetic factors, a concerted effort into whole-genome sequencing has the potential to provide a novel insight into the genetic overlap between diabetes and cancer. A greater understanding into the associations between T2D and cancer through a combination of approaches is essential to improve treatments and patient outcomes.

Conclusion

Despite significant efforts across the fields of diabetes and cancer research, the biological drivers shared between these two diseases are complex, and much remains to be understood. The heterogeneity shared by both diseases highlights the growing need for novel and innovative research to understand the underlying mechanisms to improve current therapeutics. Existing studies have taken a pan-cancer approach to extensively investigated genetic variants, impacting both diabetes and cancer. A shared genetic aetiology between T2D and cancer provides a plausible explanation for an increased cancer risk within individuals with T2D, most notably through *TCF7L2*. However, while many T2D-susceptibility genes are also involved in cancer development, this does not necessarily imply there is a shared causality. Increasingly highly powered datasets and advancing *in silico* methods are providing novel insights into the genetic drivers. Methods such as MR provide insight into causality which has previously been difficult to determine. This review sets out to highlight the relationship between diabetes and

cancer, not only focussing on shared genetic variants but also emphasising the importance of lifestyle and clinical factors which influence an individuals' risk of diabetes and cancer. Moving forward in this field, third-generation sequencing is providing a novel opportunity to investigate this complex relationship. Long-read whole-genome sequencing is beginning to uncover large structural variants which have previously been left undiscovered when using short-read sequencing techniques. Precision medicine approaches such as nanopore technologies are enabling research into both the genetic and epigenetic landscape of cancer and subsequently the impact of diabetes on cancer biology. In addition, prospective population-based studies are also providing novel discoveries into this relationship, with new robust MR methods and larger datasets beginning to investigate site-specific, sex-specific, and ancestral differences. These advances are working to differentiate the possible mechanisms involved in the interactions of diabetes and cancer, which will allow improvements to clinical care through precision medicine.

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