

Type 2 diabetes mellitus and gastrointestinal cancer

Citation for published version (APA):

de Jong, RGPJ. (2019). *Type 2 diabetes mellitus and gastrointestinal cancer: Disease, drugs, or distortion?* [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20190605rj>

Document status and date:

Published: 01/01/2019

DOI:

[10.26481/dis.20190605rj](https://doi.org/10.26481/dis.20190605rj)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

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Valorisation

Valorisation

Value for society

Over the past decades a rise in the incidence and prevalence of both type 2 diabetes mellitus (T2DM) and gastrointestinal (GI) cancer has been observed. Determining whether T2DM is an important risk factor for the development of GI cancer - and to what degree - helps governmental and medical institutions decide if T2DM is a possible target for cancer prevention or if patients with T2DM form a population that needs targeted (GI) cancer screening. In this thesis, we investigated the complex association between T2DM and GI cancer, focussing on the influence of a variety of factors on the association. In **Chapter 2** we found higher incidence rates of liver, pancreatic and colon cancer in patients with T2DM compared with individuals without T2DM. In **Chapter 3**, a 40% increased risk of GI cancer was found, which seemed mainly driven by increased risks of hepato-pancreatico-biliary type cancers. In both chapters, evidence of detection bias influencing the strength of the association was seen. The results of these studies help to determine the strength of the association between T2DM and GI cancer, which can be used for future scientists and policymakers to decide whether targeted cancer screening of individuals with T2DM is needed.

In the past, multiple studies have pointed to lower risks of (GI) cancers in users of metformin compared to users of other anti-diabetic drugs. The results of these studies formed the basis for the launch of numerous drug trials to investigate the possibility of repurposing metformin as globally used first-line anti-diabetic drug to a more chemotherapeutic agent. There are currently over 100 clinical drug trials being conducted investigating the effect of metformin as therapeutic agent in the treatment of various cancers (www.clinicaltrials.gov; accessed on April 11, 2019). However, evidence has come to light that many previous studies on the risk of cancer with use of metformin have been afflicted by time-related biases, thereby inflating the protective effects of metformin on cancer development. More recent studies and our study presented in **Chapter 5**, using a time-dependent definition of drug exposure in order to minimize time-related bias, showed no differences in risk of GI cancers in users of metformin compared to users of other non-insulin anti-diabetic drugs. Therefore, our results add to the debate whether performing costly drug trials is justified when purely based on (biased) information from observational studies. We recommend to replicate well-designed pharmaco-epidemiological studies with minimal time-related bias to gain more robust evidence that indeed no association is present between the use of metformin and (GI) cancer risk.

Value for professionals

Investigating complications of type 2 diabetes mellitus, including the risk for cancer development, is important for clinical practice. Generally, clinicians managing patients with T2DM are aware of the development of diabetic retinopathy, nephropathy, and neuropathy. If future research shows more concrete evidence of a causal biological link between T2DM and development of cancer, then clinicians can be more aware of this additional serious complication. Based on the evidence presented in this thesis, an association between T2DM and GI cancer is present, with a 40% increased risk of GI cancer in the T2DM population versus the non-diabetic population (**Chapter 2**). However, a causal link could not be proven with the studies in this thesis, and detection bias (**Chapters 2 and 3**) and residual confounding due to unmeasured confounding variables may be present. Furthermore, in **Chapter 8**, a lower risk of GI cancer was found in patients with T2DM without glycaemic burden compared to patients with up to one year of glycaemic burden. Although future studies are needed to confirm these findings, our results indicate that more stringent glycaemic control in patients with T2DM may be beneficial by reducing the risk of GI cancer.

Value for future research

Most of the research in this thesis is part of an endeavour to learn more about the complex association between T2DM and GI cancer. First, the evidence presented in Chapters 2 through 9 will help to develop future research on the link between T2DM and GI cancer. For example, it is important to perform sensitivity analyses that include one or more years of lag period between the (assumed) onset of T2DM and the diagnosis of a (GI) cancer in order to minimize detection bias (**Chapter 2**). Furthermore, when investigating the association between (anti-diabetic) drugs and (GI) cancer, it is important to use a time-dependent covariate of drug exposure in order to capture variations in drug exposure over time (**Chapters 3 and 6**).

Second, in **Chapter 4** we showed that the age- and sex distribution of the Clinical Practice Research Datalink (CPRD) is comparable to that of the total Dutch population. Investigating the generalizability of populations contained in large population-based databases will help translating study results to other populations. The results of our study can encourage scientists from other countries with similar healthcare systems to perform studies of CPRD representativeness.

Third, we were the first to investigate the association between a novel marker of hyperglycaemia of time, called 'glycaemic burden', and the risk of GI cancer (**Chapter 8**). As this is the first study more research is needed to confirm our findings and build on evidence that is currently presented.

Finally, based on our data no causal link between T2DM and GI cancer can be established. As the underlying pathophysiological mechanisms between T2DM and GI cancer remain to be elucidated, more basic research focusing on mechanistic aspects is needed.

In summary, while an association between T2DM and GI cancer has been clearly established, much is to be learned about their causal relationship and biological mechanisms that lead up to it. The results of the studies in this thesis will help develop future (observational) research on the link between T2DM and GI cancer and encourage other scientist to study the complex association.