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The number of people with type 2 diabetes (T2D) is rising across the world. This rise is likely due to an aging population, economic development and increasing urbanisation leading to more sedentary lifestyles and greater consumption of unhealthy foods linked with obesity. These risk factors are also among the known risk factors for cancer and in the Netherlands, the 10-year prevalence of cancer almost doubled since 1999 (from 1.8% in 1999 to 3.5% in 2018). The question whether these two diseases are associated has been raised and different epidemiological studies showed an increased risk of many forms of cancer among people with T2D. Several mechanisms are proposed to explain this increased risk, such as common risk factors, metabolic derangements of diabetes and the use of blood glucose lowering drugs. Additionally, many methodological challenges are present when studying the association between diabetes and/or blood glucose lowering drugs and cancer.

This thesis describes the results of population-based observational studies on T2D, its treatment and associations with cancer using data from the PHARMO DIAbetes MANagement and Treatment (DIAMANT) cohort.

To put the relevance of these studies in perspective, this thesis starts with a study determining the number of people in the Netherlands suffering from diabetes and a study describing the treatment patterns among people with T2D (Part I). Because a reliable trend regarding the prevalence of diabetes in the Netherlands is lacking, Chapter 2 describes the prevalence of diabetes in the Netherlands and whether this prevalence in- or decreased over time. Furthermore, the impact of changes in population demographics on this trend was investigated. The Out-patient Pharmacy Database of the PHARMO Database Network was used, covering about 3,000,000 Dutch inhabitants. In the period 1999-2014, the prevalence more than doubled (from 1.8% in 1999 to 4.9% in 2014) and only 56% of this increase was explained by demographic changes. The remaining 44% was explained by other factors. Obesity might be one of these other factors because the prevalence of this risk factor doubled in the Netherlands in the past 30 years. As diabetes is a burden for both people and society, this increasing prevalence of T2D reflects the size of this major health problem.

Chapter 3 provides an overview on the treatment of people with T2D in the Netherlands compared to four other European countries. Data from the Netherlands, Italy, Spain, France and the United Kingdom (UK) was analysed at the site of each database holder by using a common data model. To ensure a homogeneous analysis within the different databases, an analysis tool creating treatment patterns was developed and validated. Therefore differences regarding treatment patterns between the countries reflected actual differences that could not be explained by differences in methodology/analysis. Overall, metformin was the most common initial treatment in all countries, as expected based on national and European guidelines for T2D. Subsequent treatments differed per country. Most patients in the
Netherlands, Spain and the UK switched to a combination of metformin and a sulfonylurea derivative (SU). In Italy, this combination was outnumbered by “other treatments”, mainly repaglinide. In France, treatments including dipeptidyl peptidase-4 (DPP-4) inhibitors were most frequently used. These variations reflect the differences between the national guidelines of the countries and were especially seen regarding the uptake of the newer incretin-based treatments.

As observational studies comparing the clinical effectiveness of incretin-based treatments are limited, Chapter 4 describes the clinical effectiveness of liraglutide versus basal insulin in terms of changes in glycated haemoglobin (HbA$_1c$), weight, body mass index (BMI), blood pressure, and blood lipids, including total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL). Obese people with T2D initiating liraglutide (n = 544) were matched to obese people with T2D initiating basal insulin supported oral therapy (n = 613). From 3 months onwards, glycaemic control improved in both groups, but improved significantly more with liraglutide than with basal insulin (12 months: -12.2 mmol/mol vs -8.8 mmol/mol). In addition, after 12 months weight and BMI were significantly lower for treatments with liraglutide vs basal insulin (-6.0 kg vs -1.6 kg and -2.1 kg/m$^2$ vs -0.5 kg/m$^2$, respectively). No significant differences were seen in changes in cardiovascular risk factors.

Glycaemic control is associated with a lower risk of micro- and macrovascular complications. Chapter 5 describes the relation between different measures of glycaemia and micro- (diabetic foot, retinopathy, and renal complications) and macrovascular (coronary artery disease and cerebrovascular disease) complications. All recorded HbA$_1c$ measurements were used to express glycaemic exposure in four ways: index HbA$_1c$, time-dependent HbA$_1c$, exponential moving average (EMA) and glycaemic burden. Index HbA$_1c$ showed the weakest relation between all micro- and macrovascular complications. The time-dependent HbA$_1c$ and the EMA-defined model showed similar results and only a significant association for microvascular complications was found. A statistically significant relation with glycaemic burden was found for all selected micro- and macrovascular complications.

The second part of this thesis focuses on the association between T2D and/or blood glucose lowering drugs and characteristics of site-specific cancer (Part II, Chapters 6-9).

Epidemiological studies showed that the risk of cancer among people with T2D differ per site; relative risks range from 0.84 for prostate cancer to 2.23 for hepatocellular carcinoma. Since the upcoming use of DPP-4 inhibitors for treatment of T2D, concerns about the risk of pancreatitis and pancreatic cancer associated with the use of DPP-4 inhibitors have been raised. As DPP-4 is a rather unselective enzyme present in many tissues and cancer has a diverse and complex nature, a systematic review and meta-analysis was conducted to summarise the evidence on the association between DPP-4 inhibitors and the incidence of all specific cancer types compared with placebo or active antidiabetic drugs (Chapter...
Twenty-five studies met the inclusion criteria and sample sizes of the DPP-4 inhibitor groups ranged from 29 to 8,212 participants for randomised controlled trials and from 2,422 to 71,137 people for observational studies. Based on the available literature, no evidence for an association between DPP-4 inhibitors and site-specific cancer was found. However, as the existing evidence was limited, it was not possible to conclude whether DPP-4 inhibitors were associated with an increased short-term risk of site-specific cancer. The majority of studies included in this review suffered from methodological limitations and the duration of the studies was relatively short.

Insulin (analogues) are also raised as potential candidates to explain the increased risk of cancer among people with T2D. The association between insulin (analogues) treatment and the incidence of breast cancer has been studied extensively, but literature regarding the influence of insulin (analogues) treatment before breast cancer diagnosis on the aggressiveness of the breast tumour is scarce. In Chapter 7 the association between insulin (analogues) treatment and specific pathologic breast tumour characteristics was investigated using the linkage between the Netherlands Cancer Registry (NCR) and the PHARMO DIAMANT cohort. Linking these data resulted, as far as we know, in one of the largest, detailed cohorts of women with breast cancer and T2D/insulin (analogues) treatment. This nested case-control study showed that women with T2D (n=1,567) are at increased risk to be diagnosed with a more advanced tumour stage and a higher grade though less often with a PR-negative breast tumour than women without T2D (n=6,267). The study did not show that women with T2D using insulin (analogues) (n=388) develop more aggressive breast cancer tumours than women with T2D not using insulin (analogues) (n=1,179).

Chapter 8 describes the influence of T2D on the sex- and site-specific risk of colorectal cancer. A matched cohort study including people with T2D and people without diabetes was conducted. Both men and women with T2D were 1.3 times more likely to develop colorectal cancer compared to their diabetes free-, sex matched-control. This increased risk was especially pronounced among men with T2D regarding distal colon cancer (HR (95% CI): 1.42 (1.08-1.88)) and among women with T2D regarding proximal colon cancer (HR (95% CI): 1.58 (1.13-2.19)). Furthermore, women with T2D aged ≥70 years were more likely to be diagnosed with a proximal colon cancer than with a distal colon cancer. More tailored screening strategies among people with T2D may optimize the effectiveness of colorectal cancer screening in terms of reducing colorectal cancer incidence and mortality.

Many methodological challenges exist when studying the association between diabetes and/or blood glucose lowering drugs and cancer. In Chapter 9 the influence of study design (matched versus non-matched) and censoring or excluding people with incident diabetes during follow-up on risk estimation was studied. In both designs, using three different censoring definitions, similar non-significant increased risks of breast cancer were found. Regarding prostate cancer, all analyses in the non-matched cohort study resulted in a non-
significant decreased risk, while in the matched cohort study they all resulted in a significant decreased risk. A consistent increased risk of colorectal cancer was seen in all analysis designs; non-significant in men and significant in women. Overall, the study demonstrates the relative insensitivity of the direction of the association between T2D and breast, prostate and colorectal cancer. Matching can prevent confounding by the matched variables, but is not always appropriate (e.g. the matched variables are not regarded as confounders). It is preferable that people developing diabetes contribute person time to both the control group (i.e. person time prior to the diagnoses of diabetes) and the exposed group (i.e. person time after the diagnosis of diabetes) in order to minimise information bias.

In conclusion, this thesis provides a reliable prevalence of diabetes over time in the Netherlands. Furthermore, it contributes to the knowledge regarding the association between T2D and/or blood glucose lowering drugs and cancer. We showed that detailed data is required to perform methodologically sound studies regarding this association. The PHARMO DIAMANT cohort is a unique and detailed database for these types of (pharmaco) epidemiological studies. Although associations between T2D and/or blood glucose lowering drugs and characteristics of site-specific cancers have been shown, residual confounding cannot be ruled out because of the complex relationship between diabetes and cancer. Based on the current status of the field and the research presented in this thesis, we could not substantiate that drugs used to treat diabetes increase the risk of developing cancer.