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Detection bias may be the main cause of increased cancer incidence among diabetics: Results from the Rotterdam Study

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Abstract ***Aim:*** Type 2 diabetes is associated with an increased cancer risk. Most studies on this topic analyse diabetes as a risk factor without adjusting for diabetes duration before cancer occurrence. This study aimed to investigate the association between diabetes duration and cancer risk in more detail.

Methods: In this prospective cohort study, diabetes diagnosis was based on clinical information and use of glucose lowering medication. Details on incident cancers were obtained via general practitioners and linkage to pathology registers. Cox proportional hazards models were used with onset and duration of diabetes as time-varying determinants.

Results: The study comprised 10,181 individuals. Diabetes was associated with an increased overall risk of incident cancers (hazard ratio (HR) 1.2, 95% confidence interval (CI) 1.07–1.39) and pancreatic cancer (HR 2.9, 95% CI 1.75–4.89). A diagnosis of diabetes less than three months before the diagnosis of cancer was associated with strongly increased risks of all- (HR 3.3, 95% CI 2.50–4.32) and pancreatic cancers (HR 28.7, 95% CI 6.32–130.58).

Conclusion: The magnitude of the association between diabetes and an increased risk of cancer seems to be inflated by detection- or protopathic bias. Future studies investigating this association should adjust for diabetes duration and include a plausible aetiological risk window.

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1. Introduction

There is increasing evidence that type 2 diabetes is associated with an increased risk of cancer [1]. However, risk estimates vary per specific cancer site [2–7] and moreover, with regard to prostate cancer, diabetes seems to be a protective factor [8–10]. Several possible mechanisms have been proposed as an explanation for the association between type 2 diabetes and the increased cancer risk [11]. Obesity is a major acquired risk factor for diabetes as well as for cancer [12]. Another possible mechanism is via hyperinsulinaemia – that exists in both diabetic and obese patients and that stimulates the insulin and insulin-like growth factor (IGF) axis [11]. Furthermore, evidence suggests that certain oral glucose-lowering drugs (e.g. metformin) have a protective effect on cancer risk but that certain forms of insulin therapy may increase cancer risk [13–16].

Despite the growing body of evidence on the association between type 2 diabetes and an increased risk of cancer, several points should be emphasised. First, the association is complex as, for example, age and obesity are risk factors associated with both outcomes [1]. Thus, it is important that studies should adjust for these potential confounders. Second, most observational studies on this topic analyse diabetes as a dichotomous risk factor without taking into account the moment of onset or duration of diabetes before cancer occurrence [1,17]. In this way, detection bias, to which the increased cancer risk has partially been attributed [18–20], cannot be assessed. To account for detection bias, duration of diabetes should be studied in more detail, with duration of diabetes divided into groups of increasing duration. In this way, impact of diabetes per time window can be assessed more accurately.

Finally, carcinogenesis is a slow and multistage process that develops over a period of several years [21]. The latency and so-called sojourn periods differ per cancer type – and sometimes amount to a few decades – [22] thus making it difficult to analyse when diabetes has its impact in carcinogenesis.

We tested the hypothesis that the long-term exposure of diabetes in the elderly is associated with an increased risk of some cancers whereas increased risk associated with the peri-diagnosis of diabetes reflects biases like detection bias and protopathic bias. Therefore, the objective of this study was to investigate the association between diabetes duration and cancer risk in detail in order to confirm results with regard to detection bias and possibly resolve problems from earlier studies on this topic.

2. Patients and methods

2.1. Setting

Data were obtained from the Rotterdam Study, a large population-based prospective cohort study. The objectives and design were extensively described elsewhere [23,24]. In brief, since 1990, inhabitants of the suburb Ommoord, aged 55 years or older were invited to participate. Of all 10,275 invited subjects 7983 entered the study (78%). In 2000, a second cohort with 3011 participants (of 4472 invitees, 67%) was added (Rotterdam Study II). Cancer cases were registered via the general practitioners, on the basis of discharge letters, and by linkage with the academic and regional laboratory for clinical pathology through a nationwide registry of histo- and cytopathology in the Netherlands (PALGA). The Rotterdam Study has been approved by the Medical Ethics Committee and all participants have received written and oral informed consent.

2.2. Definition of diabetes duration

Diabetes mellitus was diagnosed on the basis of a fasting plasma glucose level of $\geqslant$7.0 mmol/L ($\geqslant$126 mg/dL), or non-fasting plasma glucose levels of $\geqslant$11.1 mmol/L ($\geqslant$200 mg/dL), or use of blood glucose lowering medication. Date of onset of diabetes was estimated by reference to the date of first prescription of a glucose-lowering drug (Anatomical Therapeutical Chemical code (ATC-code) A10 [25]) based on linkage with pharmacies that serve the Ommoord district. Duration of diabetes was defined as the time interval between the date of onset of diabetes and the date of cancer diagnosis in cases and the same follow-up date in the remainder of the non-censored part of the cohort. Cohort members were censored on the date of first cancer, death or end of the study period, whichever came first.

Regarding the non-diabetic participants the follow-up period started at the moment of inclusion in the study, until the date of first cancer, death or end of the study period, whichever came first.

2.3. Outcome

The outcomes of interest were all incident cancers combined, further specified into separate models for the five most frequently occurring cancer types in the Rotterdam Study: breast cancer, prostate cancer, pancreatic cancer, lung cancer and colorectal cancer. With regard to the cancer diagnoses, haematological cancers and non-melanoma skin cancers (NMSC) were excluded. Cancers were classified according to the International Statistical Classification of Diseases and Related Health problems, 10th revision (ICD-10) [26] and the International Classification of Primary Care, 2nd edition (ICPC-2) [27]. All cancer cases were confirmed by pathology records.

2.4. Covariables

The following baseline patient characteristics, all determined by baseline interview or during the visits to