The Value of Glycemic Control Prior to Cancer Diagnosis on All-Cause Mortality among Patients with Type 2 Diabetes in Dutch Primary Care

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ABSTRACT

Background: Poor glycemic control prior to cancer diagnosis for patients with preexisting type 2 diabetes (T2DM) may predict a worse cancer diagnosis. We investigated the association between pre-diagnosis glycemic control and all-cause mortality in patients with T2DM who develop cancer.

Methods: This prospective cohort study linked data from three sources covering 1989 to 2019: a T2DM benchmarking database, the Netherlands Cancer Registry, and the Personal Records Database. We included patients with T2DM and incident primary breast, colorectal, or prostate cancer (stage 0–III), with target glycemic control defined according to Dutch guidelines. Analysis involved estimating the association between glycemic control and all-cause mortality with Cox proportional hazard models, accounting for individual expected survival relative to the general population and relevant disease (e.g., diabetes duration and medications) and individual (e.g., age and gender) characteristics.

Results: Of the 71,648 linked cases, 620 had breast cancer, 774 had colorectal cancer, and 438 had prostate cancer, with follow-up data available for 6.4 (4.2–8.4), 5.6 (2.7–7.6), and 6.3 (4.5–8.2) years, respectively. Compared with patients with pre-diagnosis glycemic control at target, the HRs and 95% confidence intervals for mortality among those with pre-diagnosis glycemic control not at target were 1.40 (1.00–1.96) for breast cancer, 1.45 (1.12–1.88) for colorectal cancer, and 1.39 (0.98–1.98) for prostate cancer.

Conclusions: Among patients with T2DM in Dutch primary care, poor glycemic control before diagnosis with breast and colorectal cancer can increase mortality compared with good control.

Impact: Glycemic control prior to cancer diagnosis is of prognostic value.

Introduction

Significant improvements in survival from breast, colorectal, and prostate cancer, coupled with the high prevalence of type 2 diabetes (T2DM; refs. 1, 2), mean that many patients now live with comorbid cancer and diabetes (3–5). However, despite many patients receiving diabetes treatment in primary care, there is a paucity of research in this population (6). Given that research has also shown diabetes may predict a worse prognosis in patients with cancer (7, 8), with more recent findings suggesting a key role for poor glycemic control (9–12), this topic warrants further study. Indeed, few studies have evaluated the association between glycemic control and survival in patients with both cancer and diabetes (13), possibly due to the reduced priority given to diabetes management after a diagnosis of cancer. In oncologic care, for example, oncologists and patients may prioritize cancer treatment (14–18) and accept less stringent glycemic control as a justifiable adverse effect of that treatment (19). Patients with cancer also increasingly receive T2DM management in primary care in the Netherlands, where research indicates that more than 70% achieve their target glycemic control (20). An evaluation of the quality of glycemic control between patients with colorectal cancer and no cancer in primary care revealed comparable probabilities of reaching the target level (20). Among patients with comorbid cancer and T2DM, it is suspected that glycemic control plays an important role on survival (21).

The complex interplay between a cancer diagnosis and its treatment on glycemic control led us to focus on the pre-diagnosis hemoglobin A1c (HbA1c). Therefore, this study investigated the role of glycemic control before cancer diagnosis on all-cause mortality among patients with incident breast, colorectal, or prostate cancer who received treatment for T2DM in primary care.

Materials and Methods

Data source

This prospective cohort study used data linked between the Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC) cohort, the Netherlands Cancer Registry (NCR), and the Personal Records Database (BRP). Data linkage was updated in January 2021 to include cancer and mortality data for January 1, 1998, to December 31, 2019. The Dutch Medical Research with Human Subjects Law exempts this data linkage from the need for formal medical ethics committee review (METC NO. 16.12216 and 16.12214).

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The data linkage is described in detail elsewhere (22). The ZODIAC cohort is an annual benchmarking database of patients with T2DM that receives input from 731 general practitioners in Dutch primary care. Initiated in 1998 to evaluate the quality of structured shared care provided by diabetes specialist nurses and general practitioners for patients with T2DM in Zwolle, it became a standard component of diabetes care and has been expanded to other regions. It includes patients diagnosed with T2DM who received their diabetes treatment exclusively in Dutch primary care, but it excludes patients considered by the general practitioner to have short life expectancy or insufficient cognitive function. Recruitment occurred gradually between 1998 and 2012 as the structured shared care expanded in the Netherlands, with follow-up data included to 2014 (23). All patients were invited to annual reviews by the structured shared care teams, who prospectively collected the following clinical data at each assessment: demographic data, vital signs, history of macrovascular events, medications, body mass index (BMI), smoking status, and laboratory tests (24).

The NCR has registered cancer diagnoses in the Dutch population since 1989 (25). Its linkage added data about cancer diagnosis, tumor characteristics, and initial treatment during the first 9 months after a cancer diagnosis. Finally, the BRP contains the personal records of people in the Netherlands, including vital statuses and postal codes.

Study population

All patients diagnosed with primary breast, colorectal, and prostate cancer between 1998 and 2014 were identified on the basis of the availability of diabetes-related data in primary care (**Fig. 1**). The following exclusion criteria were then applied: cancer diagnosed before the diabetes diagnosis; prevalent cancer diagnosed within 1 year after the diabetes diagnosis; stage IV cancer, which might not be treated with curative intent; and males with breast cancer, due to the small number.

Definitions and glycemic control measurement

Baseline was defined as the date of cancer diagnosis for patients with cancer. Follow-up ended on the date of death or the end of the study (December 31, 2019), whichever came first. Glycemic control was measured at baseline for patients with and without cancer, using the HbA1c level (26). To ensure that HbA1c records reflected the period before a cancer diagnosis, measurements taken in the year of a cancer

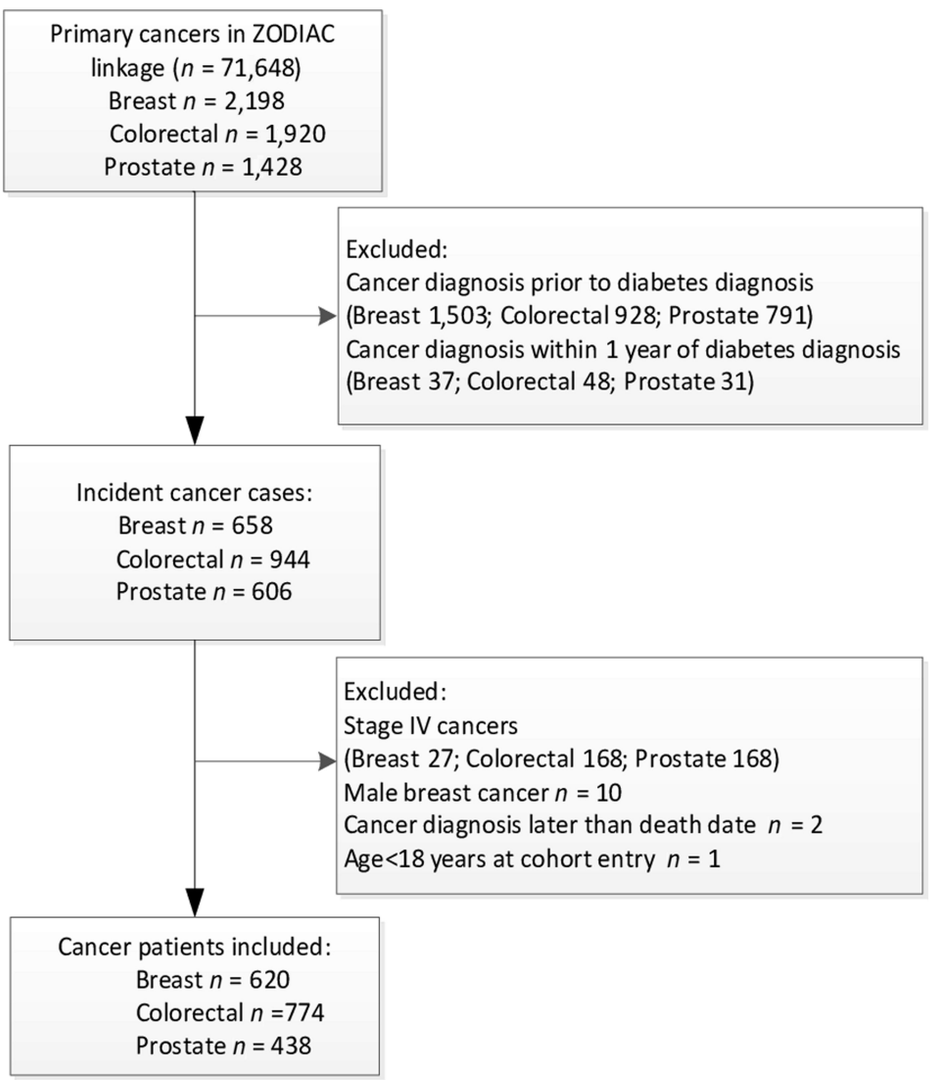

Figure 1.
Study flowchart. The ZODIAC linkage included data from the Dutch National Cancer Registration and the BRP, combining data on T2DM, cancer cases, and deaths. This included incident cancer events up to 2014, with data censored on December 31, 2019.

diagnosis were only used if the date of annual T2DM review was earlier than the date of cancer diagnosis; otherwise, the HbA1c measured in the year before the cancer diagnosis was used.

Target HbA1c levels was set as a binary variable according to the Dutch primary care guideline. Before 2013, this defined the target HbA1c level for T2DM as ≤ 53 mmol/mol (27). Since 2013, this target HbA1c was relaxed for patients older than 70 years, allowing either a target HbA1c of ≤ 58 mmol/mol if diagnosed within the last 10 years and receiving treatment beyond metformin monotherapy or a target HbA1c of ≤ 64 mmol/mol if diagnosed more than 10 years ago (28). We estimated missing HbA1c values using the closest pre-baseline HbA1c measurement, up to a maximum of 3 years, and analyzed the remaining missing values as a missing category.

Study outcomes

The primary study outcome was the relative risk of mortality for patients with comorbid cancer and T2DM having glycemic control not at target compared with those having glycemic control at target. The secondary outcome was the relative risk of mortality per unit increase in HbA1c above 53 mmol/mol compared with a HbA1c ≤ 53 mmol/mol.

Baseline covariates

Adjustment was made for the confounders age, gender, diabetes duration, history of macrovascular events, BMI, smoking, socioeconomic status (SES), drug use (metformin, insulin, and lipid-lowering drugs), cancer stage, and baseline year. All covariates were measured at baseline.

The history of macrovascular events, BMI, smoking, and medication use before cancer diagnosis were measured using the same method as for HbA1c to ensure the correct temporal order. Macrovascular events were defined as the use of antithrombotic drugs or a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, or transient ischemic attack.

SES was estimated from postal codes registered in the BRP, with overall scores aggregated to 4-digit postal code areas by the Dutch governmental organization *Sociaal Cultureel Planbureau* according to the income, unemployment, and education levels, which was relative to other areas in the Netherlands (29). A high score represents high social deprivation (low SES) and a low score represents little social deprivation (high SES). We used the SES scores estimated in 2010 because around half of the patients were diagnosed with cancer or enrolled at this time, and divided them into low, intermediate, and high SES tertiles (30).

Missing BMI and smoking data were handled in the same way as missing HbA1c values. The few patients (<2%) without a valid postal code or without an overall SES score due to small local populations were considered missing at random.

Statistics

Descriptive analyses are presented by cancer type as proportions, medians with interquartile ranges, or means with SDs. The cause of death for patients with comorbid cancer and T2DM could not be determined reliably, so we applied relative survival to provide an accurate estimation of mortality compared with the general population (31). The cumulative relative survival was defined as the ratio of observed cumulative survival in our study population divided by the expected cumulative survival for a Dutch general population matched by age, gender, and calendar year. We extracted the mortality table from the Human Mortality Database (32) and plotted the survival curve using the Ederer II method (33).

To account for the relative survival rate and predefined confounders, we used the "relsurv" package in R to apply a Cox proportional hazards model with survival time transformed into a time-scale range from 0 to 1 based on the cumulative distribution function of a given age, gender, and calendar year in the general population (31, 34). This conversion removed expected survival differences due to age, gender, and calendar year in the general population, allowing the attribution of any remaining differences to the comorbid cancer and T2DM. In this way, we could adjust the predefined baseline confounders after accounting for life expectancy at the individual level. Age and duration of diabetes were used as categorical variables in violation of the assumption when used as continuous variables.

The Cox proportional regression model assumed that all patients experienced the same baseline hazard. Given the possibility that mortality due to cancer may change over time, we stratified the data by baseline year. Analysis then proceeded by fitting the Cox model within each stratum and computing the regression coefficients as the sum of the analyses (35). The assumption of proportionality for this model was checked by graphical examination and Brownian bridges (36). All statistical tests were two-sided using a 5% significance level. The HRs and 95% confidence intervals (CI) were estimated in R studio (version 1.4.1103) and all other analyses were performed in STATA (version 17.0).

Sensitivity analyses

We expected more pronounced benefits from good glycemic control among patients with shorter disease durations and other characteristics indicative of better health (37). Therefore, sensitivity analyses were planned for the following baseline characteristics: diabetes duration <10 years, age <70 years, no history of macrovascular events, no insulin treatment (because insulin use might indicate a different phase of diabetes), metformin monotherapy, and stage 0 to II cancer. We included all covariates adjusted in the primary analyses, except for the variable used to select the study population for the sensitivity analyses (e.g., in the analysis among patients with a diabetes duration <10 years, we made no adjustment for diabetes duration). To detect the potential role of cancer treatment, we also performed analyses excluding patients treated with chemotherapy or radiotherapy. Because of the few patients with incident cancer each year between 1998 and 2005, which might have resulted in underpowering when stratified by baseline year, we performed a final sensitivity analysis using incident cancer cases developed since 2006.

Improved glycemic control among patients with T2DM was previously found to improve survival (38); however, an evaluation in 2009 revealed no association between glycemic control and relative survival in participants with only T2DM in the ZODIAC cohort (39). This might reflect either insufficient sample size and follow-up or a well-regulated diabetes population (i.e., >70% of patients were at their HbA1c target). To facilitate interpretating the association among patients with cancer, we therefore performed a sensitivity analysis among patients with T2DM only, randomly matching them to cases with incident cancer by age (±1 year) and gender (male/female) in a 5:1 ratio. All patients with no history of cancer were eligible for matching to patients with cancer (Supplementary Fig. S1). Baseline was defined as 2 years after the cohort entry date for patients without cancer, because patients were enrolled until 2012 and had follow-up until 2014. These definitions ensured comparable distributions of

baseline years for both patient groups (Supplementary Table S1). Differences between the cancer group and no cancer matched group were evaluated by paired *t* test for normally distributed continuous variables, Wilcoxon matched-pairs signed-rank test for non-normally distributed continuous variables, and McNemar (exact) test for nominal data. The analyses and covariates were the same as for patients with cancer, except the absence of cancer stage for patients without cancer.

Results

Table 1 shows the characteristics of patients with T2DM and incident cancer in Dutch primary care, while Supplementary Table S2 provides information about cancer treatment by stage for each cancer. The relative survival rates for patients with cancer with pre-diagnosis glycemic control at target level was slightly higher than those not at target during the 10-year follow-up (**Fig. 2**). Details of the estimated relative survival rates have been listed in Supplementary Table S3.

Table 2 summarizes the HRs for mortality in patients with cancer, comparing those with baseline HbA1c values at target and not at target. Patients with cancer who had a baseline HbA1c not at target tended to be at increased risk of all-cause mortality compared with those with a baseline HbA1c at target, showing corresponding HRs (95% CI) for breast, colorectal, and prostate cancer of 1.40 (1.00–1.96), 1.45 (1.12–1.88), and 1.39 (0.98–1.98), respectively. Supplementary Table S4 provides the results for the full model.

In general, the sensitivity analyses produced similar results to the primary analyses, though the HRs for patients with colorectal cancer were consistently higher. Unfortunately, we had to omit the sensitivity analysis for patients treated with metformin monotherapy due to the small sample size. To help interpret the results, Supplementary Table S5 details the quality of glycemic control by cancer stage for each type of cancer. This shows that the quality of glycemic control among patients with a more advanced cancer stage was not worse than for patients with a less advanced cancer stage. Finally, Supplementary Table S6 summarizes the comparable findings to the primary analyses when including cancers that developed since 2006.

Patients with T2DM but not cancer tended to have a shorter duration of diabetes at baseline and a longer follow-up by the end of the study, while also being at their target HbA1c level more often, when compared with age- and gender-matched patients with cancer at cohort entry (Supplementary Table S7). Similar to patients with

Table 1. Baseline characteristics of patients with incident cancer diagnosed with T2DM in Dutch primary care.

Cancer patient characteristics	Breast (*n* = 620)	Colorectal (*n* = 774)	Prostate (*n* = 438)
Age (years)	71.0 ± 10.6	72.8 ± 8.7	71.9 ± 7.1
Male *n* (%)	0	436 (56.3)	100
Duration of diabetes (years)	6.6 (4.0–10.1)	7.3 (4.4–11.3)	6.6 (3.6–10.0)
History of macrovascular events[†] *n* (%)	189 (30.5)	303 (39.2)	208 (47.5)
At target HbA1c *n* (%)			
Yes	439 (70.8)	545 (70.4)	314 (71.7)
No	145 (23.4)	180 (23.3)	110 (25.1)
Unknown	36 (5.8)	49 (6.3)	14 (3.2)
BMI (kg/m^2)	30.6 ± 5.6[a]	28.8 ± 4.9[b]	28.8 ± 4.2[c]
SES *n* (%)			
Intermediate or high	281 (45.3)	379 (49.0)	221 (50.5)
Low	331 (53.4)	383 (49.5)	211 (48.2)
Unknown	8 (1.3)	12 (1.6)	6 (1.4)
Smoking *n* (%)			
No	457 (73.7)	497 (64.2)	295 (67.4)
Ever	115 (18.6)	210 (27.1)	118 (26.9)
Unknown	48 (7.7)	67 (8.7)	25 (5.7)
Use of metformin *n* (%)	337 (54.4)	450 (58.1)	258 (58.9)
Use of insulin *n* (%)	23 (3.7)	46 (5.9)	16 (3.7)
Use of lipid-lowering drugs *n* (%)	394 (63.6)	510 (65.9)	308 (70.3)
Median follow-up years	*6.4 (4.2–8.4)*	*5.6 (2.7–7.6)*	*6.3 (4.5–8.2)*
Cancer-related characteristics			
Cancer stage *n* (%)			
In situ	55 (8.9)	91 (11.8)	0
I	249 (40.2)	139 (18.0)	171 (39.0)
II	230 (37.1)	238 (30.8)	178 (40.6)
III	74 (11.9)	276 (35.7)	82 (18.7)
Unknown	12 (1.9)	30 (3.9)	7 (1.6)

Note: Normally distributed variables presented as Mean ± SD. Non-normally distributed data presented as Median (Interquartile range).
[†]History of macrovascular events was defined as the use of thrombocyte aggregation inhibitors or a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, or transient ischemic attack.
Missing.
[a]49 missing.
[b]62 missing.
[c]20 missing.

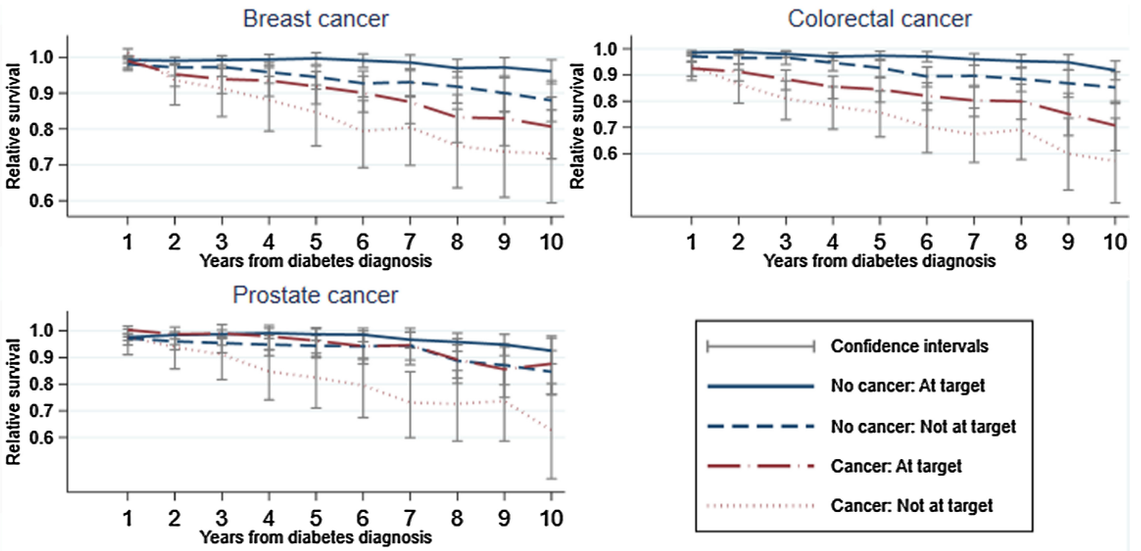

Figure 2.

Relative survival rates for patients with T2DM in Dutch primary care with and without a cancer diagnosis. Patients without cancer were matched to the group with cancer by age and gender. The results are stratified by the quality of glycemic control. The horizontal line at 1.0 represents the survival of the general population with the same age, gender, and calendar year.

cancer, relative survival rates were generally higher among those at their target HbA1c level compared with those with HbA1c not at target level at baseline (**Fig. 2**). In the relatively well-controlled diabetes care setting, glycemic control was associated with all-cause mortality among patients with T2DM only, with HRs (95% CI) of 1.22 (1.05–1.42), 1.15 (1.15–1.29), and 1.27 (1.07–1.50) for breast, colorectal, and prostate cancer, respectively (Supplementary Table S8).

Discussion

Among patients with T2DM in Dutch primary care, having an HbA1c result not at target before a diagnosis of breast or colorectal cancer was associated with a 40% to 45% increased risk of all-cause mortality over a median follow-up of 6 years after cancer diagnosis. This suggests the prognostic value of glycemic control prior to cancer diagnosis for patients with concurrent cancer and T2DM.

Comparison with the literature

Only a single study in the UK has evaluated the association between glycemic control and survival in patients with both diabetes and cancer (13). Although this found no association between increased HbA1c levels and overall survival in patients with breast, colorectal, and prostate cancer, our study differs from literature in follow-up time and mortality rates. While the UK study reported median follow-up times of 3.6 (1.8–6.5) years for breast cancer, 2.5 (0.9–5.2) years for colorectal cancer, and 3.4 (1.6–6.1) years for prostate cancer, we achieved follow-up times approximately 3 years longer (**Table 1**). Moreover, the mortality rates were lower in our study for patients with breast cancer [54 (47–61) vs. 56 (48–64) per 1,000 person-years], colorectal cancer [82 (74–90) vs. 119 (111–128) per 1,000 person-years], and prostate cancer [59 (51–69) vs. 67 (62–73) per 1,000 person-years; **Table 2**]. We consider that the higher mortality rates in the UK study reflect either their inclusion of patients with a more advanced stage of cancer at diagnosis or lower quality of diabetes care. Unfortunately, no information about cancer stage was provided in that study. Dutch primary care has been shown to provide diabetes management of good quality (40), reportedly achieving life expectancy comparable to the general population (39). This is reflected by the lower median HbA1c (49 vs. 53 mmol/mol) and the smaller proportion of insulin users (3.7%–5.9% vs. 12.1%–15.2%) in our research compared with the UK study (13). In the UK study, all patients with diabetes without specifying the type (I or II) were included, where the higher percentage of insulin users might be explained by including type I diabetes. Our sensitivity analysis of patients with T2DM only confirmed the benefits of good glycemic control regarding survival, which the report ZODIAC in 2009 did not find probably because the average age was 5 years younger and the median follow-up was 2 years shorter with a total sample size of 973 patients (39).

Explanation for the role of glycemic control prior to cancer diagnosis

We demonstrated an association between the quality of glycemic control in primary care before a cancer diagnosis and subsequent all-cause mortality. Although advanced cancer was associated with an increased risk of mortality, the quality of glycemic control was not worse in these patients (Supplementary Table S4), suggesting that glycemic control independently affects survival in patients with cancer. Furthermore, despite evidence that chemotherapy may influence glycemic control and induce cardiovascular toxicity (41), the exclusion of patients treated with chemotherapy did not affect the primary results. This implies that chemotherapy alone does not fully explain the association between glycemic control and overall survival among patients with cancer. Finally, in the sensitivity analyses that included patients with diabetes for <10 years and patients aged <70 years at cancer diagnosis, the HRs were higher than in the primary analyses for all cancer types, despite having fewer death events. This is consistent with our expectation that the value of glycemic control would be more profound in patients with characteristics indicative of better health.

Table 2. The role of glycemic control on all-cause mortality in patients with incident cancer with T2DM in Dutch primary care.

Analysis	Total *n*	Death *n*	Person-years	Mortality rate per 1000 person-years	At target *n* (%)	Adjusted by age and/or gender HR (95% CI)	Fully adjusted[a] HR (95% CI)
Breast							
Primary analysis	620	212	3,940.2	53.8 (47.2–61.3)	439 (70.8)	1.36 (0.99–1.85)	**1.40 (1.00–1.96)**
Per unit increase in HbA1c above 53 mmol/mol	584	199	3,729.5	53.5 (46.6–61.1)	439 (75.2)	1.01 (0.99–1.03)	1.02 (1.00–1.04)
DMD <10 years	464	144	3,115.8	46.2 (39.4–54.2)	349 (75.2)	**1.78 (1.20–2.65)**	**1.77 (1.18–2.67)**
Baseline age <70 years	282	49	2,121.9	23.1 (17.5–30.5)	191 (67.7)	1.52 (0.84–2.74)	1.55 (0.80–3.01)
No history of macrovascular events[b]	431	116	2,915.3	39.8 (33.3–47.6)	301 (69.8)	1.32 (0.86–2.02)	1.29 (0.80–2.09)
No insulin use	597	204	3,830.0	53.3 (46.6–60.9)	427 (71.5)	1.36 (0.99–1.87)	**1.41 (1.00–1.99)**
Stage 0–II	534	158	3,505.9	45.1 (38.7–52.5)	380 (71.2)	1.29 (0.89–1.85)	1.31 (0.88–1.94)
Chemotherapy excluded	493	184	3,076.7	59.8 (52.0–68.8)	352 (71.4)	1.30 (0.92–1.82)	1.38 (0.96–2.00)
Radiotherapy excluded	261	126	1,445.4	87.2 (73.8–103.0)	184 (70.5)	1.03 (0.68–1.56)	1.06 (0.67–1.68)
Colorectal							
Primary analysis	774	344	4,210.5	81.7 (73.8–90.4)	545 (70.4)	**1.31 (1.03–1.67)**	**1.45 (1.12–1.88)**
Per unit increase in HbA1c above 53 mmol/mol	725	318	4,007.4	79.4 (71.4–88.2)	545 (75.2)	**1.02 (1.00–1.03)**	**1.02 (1.00–1.04)**
DMD <10 years	542	244	3,074.3	79.4 (70.4–89.5)	412 (76.0)	**1.38 (1.01–1.88)**	**1.56 (1.12–2.17)**
Baseline age <70 years	277	81	1,742.0	46.5 (37.6–57.5)	188 (67.9)	**1.64 (1.01–2.66)**	1.52 (0.90–2.55)
No history of macrovascular events[b]	471	189	2,664.2	70.9 (61.8–81.4)	326 (69.2)	**1.48 (1.06–2.06)**	**1.52 (1.06–2.17)**
No insulin use	728	327	4,013.4	81.5 (73.4–90.4)	527 (72.4)	**1.37 (1.06–1.77)**	**1.49 (1.14–1.94)**
Stage 0–II	468	194	2,716.9	71.4 (62.4–81.8)	326 (69.7)	1.28 (0.92–1.78)	1.41 (0.99–1.99)
Chemotherapy excluded	609	291	3,201.4	90.9 (81.5–101.4)	428 (70.3)	1.25 (0.96–1.63)	**1.41 (1.06–1.87)**
Radiotherapy excluded	616	269	3,297.1	81.6 (72.8–91.5)	439 (71.3)	**1.38 (1.05–1.80)**	**1.57 (1.18–2.10)**
Prostate							
Primary analysis	438	163	2,761.0	59.0 (50.9–68.5)	314 (71.7)	**1.56 (1.12–2.17)**	1.39 (0.98–1.98)
Per unit increase in HbA1c above 53 mmol/mol	424	158	2,707.0	58.4 (50.2–67.9)	314 (74.1)	1.02 (1.00–1.05)	1.01 (0.98–1.04)
DMD <10 years	327	124	2,138.0	58.0 (48.9–68.8)	246 (75.2)	**1.60 (1.09–2.35)**	1.44 (0.95–2.16)
Baseline age <70 years	182	43	1,326.8	32.4 (24.2–43.5)	129 (70.9)	**1.95 (1.05–3.63)**	1.91 (1.00–3.64)
No history of macrovascular events[b]	230	66	1,527.6	43.2 (34.1–54.7)	172 (74.8)	1.44 (0.83–2.48)	1.50 (0.83–2.69)
No insulin use	422	153	2,700.2	56.7 (48.6–66.1)	305 (72.3)	**1.44 (1.02–2.04)**	1.32 (0.91–1.92)
Stage 0–II	349	132	2,208.5	59.8 (50.7–70.5)	247 (70.8)	**1.50 (1.03–2.17)**	1.39 (0.94–2.07)
Chemotherapy excluded	438	163	2,761.0	59.0 (50.9–68.5)	314 (71.7)	**1.56 (1.12–2.17)**	1.38 (0.98–1.98)
Radiotherapy excluded	286	117	1,737.1	67.4 (56.5–80.2)	204 (71.3)	1.36 (0.92–2.03)	1.37 (0.88–2.12)

Note: For all the analyses, HRs were estimated among patients with an HbA1c level not at target level compared with at the target level.
Abbreviation: DMD, duration of diabetes.
[a]Adjusted by age, gender, duration of diabetes, history of macrovascular events, smoking, BMI, social economic status, metformin use, insulin use, lipid-lowering drug use, cancer stage, and baseline year as a stratification variable.
[b]History of macrovascular events was defined as the use of thrombocyte aggregation inhibitors or a history of angina pectoris, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, stroke, or transient ischemic attack.

Strengths and limitations

The ZODIAC cohort covers more than 90% of the T2DM population in its region of the Netherlands (42), while the linked NCR provides a complete national cancer registry (25). Together they generated data for a representative population with T2DM who developed incident cancer and could include follow-up data for a median of 6 years. Furthermore, the sensitivity analyses not only confirmed the results of our primary analyses but also offered guidance for future studies, such as the evidence that the association between good glycemic control and survival might be greater among patients diagnosed with cancer at a younger age or who have had a shorter duration of diabetes.

The importance of glycemic control among patients with both cancer and T2DM tends to be underestimated, giving greater attention to cancer treatment (14–18). By presenting the value of glycemic control among patients with and without cancer, we could draw attention to glycemic control among patients with preexisting T2DM who developed incident cancer. A challenge when evaluating mortality in this cohort is that the cause of death cannot usually be determined reliably, with possible causes of death including cancer, cardiovascular diseases secondary to T2DM, other comorbidities, and aging. We therefore consider the relative survival analysis suitable. By accounting for the life expectancy in the general population, we could attribute the difference in mortality to cancer and/or the increased risk of cardiovascular disease resulting from T2DM (31).

Several important limitations also deserve consideration when interpreting the study results. First, we used annually recorded HbA1c values, and in some cases, values taken in the year before the cancer diagnosis. Measurements taken within 6 months before the diagnosis would have been preferable. Second, the study only evaluated the association between glycemic control prior to cancer diagnosis and

mortality. To understand what causes the increased mortality and how to optimize disease management, future studies need to evaluate the role of glycemic control throughout cancer treatment and survivorship (18). Third, we could not account for unmeasured confounders in the analysis, including comorbidities, diet, physical activity, and alcohol consumption. Patients with more comorbidities might be less able to achieve good glycemic control and might receive less aggressive cancer treatment, which could affect survival (43, 44). Finally, although statistically insignificant, it is likely that worse glycemic control prior to prostate cancer diagnosis would also be associated with increased mortality given the relatively small sample size and that the CI was close to one.

Our findings highlight the importance of glycemic control for patients with T2DM who develop concurrent cancer. To improve disease management and survival, efforts must now focus on large-scale population studies of glycemic control during cancer treatment and survivorship.

Authors' Disclosures

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Authors' Contributions

J. de Haan-Du: Conceptualization, formal analysis, funding acquisition, investigation, methodology, writing–original draft, project administration. **K.H. Groenier:** Formal analysis, supervision, investigation, methodology, writing–review and editing. **B. Wauben-Spaetgens:** Writing–review and editing. **M. Jalving:** Conceptualization, investigation, writing–review and editing. **N. Kleefstra:** Resources, supervision, writing–review and editing. **G.W.D. Landman:** Conceptualization, resources, supervision, funding acquisition, investigation, writing–review and editing. **G.H. de Bock:** Resources, supervision, funding acquisition, investigation, writing–review and editing.

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Note

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