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Serum glucose and hemoglobin A1C levels at cancer diagnosis and disease outcome

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Abstract

Background—Despite the lack of scientific data, many cancer patients hold the belief that glucose “feeds” cancer and might affect disease outcome. We aimed to evaluate associations between glucose, hemoglobin A1C (HbA1C), and survival among individuals with diabetes and diabetes associated cancers.

Methods—Five retrospective cohort studies were conducted in a large population-representative database. The study population included all patients with diabetes and an incident diagnosis of colorectal, breast, bladder, pancreatic and prostate cancers. Exposure of interest was serum glucose or HbA1C levels within 6 months prior to cancer diagnosis. Cox regression model was used to calculate hazard-ratio (HR) and 95% confidence-interval (CI) for overall survival. Analyses were adjusted for cancer-specific confounders. A subgroup analysis was performed among insulin-treated patients.

Results—Study cohorts included 7,916 individuals with incident cancers and concurrent diabetes. There was no association between HbA1C levels and overall survival in colorectal (HR 1.00, 95%CI 0.95-1.06), breast (HR 1.03, 95%CI 0.95-1.11), bladder (HR 0.94, 95%CI 0.86-1.01), pancreatic (HR 0.98, 95%CI 0.94-1.02), or prostate (HR 1.02, 95%CI 0.96-1.08) cancers. Among

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diabetes patients treated with insulin, there was increased survival with increasing serum glucose, most prominent for bladder cancer (HRs 0.91, 95%CI 0.84-0.99, per 1 mmol/L increase).

Conclusions—Higher glucose and HbA1C levels in diabetes patients with incident cancer are not associated with worse overall survival following cancer diagnosis. Among insulin-treated patients, higher glucose levels may be associated with improved survival.

Keywords

glucose; HbA1C; diabetes; insulin; cancer; survival

Introduction

More than 10% of the western population above the age of 20 are diagnosed with diabetes (1). Furthermore, the lifetime risk of cancer in this population ranges from 35% to more than 50% (2). Several studies have shown associations between type 2 diabetes and elevated risk of colorectal, breast, endometrial, bladder, pancreatic, and hepatobiliary malignancies (3-7), in contrast to lower risk of prostate cancer (8). Although bias might explain some of the associations, such as detection bias for bladder cancer (9) or reverse causality for pancreatic cancer, several large meta-analyses support the reproducibility of these observations (10,11). Additional studies showed higher mortality from colorectal (12,13), and breast cancers (14) among patients with diabetes, however the results were inconclusive and might not reflect cancer-specific mortality but rather mortality secondary to comorbidities associated with the metabolic syndrome (i.e. coronary artery disease), administration of less aggressive cancer treatment or difference in response to therapy in patients with diabetes (14-18).

The biological mechanisms underlying the association between diabetes and cancer are not clear. Cancers and diabetes share several common risk factors such as age, sex, obesity and a sedentary lifestyle. Chronic hyperinsulinemia, both endogenous secondary to insulin resistance and exogenous as part of therapy in patients with diabetes, was shown to have proliferative effects that can promote cancer formation through activation of insulin-like growth factor (IGF) receptors (19-22). Finally, the direct effect of hyperglycemia, independent of insulin, was suggested to increase cancer risk and promote cancer growth, mainly due to cancer dependence on aerobic glycolysis for adenosine triphosphate (ATP) generation (known as the Warburg effect) (23,24).

Several studies investigated the association between serum glucose and HbA1C levels with the risk of cancer and precancerous lesions, both in the general as well as in the diabetic population, with conflicting results (25-27). To date, only a few studies have evaluated the effect of glucose levels on cancer outcome (28-30). Those studies did not adjust for specific cancer risk factors or variables associated with the metabolic syndrome (such as hypertension and hyperlipidemia); focused on individuals without diabetes; did not evaluate the effect of anti-diabetes medications; and did not measure glucose at the time of cancer diagnosis. In addition, some of those studies analyzed mortality from all cancers combined instead of mortality from specific cancers. Thus, it is uncertain if glucose levels are associated with survival among patients with any or all cancers. Despite the lack of scientific data, many patient with cancer hold the belief that glucose “feeds” cancer and thus might

affect disease outcome. As a consequence, many patients adopt extreme diets that influence both caloric intake during treatments as well as quality of life.

The aim of the current study was to evaluate the association between glucose, HbA1C levels and overall survival in patients with diabetes and incident cancer using a large population-representative database with comprehensive and high quality clinical data. This association is of importance not only for understanding the effect of glucose on tumor biology but also for the clinical management of these patients, primarily whether it is beneficial to achieve tight glycemic control in this population.

Methods

Five retrospective cohort studies were conducted to evaluate the association between glycemic control and outcome of diabetes-associated cancers, including colorectal, breast, bladder and pancreatic cancers that are known to have a positive association with diabetes and prostate cancer that is known to have an inverse association with diabetes.

Data Source

The study used data from The Health Improvement Network (THIN), a large primary care electronic medical record database from the United Kingdom (UK) (<http://www.csdmruk.imshealth.com/>). THIN contains information of over 11 million individuals, more than 5% of the UK population, and has been shown to be population representative (31). The data includes demographic information, medical diagnoses, drug prescriptions, lab values and lifestyle habits. Medical diagnoses entered into the database are recorded using Read codes, the standard primary care classification system in the UK (32). Medication prescriptions are coded using British National Formulary codes. The validity and completeness of THIN for cancer research was demonstrated in previous studies (31,33-35).

Study Cohort

Eligible patients included those with an initial diagnosis of colorectal, breast, bladder, pancreatic or prostate cancer by a THIN practitioner between 1995 and 2013. Patients were required to have a diabetes diagnosis with recorded measurements of either serum glucose or HbA1C levels in the 6 months prior to their cancer diagnosis. Patients were excluded if they were <40 years old at the time of cancer diagnosis; had a diagnosis with familial cancer syndromes or inflammatory bowel disease (only for colorectal cancer (CRC) in order to evaluate only sporadic cancer patients); or were diagnosed with the diabetes-associated cancer within the first 6 months after registration with a primary-care practice in order to avoid prevalent cases (33). Follow-up began on the date of the first cancer diagnosis and ended at the earliest of: death; transfer out of a THIN practice; or end of follow-up. The study was approved by the Institutional Review Board at the University of Pennsylvania and by the UK Scientific Review Committee of THIN.

Exposure and covariates

Primary exposure was the last HbA1C levels recorded during the 6 months prior to the cancer diagnosis. The last glucose level recorded during the same time period was a

secondary exposure variable. Additional covariates that have known effects on cancer risk and outcome were examined including: age; sex; obesity (defined as a body mass index (BMI)>30kg/m²); smoking history (ever); alcohol consumption (according to medical code); medical co-morbidities including coronary artery disease (CAD), hypertension and hyperlipidemia; and medical therapies such as chronic aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) use (cumulative duration of more than one year with last prescription within 6 months before cancer diagnosis), hormone replacement therapy and anti-diabetic medications (any use). All covariates were measured prior to the cancer diagnosis date.

Outcome

The primary outcome was overall survival after diagnosis with a specific cancer. In a secondary analysis we evaluated survival using a cohort of individuals who died within 5 years after the cancer diagnosis. This time period was selected in order to include the vast majority of patients with advanced cancer whose death was likely due to the cancer, since only 10-20% of patients with metastatic cancer survive 5 years (<http://www.cancerresearchuk.org/>). Date of death was recorded for all patients in the THIN database. Patients that were alive or withdrew from the primary care practice were censored from analysis at the date of last follow-up.

Statistical Analysis

The analyses for both HbA1C and glucose levels were performed using univariate and multivariable Cox regression model to calculate hazard ratio (HRs) and 95% confidence intervals (CIs) for overall survival. The analyses included only individuals with HbA1C or glucose measurements within the 6 months prior to cancer diagnosis. Separate multivariable Cox regression analyses were performed for each cancer. HbA1C and glucose concentration were included as continuous variables and hazard ratios are reported for 1 unit and 1mmol/L increase, respectively. Each analysis was adjusted for all known cancer-specific risk factors, as well as for variables of the metabolic syndrome. For CRC we adjusted for obesity, ever smoking, alcohol consumption, coronary artery disease (CAD), hypertension, hyperlipidemia, chronic NSAIDs/aspirin use and hormone replacement therapy; for breast cancer we adjusted for obesity, ever smoking, alcohol consumption, CAD, hypertension, hyperlipidemia and hormone replacement therapy; for bladder cancer we adjusted for obesity, ever smoking, CAD, hypertension, hyperlipidemia, chronic NSAIDs/aspirin use, and oral anti-diabetes medications other than metformin; for pancreatic cancer we adjusted for obesity, ever smoking, CAD, hypertension and hyperlipidemia; and for prostate cancer we adjusted for obesity, ever smoking, CAD, hypertension, and hyperlipidemia. In a subgroup analysis we evaluated in each cohort only diabetes patients that were treated with insulin at the time of cancer diagnosis. Since insulin therapy is associated with cancer risk (22) and glucose levels, this analyses allowed us to assess for possible confounding and to evaluate diabetes patients with similar disease severity and treatment. Additionally, we performed a secondary analysis looking at survival in a cohort of patients who died within 5 years after cancer diagnosis. All p-values were two-sided, and p-values < 0.05 were considered significant. For each model we also evaluated for collinearity between variables. All analyses were performed using STATA 13 (Stata Corp., College Station, Tx, USA).

Results

Our study cohorts included 7,916 individuals with diabetes, incident colorectal, breast, prostate, bladder or pancreatic cancers and either glucose or HbA1C levels within 6 months prior to cancer diagnosis. The characteristics of the study population are presented in Table 1.

There was no association between HbA1C levels measured during the 6 months prior to cancer diagnosis and overall survival for colorectal (HR 1.00, 95%CI 0.95-1.06), breast (HR 1.03, 95%CI 0.95-1.11), pancreatic (HR 0.98, 95%CI 0.94-1.02) and prostate (HR 1.02, 95%CI 0.96-1.01) cancers, however there was a nearly significant increase in survival for bladder cancer with higher HbA1C levels (HR 0.93, 95%CI 0.86-1.01). Similar results were observed for the subgroup of patients treated with insulin (Table 2).

In addition, there was no association between glucose levels and overall survival for colorectal (HR 1.01, 95%CI 0.98-1.04), breast (HR 1.00, 95%CI 0.96-1.04), bladder (HR 0.97, 95%CI 0.94-1.01), pancreatic (HR 1.01, 95%CI 0.99-1.04) and prostate cancers (HR 1.03, 95%CI 0.99-1.05). Among diabetes patients treated with insulin there was increased survival with higher glucose levels for bladder and prostate cancers with HRs of 0.91 (95%CI 0.84-0.99) and 0.95 (95%CI 0.88-1.02) respectively (Table 3).

In a secondary analysis of cancer patients with death within 5 years of diagnosis, as a surrogate for cancer-specific mortality, there was no association between HbA1C and glucose levels measured within 6 months prior to diagnosis and survival (Tables 4, 5). Among patients treated with insulin there was a slightly lower risk of death with higher glucose levels for bladder, colorectal and prostate cancers with HRs of 0.88 (95%CI 0.79-0.99), 0.93 (95%CI 0.86-1.02) and 0.96 (95%CI 0.85-1.08) respectively (Table 5).

Discussion

Although patients with concurrent diabetes and cancer are frequently encountered in the clinic it is unknown whether and how glycemic control impact cancer prognosis. The current large population-representative study evaluated the association between glycemic control and survival in five diabetes associated malignancies (colorectal, breast, bladder, pancreatic and prostate cancers). HbA1C levels were not associated with survival among patients with cancer and concurrent diabetes. There was also no association between glucose levels and survival in patients with those malignancies. Moreover, when survival was analyzed only among individuals who died within 5 years of cancer diagnosis there was no effect for HbA1C and glucose levels on disease outcome. In a subgroup analysis of diabetes patients treated with insulin there was decreased risk of death with higher glucose levels in patients with bladder and prostate cancers (HRs 0.91 and 0.95, respectively).

While the literature regarding glycemic control and cardiovascular outcome in diabetes patients is abundant with large randomized controlled trials, such as the United Kingdom Prospective Diabetes Study (UKPDS) and the Veteran Affairs Diabetes Trial (VADT) (36-38), only limited number of studies evaluated the effect of glucose and glycemic control on cancer outcome (29). Most studies focused on the pharmacological effects of anti-

diabetic medications commonly used, mainly metformin, on tumor formation and progression, however those effects are not necessarily mediated through glycemic control but rather through other genetic pathways, such as the PI3K/AKT/mTOR pathway (39,40).

The Emerging Risk Factors Collaboration (ERFC) study evaluated the association between glucose level categories and non-cardiovascular outcome, including cancer related death, among subjects with and without diabetes (29). This ERFC analysis included information from 97 different prospective studies where glucose levels were measured at baseline and reported HR of 1.05 (95%CI 1.03-1.06) for every 1mmol/L increase in glucose levels above 5.6 mmol/L and cancer death. However, the glucose measurements were not conducted near cancer diagnosis and thus do not reflect the levels of glycemic control at that time. It is possible that those measurements are more relevant for assessing cancer risk rather than outcome. In addition, because the study looked at all cancer related deaths instead of death from specific types of cancer, there was no adjustment for cancer-specific risk factors.

In contrast to the ERFC study, the current study focused on diabetes patients, a population with frequent measures of glycemic control. Analyzing the IQR of glucose levels in the current cohorts compared to non-diabetes cancer patients with glucose levels in the THIN database showed larger variability among the diabetes patients (4.8-6.0mmol/l among those without diabetes compared to 6.5-11.4mmol/l among diabetes patients), moreover, this variability was observed in the range that was previously shown to be associated with specific mortality from cancer and other non-vascular conditions-(>5.6 mmol/l) (29).

The improved survival that we observed with increasing glucose or HbA1C levels among insulin treated patients with bladder cancer could be a consequence of endogenous hypoinsulinemia with more advanced diabetes. Circulating concentrations of insulin-like growth factor (IGF) and certain insulin-like growth factor binding proteins (IGFBP) are associated with higher risk and worse outcome among patients with bladder, as well as colorectal, prostate and breast cancers (41). Thus, it is possible that patients with worse glycemic control had lower levels of insulin in the serum and thus improved prognosis. This hypothesis should be directly tested in future studies.

The main strengths of our study included the use of a population representative primary care database with valid data on medical diagnoses including diabetes and cancer, medication prescriptions, lab values, and cancer specific risk factor (such as chronic use of NSAIDs for colorectal cancer and hormone replacement therapy for breast cancer). Additionally, the study had relatively long duration of follow-up, allowing analysis of only incidence cancer cases diagnosed more than six months after registration with a THIN practice site as well as analysis of most deaths due to cancer. Finally, lab values were available 6 months prior to cancer diagnosis, thus allowing measurement of glycemic control at the time of diagnosis.

Cancer diagnoses were based on Read codes and not an actual pathologic reports. Although the validity and completeness of THIN for cancer research was previously demonstrated (31,33-35), we lacked information regarding histopathology and disease stage. Data presented in Table 1 describing the median survival of patients in each cancer cohort further support the accuracy of diagnosis. For example the median survival shown for pancreatic

cancer patients was 0.4 years identical to the known survival in patients with pancreatic adenocarcinoma and shorter than the survival in other pancreatic malignancies, such as neuroendocrine tumors. THIN does not have data on several known factors associated with disease prognosis, such as hormone receptor status in breast cancer patients, as well as suspected prognostic factors, such as insulin levels in the serum. Additionally, THIN does not include detailed information regarding cancer specific therapies. However, if treatment was in any way related to pre-diagnosis glycemic control, those patients with less good glycemic control would likely be treated less aggressively for their cancer. As such, lack of adjustment for cancer treatment is unlikely to have masked a true association between poor glycemic control and cancer-related mortality.

Socioeconomic status might be associated with both worse glycemic control and shorter survival among cancer patients. We repeated the analysis with adjustment to Townsend deprivation score and observed no change in results although the confidence intervals were larger. To the extent that the Townsend deprivation score captures socioeconomic status, if socioeconomic status was indeed a significant confounder in the current context, we would have expected to observe a noticeable difference in these estimates before and after adjusting for the Townsend score. The fact that there was virtually no difference observed would indicate that socioeconomic status was unlikely to be a significant confounding factor.

Similar to previous studies, we used a single HbA1C measurement at the time of diagnosis in order to assess glycemic control (29). While in a previous study from our group (27) we evaluated longitudinal HbA1C measures and colorectal cancer risk, in the current study, since glucose levels change with cancer therapies and as a function of disease stage and performance status (i.e. septic episodes in advanced cancers) we decided to use only levels prior to treatment initiation. In addition, a single HbA1C level reflects the glycemic control in the 3 months prior to the test date. Of note, no difference was observed in our results between the analyses according to glucose levels and the analyses according to HbA1C.

While HbA1C levels do not require fasting and reflect glycemic control in the 3 months prior to the test, for most glucose levels there was no information in THIN specifying whether the test was performed during fasting. An analysis of median glucose levels among cancer patients without diabetes support the assumption that most of the tests were performed during fasting with median values below 5.6 mmol/l for CRC (median 5.4, IQR 4.9-6.2), breast (median 5.2, IQR 4.7-5.8), bladder (median 5.3, IQR 4.8-6.0) and prostate (median 5.3, IQR 4.8-5.9).

Finally, because THIN does not capture cause-specific mortality, we conducted an analysis among patients with cancer diagnosis and subsequent death within 5 years. We used death within 5 years as a surrogate for cancer-specific mortality based on literature that only 10-20% of metastatic cancer patients survive 5 years. We did not have information regarding additional cancer related outcomes such as response to therapy, disease recurrence and disease free survival.

In summary, this study focused on a commonly held belief promulgated in the lay press that glucose “feeds” cancer. This concept, although not supported by scientific data, often leads

to major changes in the patients' lifestyle as well as considerable stress. The idea possibly originated from the Warburg effect that described the dependency of most cancer cells on aerobic glycolysis (23,24) and from the numerous studies describing the association between diabetes and cancer risk (3-8). In the current study, higher glucose and HbA1C levels were not associated with worse survival among cancer patients with concurrent diabetes. Moreover, in diabetic cancer patients treated with insulin, higher glucose levels were associated with better outcome, mainly in bladder cancer patients, possibly related to insulin levels. These results do not support a detrimental effect of glucose on cancer outcome and do not justify patients making major changes in their diet or diabetes treatment following cancer diagnosis. Future trials are needed in order to evaluate the effect of tight glycemic control in diabetic cancer patient specifically the association between insulin levels and cancer specific outcomes.

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Highlights

- Many patients believe that glucose “feeds” cancer and might affect disease outcome.
- We evaluated the effect of glycemic control on survival of cancer patients with DM.
- Higher glucose and HbA1C levels were not associated with worse survival.
- In patients treated with insulin, higher glucose was associated with better outcome.
- These results do not justify tight glycemic control following cancer diagnosis.

Table 1
characteristics of patients with incidence cancer and concurrent diabetes with either HbA1C or glucose levels 6 months prior to cancer diagnosis

Tumor type (n)	Age Mean ($\pm$ SD)	Sex N(%) male	Obesity (BMI>30) N(%)	Smoking (ever) N(%)	Median survival Yrs (IQR)
Colorectal cancer n=2,070	73.3 ($\pm$ 8.8)	1,297 (62.7)	982 (47.4)	1,333 (64.4)	2.5 (0.9-5.2)
Breast cancer n=1,530	70.8 ($\pm$ 11.2)	NA	825 (53.9)	745 (48.7)	3.6 (1.8-6.5)
Bladder cancer n=1,325	73.4 ($\pm$ 9.0)	1,077 (81.3)	591 (44.6)	962 (72.6%)	3.2 (1.3-6.1)
Pancreatic cancer n=752	72.4 ($\pm$ 10.0)	398 (52.9)	299 (39.8)	476 (63.3)	0.4 (0.1-1.2)
Prostate cancer n=2,239	73.8 ($\pm$ 8.1)	NA	929 (41.5)	1,484 (66.3)	3.4 (1.6-6.1)

Table 2
Association between HbA1C levels at cancer diagnosis and overall survival in cancer cases with diabetes

Tumor type	Total N	N(%) death	Incidence rate Per 1000 person years	Median HbA1C (IQR 25%-75%)	Unadjusted HR [†] (95% CI)	Adjusted HR ^{**} (95% CI)
Colorectal cancer						
All cancer patients with diabetes	1,850	769 (41.6)	119 (111-128)	7.0 (6.4-7.9)	1.02 (0.97-1.07)	1.00 (0.95-1.06)
All cancer patients with diabetes and insulin treatment	296	129 (43.6)	119 (100-141)	8.1 (7.2-9.1)	1.01 (0.90-1.13)	0.99 (0.88-1.11)
Breast cancer						
All cancer patients with diabetes	1,382	332 (24.0)	54 (49-60)	7.1 (6.4-8.0)	1.04 (0.97-1.12)	1.03 (0.95-1.11)
All cancer patients with diabetes and insulin treatment	240	62 (25.8)	55 (43-71)	8.2 (7.4-9.0)	1.06 (0.89-1.25)	1.05 (0.88-1.25)
Bladder cancer						
All cancer patients with diabetes	1,168	403 (34.5)	84 (76-92)	7.1 (6.4-8.0)	1.00 (0.93-1.07)	0.94 (0.86-1.01)
All cancer patients with diabetes and insulin treatment	194	76 (39.2)	97 (78-121)	8.1 (7.2-9.3)	0.94 (0.82-1.09)	0.91 (0.78-1.06)
Pancreatic cancer						
All cancer patients with diabetes	634	519 (81.9)	681 (625-742)	8.0 (6.9-9.8)	0.98 (0.94-1.02)	0.98 (0.94-1.02)
All cancer patients with diabetes and insulin treatment	142	113 (79.6)	658 (547-791)	8.7 (7.5-10.1)	0.99 (0.91-1.08)	0.98 (0.90-1.07)
Prostate cancer						
All cancer patients with diabetes	1,994	564 (28.3)	67 (62-73)	6.9 (6.3-7.7)	1.02 (0.96-1.09)	1.02 (0.96-1.08)
All cancer patients with diabetes and insulin treatment	295	88 (29.8)	72 (58-89)	7.8 (7.1-9.0)	0.91 (0.78-1.06)	0.91 (0.78-1.07)

[†] HR was calculated per 1 unit increase in HbA1C levels.

^{*} Adjustment to age and sex only.

^{**} For CRC adjustment for obesity, smoking history, alcohol consumption, coronary artery disease (CAD), hypertension, hyperlipidemia, chronic NSAIDs/aspirin use and hormone replacement therapy. For breast cancer adjustment for obesity, smoking history, alcohol consumption, CAD, hypertension, hyperlipidemia and hormone replacement therapy. For bladder cancer adjustment for obesity, smoking history, CAD, hypertension, hyperlipidemia, chronic NSAIDs/aspirin use, and oral anti-diabetes medications other than metformin. For pancreatic cancer adjustment for obesity, smoking history, CAD, hypertension and hyperlipidemia. For prostate cancer adjustment for obesity, smoking history, CAD, hypertension, and hyperlipidemia.

Table 3
Association between glucose levels at cancer diagnosis and overall survival among patients with diabetes

Tumor type	Total N	N(%) death	Incidence rate Per 1000 person years	Median glucose [†] (IQR 25%-75%)	Unadjusted HR [§] (95% CI)	Adjusted HR ^{**} (95% CI)
Colorectal cancer						
All cancer patients with diabetes	1,118	460 (41.1)	111 (102-122)	8.4 (6.5-11.1)	1.01 (0.98-1.04)	1.01 (0.98-1.04)
All cancer patients with diabetes and insulin treatment	163	62 (38.0)	93 (72-119)	11 (7.3-13.5)	0.97 (0.91-1.03)	0.98 (0.92-1.04)
Breast cancer						
All cancer patients with diabetes	744	193 (25.9)	56 (48-64)	8.3 (6.4-11.2)	1.00 (0.96-1.04)	1.00 (0.96-1.04)
All cancer patients with diabetes and insulin treatment	101	32 (31.7)	61 (43-86)	11 (8.2-14.3)	0.96 (0.87-1.05)	0.99 (0.90-1.09)
Bladder cancer						
All cancer patients with diabetes	688	255 (37.1)	90 (80-102)	8.2 (6.4-11.0)	1.00 (0.96-1.03)	0.97 (0.94-1.01)
All cancer patients with diabetes and insulin treatment	91	35 (38.5)	108 (78-151)	11 (7.0-14.3)	0.93 (0.86-1.00)	0.91 (0.84-0.99)
Pancreatic cancer						
All cancer patients with diabetes	470	374 (80.0)	574 (518-635)	11 (7.8-14.6)	1.01 (0.99-1.04)	1.01 (0.99-1.04)
All cancer patients with diabetes and insulin treatment	87	63 (72.4)	446 (349-571)	11 (7.9-16)	1.06 (1.00-1.12)	1.05 (0.99-1.12)
Prostate cancer						
All cancer patients with diabetes	1,258	384 (30.5)	71 (65-79)	8.1 (6.4-11.1)	1.03 (0.99-1.05)	1.03 (0.99-1.05)
All cancer patients with diabetes and insulin treatment	160	46 (28.8)	72 (54-96)	10 (7.6-13.9)	0.95 (0.88-1.02)	0.95 (0.88-1.02)

[†] 1 mmol/l = 18 mg/dl.

[§] HR was calculated per 1 mmol/L increase in glucose levels.

* Adjustment to age and sex only.

** Adjustment as described in table 2.

Table 4
Association between HbA1C levels at cancer diagnosis and overall survival among patients who died within 5 years of diagnosis

Tumor type	Total N	Median glucose [†] (IQR 25%-75%)	Unadjusted HR ^{§*} (95% CI)	Adjusted HR ^{**} (95% CI)
Colorectal cancer				
All cancer patients with diabetes	724	7.0 (6.4-7.8)	1.03 (0.98-1.09)	1.01 (0.96-1.07)
All cancer patients with diabetes and insulin treatment	117	8.1 (7.1-9.0)	1.04 (0.91-1.19)	1.03 (0.90-1.18)
Breast cancer				
All cancer patients with diabetes	282	7.0 (6.3-8.0)	0.95 (0.89-1.02)	0.95 (0.88-1.02)
All cancer patients with diabetes and insulin treatment	50	8.2 (7.2-9.4)	1.02 (0.83-1.27)	1.05 (0.85-1.31)
Bladder cancer				
All cancer patients with diabetes	349	7.1 (6.4-7.9)	1.06 (0.98-1.15)	1.05 (0.96-1.16)
All cancer patients with diabetes and insulin treatment	65	7.9 (6.9-9.0)	1.04 (0.88-1.23)	0.97 (0.80-1.18)
Pancreatic cancer				
All cancer patients with diabetes	517	8.0 (6.9-9.7)	1.01 (0.97-1.05)	1.01 (0.97-1.05)
All cancer patients with diabetes and insulin treatment	113	8.7 (7.5-10.0)	1.00 (0.92-1.10)	1.00 (0.92-1.10)
Prostate cancer				
All cancer patients with diabetes	472	6.8 (6.3-7.7)	0.97 (0.91-1.03)	0.97 (0.91-1.03)
All cancer patients with diabetes and insulin treatment	69	7.8 (7.0-8.8)	0.96 (0.81-1.14)	0.98 (0.82-1.17)

[†] 1 mmol/l = 18 mg/dl.

[§] HR was calculated per 1 mmol/L increase in glucose levels.

* Adjustment to age and sex only.

** Adjustment as described in table 2.

Table 5
Association between glucose levels at cancer diagnosis and overall survival among patients who died within 5 years of diagnosis

Tumor type	Total N	Median glucose [†] (IQR 25%-75%)	Unadjusted HR ^{§*} (95% CI)	Adjusted HR ^{**} (95% CI)
Colorectal cancer				
All cancer patients with diabetes	429	8.4 (6.4-11.2)	1.01 (0.99-1.05)	1.02 (0.99-1.05)
All cancer patients with diabetes and insulin treatment	55 (12.8%)	9.9 (6.1-12.9)	0.94 (0.87-1.01)	0.93 (0.86-1.02)
Breast cancer				
All cancer patients with diabetes	165	8.5 (6.7-11.0)	0.99 (0.95-1.04)	0.99 (0.94-1.04)
All cancer patients with diabetes and insulin treatment	25 (15.2%)	9.9 (7.8-12.6)	0.99 (0.89-1.10)	0.97 (0.82-1.14)
Bladder cancer				
All cancer patients with diabetes	221	8.3 (6.5-11.0)	1.00 (0.96-1.04)	1.00 (0.96-1.04)
All cancer patients with diabetes and insulin treatment	33 (14.9%)	9.8 (6.8-14.3)	0.97 (0.89-1.06)	0.88 (0.79-0.99)
Pancreatic cancer				
All cancer patients with diabetes	372	11 (7.9-14.6)	1.01 (0.99-1.04)	1.02 (0.99-1.04)
All cancer patients with diabetes and insulin treatment	63 (16.9%)	12 (8.8-16.3)	1.03 (0.97-1.09)	1.01 (0.95-1.07)
Prostate cancer				
All cancer patients with diabetes	314	8.5 (6.6-11.3)	1.00 (0.97-1.03)	1.01 (0.97-1.04)
All cancer patients with diabetes and insulin treatment	38 (12.1%)	11 (7.6-13.1)	0.95 (0.86-1.04)	0.96 (0.85-1.08)

[†] 1 mmol/l = 18 mg/dl.

[§] HR was calculated per 1 mmol/L increase in glucose levels.

* Adjustment to age and sex only.

** Adjustment as described in table 2.