

RESEARCH

Malignancy incidences by glycemic control among diabetic patients

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Abstract

Background: The aim of this study was to evaluate the difference in malignancy incidence by evaluating time-dependent HbA1c levels among diabetic patients in a longitudinal study.

Methods: We conducted a retrospective longitudinal study at large academic hospital, Tokyo, Japan, from 2006 to 2016. We included all diabetic patients who were 50 years or older and who underwent health check-ups at the Center for Preventive Medicine. Those patients with a prior history of malignancies were excluded. We categorized patients into five groups on the basis of HbA1c measurements: <5.4, 5.5–6.4, 6.5–7.4, 7.5–8.5, >8.5%. Our primary outcome was the development of any types of malignancy. Longitudinal analyses by a mixed effect model with time-dependent HbA1c levels were applied in order to take into account fluctuations in HbA1c levels within the same patient.

Results: In total, 2729 participants were included in this study, where the mean age was 62.6 (standard deviation (s.d.): 7.8) and 2031 (74.4%) were male. The mean disease duration of diabetes was 7.6 (s.d.: 7.6) years, and 1688 (61.8%) were prescribed medications. Median follow-up was 1443.5 (interquartile range (IQR): 2508) days and 376 (13.8%) developed malignancies. Compared to the reference range of HbA1c (5.5–6.4%), the odds ratios for developing malignancies among the other HbA1c level groups were similar and not statistically different (OR: 0.98, 95% CI: 0.31–3.15 (for HbA1c <5.4%); OR: 0.88, 95% CI: 0.69–1.12 (for HbA1c 6.5–7.4%); OR: 0.88, 95% CI: 0.64–1.22 (for HbA1c 7.5–8.4%); OR 1.07, 95% CI: 0.70–1.66 (for HbA1c >8.5%)).

Conclusion: In our study, there was no association between glycemic control and the development of future malignancies. Compared to very strictly controlled HbA1c levels, both excessive control and good or bad control had a statistically similar risk of developing malignancies.

Key Words

- ▶ diabetes
- ▶ glycemic control
- ▶ malignancy
- ▶ longitudinal analysis

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Introduction

Previous systematic reviews and meta-analyses have reported that diabetic patients have a higher risk of developing malignancies compared to nondiabetic patients (1, 2, 3, 4). Based on these reports, diabetic patients may have an approximately 20% increased risk of developing

any type of cancer (3). Among diabetic patients, risk was reported for each type of cancer. For instance, previous studies have reported a higher risk of colon cancer (hazard ratio (HR): 1.40), hepatocellular carcinoma (HR: 1.97), pancreatic cancer (HR: 1.85) and cholangiocarcinoma

(HR: 1.66) (3, 5, 6, 7, 8). Other malignancies, such as esophageal cancer, gastric cancer or lung cancer, may have no association with diabetes (9, 10, 11). In contrast, specific cancers, such as prostate cancer, have been reported to have an inverse relationship to diabetes (12, 13). Thus, this previous research suggests that there could be certain associations between diabetes and malignancies.

Although the association of diabetes with malignancies among diabetic patients compared to nondiabetic patients has been well evaluated, the differences in the incidence of malignancies among diabetic patients in terms of the level of glycemic control are still controversial. Previous meta-analyses and systematic reviews, which included four randomized control trials (14, 15, 16, 17), reported no difference in malignancy development between intensively treated and standardly treated diabetic patients, even in subanalyses (18). These randomized control trials may have several limitations: malignancies were not the primary outcomes, they were unblinded and there was insufficient follow-up. In contrast, some observational studies have reported that diabetic patients who had higher hemoglobin A1c (HbA1c) levels had higher incidence rates of malignancies compared to those who had lower HbA1c levels (19, 20, 21, 22). In addition to the controversy regarding the association of glycemic control with malignancies based on previous reports, these studies did not take into account the changes in glycemic control. In other words, HbA1c levels can fluctuate over time in the same person, so a single measurement of HbA1c levels would be insufficient to evaluate the true association between glycemic control and the development of malignancies. Moreover, no previous study has evaluated the effect of excessive glycemic control, such as an HbA1c level of 5.5% or lower, on the development of malignancies.

The generalized linear model (GML) is a statistical technique that can address repeated measures. As a result, we can measure the effect of treatment/exposure at different time points. Recently, this technique has been applied in many clinical research studies for repeated measurements (23). By using this technique, we can consider the true effect of fluctuating glycemic control on the development of malignancies.

The aim of this study is to evaluate the difference in malignancy incidence by time-dependent HbA1c levels among diabetic patients.

Methods

We conducted a retrospective longitudinal study at St. Luke's International Hospital, Tokyo, Japan,

from 2006 to 2016. We included diabetic patients who were 50 years or older male and female and who underwent voluntary health check-ups at the Center for Preventive Medicine at the hospital at baseline. Diabetic patients were defined as those who reported being diagnosed with diabetes prior to the hospital visits or who were treated for diabetes at the hospital. These patients also reported their disease duration and the prescriptions they took for diabetes. We included patients if they were diagnosed as diabetes at baseline and did not exclude them due to short or long duration of disease. Those patients who had histories of malignancies prior to their first visit were excluded. However, there were no other exclusion criteria, such as risk factors. We compared the incidence of future malignancies using hemoglobin A1c levels as a longitudinal measure of glycemic control. All data were extracted from electronic medical records.

The St Luke's International Hospital Ethics Committee Institutional Review Board (IRB) approved this study (17-R022). The IRB waived to obtain written consent from each patient, because this study was a retrospective design. However, we excluded all patients who signed opt out agreements for their anonymized data to be used in research.

Hemoglobin A1c measurement

Hemoglobin A1c (HbA1c) was measured for all participants as a part of their health check-ups at each visit. HbA1c, which was measured by Japanese diabetes society values, was converted to that of the National Glycohemoglobin Standardization Program value (24). We categorized each HbA1c measurement into five groups: <5.4, 5.5–6.4, 6.5–7.4, 7.5–8.5 and >8.5% (25). We considered 5.5–6.4% of HbA1c as the reference group. Because HbA1c levels fluctuate over time in each patient, we applied longitudinal analyses with HbA1c levels as the time-dependent variable to take into account the change in HbA1c levels over time. The HbA1c measurement interval differed for each participant, with most participants revisited from 6 months to 2 years later.

Malignancy

The development of any malignancies, which were coded C00-D49 by the International Classification of Diseases (ICD)-10, was included as the primary outcome (26). Malignancy was diagnosed by a physician based on both clinical and pathological findings in the hospital. In addition to the diagnosis at the hospital, we obtained

information about those malignancies that were diagnosed in other hospitals based on participants' reports. For those patients who developed malignancies multiple times, only information about the first malignancy was used for analysis.

Data collection

We obtained information about patients' demographics and health habits based on self-reporting as a part of the health check-ups. In terms of alcohol use, we divided the participants into three categories: abstainers, social drinkers and regular drinkers. Smoking status was categorized into never, former and current. Exercise was also divided into four categories: almost none, 2–3 times a week, 4–5 times a week and almost all days.

Statistical methods

We conducted cross-sectional analyses of participants' characteristics at the first visit for each participant by baseline HbA1c category. Chi-square tests were applied to categorical variables, and analysis of variance was used for continuous variables. Then, longitudinal analyses were performed with the data from 2006 to 2016 to investigate the longitudinal association between HbA1c levels and the future development of malignancies. Adjusted odds ratios for future malignancies were obtained with the model of the binomial family with the logit link function. To account for repeated measurements of participants and random effects of observations, we applied a mixed effect model with an unstructured working correlation. To take changes in HbA1c category over time into consideration, we used HbA1c levels as time-dependent variables in the longitudinal analyses. Two sensitivity analyses were conducted to confirm the results by applying different covariates to the models and focusing on those patients who developed malignancies 2 years after their first visit. In the sensitivity analysis, by applying different covariates, we included HbA1c category and patients' demographics in model 1, patients' diabetes disease duration and treatment status were added to model 2 in addition to model 1 variables, health habits were added to model 3 in addition to model 1 variables and all the above variables were included in model 4. In the sensitivity analysis, by focusing on those patients who developed malignancies 2 years after their first visit, we excluded those patients who developed malignancies within 2 years after their first visit from the analyses in order to exclude asymptomatic cancer, which was pre-existing but had not been detected at the first visit.

All analyses were performed in 2018 using SPSS 24.0J statistical software (IBM Japan) and STATA 14 (STATA Corp.).

Results

In total, 2729 participants were included in this study, where the mean age was 62.6 (standard deviation (s.d.): 7.8) and 2031 (74.4%) were male. The mean disease duration of diabetes was 7.6 (s.d.: 7.6) years, and 1688 (61.8%) were prescribed medications (Table 1). At baseline, the proportion of males to females was higher among those with very low (less than 5.4%) or high (7.5% or more) HbA1c levels than among those with middle (5.5–7.4%) HbA1c levels. The mean disease duration of diabetes was longer among those with very low (less than 5.4%) or high (7.5% or more) HbA1c levels than among those with middle (5.5–7.4%) HbA1c levels. Those with very low HbA1c level were more regular drinkers and current smokers; they also exercised less.

The median follow-up was 1443.5 (interquartile range (IQR): 2508) days, and the median number of health check-ups was 4.0 (IQR: 6.0) times. During follow-up, 376 (13.8%) developed malignancies. Of these malignancies, 88 (23.4%) were prostate cancer, followed by 68 (18.1%) were gastric cancer and 40 (10.6%) were lung cancer. Table 2 shows the list of all malignancies. Table 3 shows the results from the mixed-effect model and sensitivity analyses. Compared to the reference range of HbA1c (5.5–6.4%), the odds ratios for developing malignancies among the other HbA1c level groups were similar and not statistically different (in model 1, OR: 0.98, 95% CI: 0.31–3.15 among those with HbA1c levels <5.4%; OR: 0.88, 95% CI: 0.69–1.12 among those with HbA1c levels of 6.5–7.4%; OR: 0.88, 95% CI: 0.64–1.22 among those with HbA1c levels of 7.5–8.4%; OR 1.07, 95% CI: 0.70–1.66 among those with HbA1c levels >8.5%).

In the sensitivity analyses with different covariates, all odds ratios of other HbA1c categories were not significantly different from the reference category (the range of ORs: 0.98–1.01 among those with HbA1c levels <5.4%; the range of ORs: 0.88–0.90 among those with HbA1c levels of 6.5–7.4%; the range of ORs: 0.88–0.92 among those with HbA1c levels of 7.5–8.4%; the range of ORs: 1.07–1.12 among those with HbA1c levels >8.5%). In the sensitivity analyses excluding those who developed malignancies within 2 years after their first visit ($n=123$), all HbA1c categories had similar odds for developing malignancies comparing to the reference category.

Table 1 Patients' baseline characteristics by hemoglobin A1c category.

	Categories by hemoglobin A1c level (%)					P value
	<5.4 (n=36)	5.5–6.4 (n=831)	6.5–7.4 (n=1121)	7.5–8.4 (n=489)	>8.5 (n=251)	
Patients' demographics						
Age, years mean (s.d.)	61.3 (6.5)	62.7 (7.9)	63.1 (8.0)	62.2 (7.6)	61.3 (7.8)	0.41
Male, n (%)	28 (77.8)	597 (71.8)	821 (73.2)	391 (80.0)	193 (76.9)	0.01
Body mass index, kg/m ² (s.d.)	23.1 (3.2)	23.8 (3.7)	24.2 (3.7)	24.7 (3.8)	25.0 (3.7)	0.71
Diabetes						
Prescription, n (%)	21 (58.3)	363 (43.7)	730 (65.1)	374 (76.5)	199 (79.3)	<0.01
Disease duration, years mean (s.d.)	8.0 (11.4)	5.5 (6.4)	7.8 (7.7)	9.5 (8.1)	9.6 (7.8)	<0.01
Health habits, n (%)						
Alcohol use						
Abstainer	15 (41.7)	325 (39.1)	497 (44.3)	198 (40.5)	109 (43.4)	<0.01
Social drinker	2 (5.6)	118 (14.2)	171 (15.2)	87 (17.8)	53 (21.1)	
Regular drinker	19 (52.8)	388 (46.7)	454 (40.5)	204 (41.7)	89 (35.5)	
Smoking status						
Never	18 (50.0)	377 (45.4)	477 (42.5)	180 (36.8)	84 (33.5)	<0.01
Former	10 (27.8)	336 (40.4)	466 (41.5)	206 (42.1)	103 (41.0)	
Current	8 (22.2)	118 (14.2)	179 (16.0)	103 (21.1)	64 (25.5)	
Exercise						
Almost none	7 (19.4)	163 (19.6)	265 (23.6)	115 (23.5)	81 (32.3)	<0.01
2–3 times a week	11 (30.6)	258 (31.1)	347 (30.9)	157 (32.1)	84 (33.5)	
4–5 times a week	11 (30.6)	218 (26.2)	250 (22.3)	128 (26.2)	49 (19.5)	
Almost all days	7 (19.4)	192 (23.1)	260 (23.2)	89 (18.2)	37 (14.7)	

s.d., standard deviation.

Table 2 The list of all malignancies developed in the study period.

Malignancy	Number of patients	Percentage
Prostate cancer	88	23.4
Gastric cancer	68	18.1
Lung cancer	40	10.6
Colorectal cancer	38	10.1
Esophagus cancer	30	8
Breast cancer	21	5.6
Bladder and ureteral cancer	18	4.8
Liver cancer	14	3.7
Others	14	3.7
Pancreatic cancer	8	2.1
Kidney cancer	7	1.9
Lymphoma	6	1.6
Skin cancer	6	1.6
Bile duct and gallbladder cancer	4	1.1
Leukemia	4	1.1
Cervical cancer	3	0.8
Mediastinal neoplasm	2	0.5
Duodenal cancer	2	0.5
Endometrial cancer	1	0.3
Thyroid cancer	1	0.3
Ovarian cancer	1	0.3

Discussion

In our longitudinal study, we demonstrated that the incidence of malignancies was not associated with glycemic control among middle-aged and elderly diabetic patients. Sensitivity analyses with different covariates supported this result. This result is supported by the findings of previous randomized control trials but contradicts the findings of previous observational studies. This discrepancy may come from the difference of inclusion/exclusion criteria and duration of disease between our study and others. Moreover, our study shows that even those patients with excessively low HbA1c may have a risk of developing malignancies similar to those patients with good HbA1c control, a finding that has not been evaluated in previous studies.

The mechanisms by which there is no association between glycemic control and future malignancy was unclear. Previous studies that have investigated the association of glycemic control with the development of malignancies among diabetic patients did not discuss the mechanisms for positive or no association (14, 15, 16). Several studies focusing on the association between diabetes and malignancies have advanced possible mechanisms. One possibility is that *H. pylori* infection may play an important role as a cofactor for diabetes and the development of gastric cancer (27). Although the



Table 3 The adjusted odds ratios for developing malignancies by hemoglobin A1c category from longitudinal analyses using a mixed effect model and two sensitivity analyses ($n=2729$, total number of hemoglobin A1c measurements= 14,179 for the analyses with all participants; $n=2606$ total number of hemoglobin A1c measurements=13,894 for the analyses excluding those who developed malignancies within two years after their first visit).

Hemoglobin A1c, % (No. of measurements, %)	Adjusted odds ratios for the development of malignancies (95% confidence interval)			
	Model 1	Model 2	Model 3	Model 4
All participants				
<5.4 (132, 0.9%)	0.98 (0.31–3.15)	0.99 (0.31–3.19)	0.99 (0.31–3.19)	1.01 (0.32–3.24)
5.5–6.4 (4174, 29.4%)	Reference			
6.5–7.4 (6488, 45.8%)	0.88 (0.69–1.12)	0.90 (0.70–1.16)	0.88 (0.69–1.13)	0.90 (0.70–1.16)
7.5–8.4 (2364, 16.7%)	0.88 (0.64–1.22)	0.92 (0.66–1.29)	0.89 (0.64–1.23)	0.92 (0.66–1.30)
>8.5 (1021, 7.2%)	1.07 (0.70–1.66)	1.12 (0.72–1.76)	1.05 (0.68–1.63)	1.10 (0.70–1.73)
Excluding those who developed malignancies within two years after their first visit				
<5.4 (127, 0.9%)	0.57 (0.07–4.43)	0.59 (0.08–4.63)	0.55 (0.07–4.30)	0.58 (0.07–4.53)
5.5–6.4 (4085, 29.4%)	Reference			
6.5–7.4 (6369, 45.8%)	0.86 (0.63–1.19)	0.92 (0.66–1.28)	0.87 (0.63–1.20)	0.92 (0.66–1.28)
7.5–8.4 (2319, 16.7%)	0.89 (0.58–1.36)	0.98 (0.63–1.53)	0.89 (0.58–1.37)	0.98 (0.63–1.53)
>8.5 (994, 7.2%)	0.97 (0.52–1.82)	1.11 (0.59–2.09)	0.96 (0.51–1.81)	1.09 (0.57–2.07)

Model 1 included a time variable and patients' demographic information, such as age and gender, for adjustment. Model 2 included information about diabetes, such as duration of disease and prescriptions, for adjustment in addition to model 1. Model 3 included health habits, such as alcohol use, smoking status, exercise and body mass index, for adjustment in addition to model 1. Model 4 included all the above for adjustments.

prevalence of *H. pylori* infection was higher among diabetic patients than among nondiabetic patients, there was no difference in the regulation of diabetes (28). Therefore, there was no difference in malignancy development between glycemic control groups. Another possible mechanism is a hormonal effect on the development of malignancies. Previous studies have reported that diabetic patients have higher levels of estrogens than nondiabetic patients due to high levels of insulin and insulin resistance (29, 30). This elevated estrogens may cause specific cancers, such as uterine or cervical cancer, among female patients (31, 32). In terms of male diabetic patients, the increased estrogens may prevent them from developing prostate cancer (33). Although a previous study suggested that poor glycemic control may be related to lower prostate-specific antigen levels (34), the effect of different estrogens levels on glycemic control may be insufficient to prevent or develop cancer. Moreover, lower testosterone levels in diabetic patients may have preventative effects on prostate cancer (35). Similar to estrogens, a previous study has reported a dose-dependent association between glycemic control and testosterone levels (36); however, the effects may be insufficient to affect the development of malignancies.

Summary statistics from national database in Japan reported that age specific all cancer incidence was 21.1 per 1000 for male in their 60s and 18.9 per 1000 for female in their 60s (37). In contrast, incidence rate of all cancer among male was 30.7 per 1000 and that among female was 21.6 per 1000 in our sample. This finding suggests that

diabetic patients had higher incidence rate of all cancers compared to general population, which was consistent to previous studies (3).

There are some limitations to our study. First, our data contained only diabetes treatment status, so the types of medication were unknown. Certain medications, such as pioglitazone or metformin, may cause or prevent cancer (38, 39). A recent meta-analysis reported that pioglitazone may increase bladder cancer risk 1.13-fold, but this was a not statistically significant effect (38). Metformin may reduce cancer risk by 0.94-fold, which can be considered a mild effect (40). In addition, sulfonylureas (41, 42) or insulin analogs (43, 44) have been related to malignancies, but this is still controversial. Therefore, bias caused by the lack of data on patient medication may be minimal. Second, we cannot consider an inverse causality that malignancies change glycemic control. Some patients may develop malignancies without awareness. These malignancies may worsen glycemic control by increasing insulin resistance or may improve glycemic control by reducing appetite. However, every study may have similar issues; therefore, our study is still of value. In addition, our sensitivity analysis excluding those who developed malignancies within 2 years after their first visit may support our results. Moreover, our median follow-up of 1443.5 days may be insufficient to evaluate the development for slow progressive malignancies, such as pancreatic cancer (45). We would report additional development of malignancies after further follow-up. Finally, we cannot take into account potential confounders of HbA1c level, such as

liver cirrhosis, which may also have effects on malignancy development. However, these confounders may be rare.

Conclusion

Our study found no association between glycemic control and the development of future malignancies. Compared to a very strictly controlled HbA1c level (5.5–6.4%), both excessive control (<5.4%) and good or bad control (6.5–7.4, 7.5–8.4, and >8.5%) had a statistically similar risk of developing malignancies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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