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Glycated Hemoglobin and Cancer Risk in Korean Adults: Results from Korean Genome and Epidemiology Study

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Conflicts of Interest
The authors declare that they have no competing interests.

ABSTRACT

The purpose of this study was to test whether elevated glycated hemoglobin A1c (HbA1c) levels are associated with cancer incidence in the Korean population. In cohorts of the Korea Genome and Epidemiology Study (KoGES) consortium, we tested whether plasma levels of HbA1c were associated with all-site cancer incidence in 7,822 participants without any known history of cancer or diabetes. Cancer developed in 117 participants during the follow-up period. Subjects were subdivided into 3 categories according observed levels of HbA1c (< 5.7%, low; ≥ 5.7% and < 6.5%, mid; and ≥ 6.5%, high). The adjusted hazard ratio for all-site cancer was 3.03 (95% confidence intervals, 1.54–5.96) for the high HbA1c group relative to the low HbA1c group after adjusting for covariates. Higher circulating HbA1c levels were associated with an increased risk of all-site cancer in Korean population.

Keywords: Glycated hemoglobins; Neoplasms; KoGES; Hazard ratio

INTRODUCTION

Diabetes and cancer are common diseases that have serious effects on health all over the world. Previous epidemiological studies have consistently reported that diabetes is associated with the incidence and/or prognosis of cancers [1]. Several studies have suggested that abnormal glucose metabolism may affect the development of certain types of cancers [1]. From the consensus report of the American Diabetes Association and the American Cancer Society, biological links between diabetes and cancer have been proposed to include hyperinsulinemia, hyperglycemia, and inflammation [2,3]. However, the exact mechanism underlying the associations is largely unknown.

While evidence for an association between diabetes as measured by fasting glucose and cancer has accumulated [4], a recent meta-analysis has shown that chronic hyperglycemia, as determined by hemoglobin A1c (HbA1c) levels, is correlated with increased cancer risk for a number of cancers, not including prostate cancer [5][REMOVED HYPERLINK FIELD]. HbA1c indicates a chronic hyperglycemic state via the non-enzymatic and irreversible glycation of hemoglobin [6]; it is commonly used to monitor glycemic control as an integrated measure of glycemia over several weeks. It has been reported that elevated HbA1c is prospectively

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associated with an approximately 25% increased risk of cancer and 60% increased risk of mortality in non-diabetic women [7]. Moreover, Hsu et al. [8] reported that HbA1c levels are superior to fasting glucose levels for predicting cancer incidence in a cross-sectional study.

In the present study, we tested the hypothesis that elevated HbA1c levels are associated with the risk of all cancers in the non-diabetic Korean population. To adequately address the question, we first tested whether HbA1c levels were associated with the incidence of all cancers in 7,822 participants without any known history of cancer or diabetes.

MATERIALS AND METHODS

Study population
The study population was based on cohorts of the Korea Genome and Epidemiology Study (KoGES) consortium, which is a longitudinal survey conducted by the Korea National Institute of Health from 2001 to 2010. The aim of KoGES is to develop biomarkers and examine risk factors for common diseases such as diabetes mellitus (DM), hypertension, obesity, and dyslipidemia. The follow-up survey consists of 2 different cohorts from urban (Ansan) and rural areas (Ansung). The initial population examined included 10,038 individuals aged 39–70 years and 8,842 of those individuals included after a removal of poor genotyping data. We excluded subjects diagnosed with any type of cancer or a diagnosis of diabetes at baseline. We also excluded individuals whose data for important variables were unavailable (such as HbA1c). Additionally, subjects diagnosed with myocardial infarction, congestive heart failure, coronary artery diseases, peripheral vascular diseases, kidney diseases, and cerebrovascular diseases were excluded from the baseline sample. A final sample of 7,822 participants was used for the statistical analysis. Each participant's person-years were calculated from the return of the baseline questionnaire until the date of loss to follow-up, the end of the follow-up period (December 2010), or the date of diagnosis of all-site cancers, whichever came first. This study was approved by the Institutional Review Board of the Korea National Institute of Health (KU-IRB-14-EX-153-A-1).

General characteristics
The KoGES data are comprised of sociodemographic, anthropometric, nutritional, and medical history variables. Sociodemographic variables included age, gender, residential area, income, physical activity, alcohol drinking, and smoking status from the baseline dataset. Residential area was divided into an urban area, Ansan (n = 5,020), and a rural area, Ansung (n = 5,018). Follow-up rate between 2001 and 2010 was approximately 66.4% including death rate and response rates for important variables (HbA1c and diagnosis of DM) were 99.9% from baseline data. Monthly income (unit: Korean won) was divided as follows: lowest (≤ 1 million), lower middle (> 1 million and ≤ 2 million), upper middle (> 2 million and ≤ 3 million), and highest (> 3 million). Physical activity was categorized according to the intensity of activity: sedentary activity for less than 30 minutes, light, moderate, and intense activity for at least 30 minutes up to more than 5 hours. With respect to alcohol drinking, participants were divided into current, previous, and nonalcoholic subjects. Likewise, a variable for smoking status was divided into current, previous, and nonsmoking subjects. Anthropometric variables including weight (kg), height (cm), waist circumstance (cm), total cholesterol (mg/dL), high-density lipoprotein (HDL; mg/dL), triglyceride (mg/dL), and HbA1c (%) were measured in the baseline data. All participants fasted for at least 8 hours before the blood collection. Waist circumstance was measured 3 times and the average value

was described. Body mass index (BMI; kg/m^2) was calculated using the weight and height of subjects and subjects were classified as underweight (< 18.5), normal weight (≥ 18.5 and ≤ 25), or obese (> 25). HbA1c (%) was categorized using the standard of the American Diabetes Association (2014) as follows: < 5.7%, low; ≥ 5.7% and < 6.5%, mid; and ≥ 6.5%, high. The average HbA1c levels in whole blood were 5.6% for Ansan cohort and 5.6% for Ansung cohort. Diagnosis of diseases (such as cancer, diabetes, hypertension, and dyslipidemia) was based on a self-reported medical history. All-site cancer diagnosed between 2005 and 2010 included gastric cancer, lung cancer, liver cancer, colorectal cancer, pancreatic cancer, uterine cancer, breast cancer, and other cancers.

Statistical analysis

Differences in the baseline characteristics among groups were determined by χ^2 tests for categorical variables. For continuous variables, means ± standard errors were described by one-way analysis of variances (ANOVAs). Bonferroni's multiple comparison tests were used to evaluate differences. A generalized linear regression model with Bonferroni correction was used to investigate linear trends in the continuous variables (i.e., total cholesterol, HDL, triglyceride) after adjusting for age and gender. The association between HbA1c and all-site cancer was analyzed by a Cox regression analysis. Confounding variables included age, sex, residential area, income, smoking status, alcohol drinking, physical activity, and BMI from the baseline. All analyses were performed using 95% confidence intervals (CIs; 2-sided) and implemented in SPSS ver. 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

General characteristics of the participants and incidence of all site cancer during follow-up period

The general characteristics of the subjects are shown in **Table 1**. The mean age of all participants was 51.7 ± 0.1 years and 46.4% were male. Percentage of current smoker was

Table 1. Baseline characteristics of the participants

Characteristic	All participants (n = 7,822)
Sex (male)	3,627 (46.4)
Age, yr	51.7 ± 0.1
BMI, kg/m^2	24.5 ± 0.04
WC, cm	82.2 ± 0.1
Smoker	
Never	4,621 (59.9)
Previous	1,132 (14.7)
Current	1,965 (25.5)
Alcohol drinker	
Never	3,592 (46.3)
Previous	465 (6.0)
Current	3,699 (47.7)
Hypertension diagnosis	1,036 (13.3)
Dyslipidemia diagnosis	185 (2.4)
Family history of cancer	183 (2.3)
Total cholesterol, mg/dL	190.9 ± 0.4
HDL-cholesterol, mg/dL	45.0 ± 0.1
Triglyceride, mg/dL	157.8 ± 1.1
HbA1c, %	5.61 ± 0.01

Values are presented as number (%) or mean ± standard deviation.
BMI, body mass index; WC, waist circumference; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c.

25.5% and current drinker was 47.7%. The family history of cancer (%) of all participants was 2.3%. The number of all-site cancer between 2005 and 2010 was 117 among the nondiabetic participants including gastric, breast, colorectal and other types of cancers.

Baseline characteristics of the participants according to HbA1c levels

The general characteristics of the subjects according to HbA1c level are shown in **Table 2**. The BMI, waist circumstance, total cholesterol, and triglyceride values were significantly higher in the highest HbA1c group than in other groups. In contrast, HDL-cholesterol levels were lower in the highest HbA1c group than they were in the other 2 groups. The diagnosis of hypertension and dyslipidemia were observed for 28.2% and 4.1% of individuals in the highest HbA1c group.

Association between HbA1c level and cancer incidence

The association between HbA1c levels and the risks for all-site cancers was evaluated (**Table 3**). The subjects whose HbA1c level was greater than 6.5% had a higher incidence of cancer than did the reference group. The hazard ratio (HR) was 3.03 (95% CIs, 1.54–5.96; p for trend = 0.046) after adjustment for age, sex, area, income, smoking status, alcohol behavior, physical activity, and BMI applying a Cox proportional hazards model from the baseline data.

Table 2. Baseline characteristics of the participants according to HbA1c levels

Characteristic	HbA1c, %			p value
	< 5.7 (n = 4,663)	≥ 5.7 and < 6.5 (n = 2,840)	≥ 6.5 (n = 319)	
Sex (male)	2,138 (45.9)	1,355 (47.7)	134 (42.0)	0.082
Age, yr	50.2 ± 0.1^a	53.6 ± 0.2^b	56.2 ± 0.5^b	< 0.001
BMI, kg/m^2	24.06 ± 0.04^a	25.03 ± 0.06^b	26.50 ± 0.18^c	< 0.001
WC, cm	80.7 ± 0.1^a	83.9 ± 0.2^b	89.2 ± 0.5^c	< 0.001
Smoker				< 0.001
Never	2,836 (61.6)	1,591 (56.8)	194 (62.1)	
Previous	674 (14.6)	422 (15.1)	36 (11.5)	
Current	1,093 (23.8)	790 (28.2)	82 (26.3)	
Alcohol drinker				< 0.001
Never	2,104 (45.4)	1,319 (46.9)	169 (53.8)	
Previous	232 (5.0)	209 (7.4)	24 (7.6)	
Current	2,296 (49.6)	1,282 (45.6)	121 (38.5)	
Physical exercise				< 0.001
Lowest	164 (4.0)	114 (4.5)	15 (5.2)	
Lower middle	1,779 (43.1)	994 (39.3)	109 (37.7)	
Upper middle	799 (19.4)	436 (17.2)	46 (15.9)	
Highest	1,384 (33.5)	986 (39.0)	119 (41.2)	
Income				< 0.001
Lowest	1,360 (29.7)	1,103 (39.6)	145 (46.6)	
Lower middle	1,406 (30.7)	758 (27.2)	83 (26.7)	
Upper middle	938 (20.5)	457 (16.4)	47 (15.1)	
Highest	883 (19.3)	467 (16.8)	36 (11.6)	
Hypertension diagnosis	461 (9.9)	485 (17.1)	90 (28.2)	< 0.001
Dyslipidemia diagnosis	90 (1.9)	82 (2.9)	13 (4.1)	0.004
Family history of cancer	109 (2.3)	70 (2.5)	4 (1.3)	0.398
Total cholesterol*, mg/dL	185.9 ± 0.5^a	197.1 ± 0.7^b	209.9 ± 2.1^c	< 0.001
HDL-cholesterol*, mg/dL	45.7 ± 0.1^a	44.2 ± 0.2^b	41.1 ± 0.5^c	< 0.001
Triglyceride*,†, mg/dL	143.9 ± 1.3^a	173.8 ± 2.0^b	218.7 ± 7.4^c	< 0.001
HbA1c, %	5.336 ± 0.003^a	5.903 ± 0.004^b	6.904 ± 0.029^c	< 0.001

The values are represented as mean ± standard error or number (%). Significance was determined by χ^2 test and one-way analysis of variance with Bonferroni's multiple comparisons test (p value < 0.05).
BMI, body mass index; WC, waist circumference; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c.
*Significance was determined using the generalized linear model with Bonferroni's multiple comparisons test after adjusting for age and gender; †The value was log-transformed. [a,b,c]Different letters indicate statistical differences at p < 0.05.

Table 3. Adjusted HR and 95% CIs for the cancer incidence according to HbA1c level

All site cancer	HbA1c, %		
	< 5.7 (n = 4,663)	≥ 5.7 and < 6.5 (n = 2,840)	≥ 6.5 (n = 319)
Unadjusted	1.00 (ref.)	0.86 (0.56–1.33)	2.98 (1.61–5.52)
Multivariate-adjusted*	1.00 (ref.)	0.80 (0.52–1.25)	2.70 (1.43–5.09)
Multivariate-adjusted†	1.00 (ref.)	0.77 (0.48–1.23)	3.03 (1.54–5.96)

HR, hazard ratio; CI, confidence interval; HbA1c, hemoglobin A1c; BMI, body mass index.
*Differences were tested using Cox regression analysis after adjusting for sex, age, area; †Differences were tested using Cox regression analysis after adjusting for sex, age, area, income, alcohol use, smoking status, physical activity, and BMI.

DISCUSSION

In the present study, we examined whether HbA1c is prospectively related to the incidence of all cancer type. The results showed that elevated HbA1c levels were associated with increased risk of all-site cancers. Previous cross-sectional and prospective studies have observed that elevated HbA1c is associated with an increased risk of cardiovascular disease [9], type 2 DM [10] and certain types of cancers [8,11-13]. For example, consistent with our findings, a cross-sectional study reported that HbA1c is independently associated with colorectal neoplasia in nondiabetic participants after an adjustment for biological risk factors including fasting plasma glucose [8]. In addition, it was reported that type 2 DM patients whose HbA1c level was greater than 8.0% had a higher cancer risk than did patients in the reference group (HbA1c < 7.0%) in a Japanese case-control study [14]. Wolpin et al. [12] also reported that a higher risk for pancreatic cancer was shown in the highest HbA1c quintiles without diabetes history compared with the lowest quintiles from five prospective US cohorts. Also, Erickson et al. [15] found that elevated HbA1c levels were independently associated with a statistically significant higher risk of all-cause mortality in breast cancer survivors.

Xu et al. [16] evaluated the association between markers of glucose metabolism and the risk of colorectal cancer using a meta-analysis approach. They reported that higher levels of glycated hemoglobin (HbA1c) were significantly associated with increased risk of colorectal cancer (relative risk, 1.22; 95% CI, 1.02–1.47). Kim et al. [17] also reported that the adjusted HRs for adenoma occurrence adenomas detected on surveillance colonoscopy comparing the fourth with the first quartiles of fasting HbA1c was 1.22 (95% CI, 1.04–1.43; p for trend = 0.024) in Korean short-term longitudinal study.

Mechanistically, several pathways explaining the relationship between diabetes and cancer have been postulated. Chronic hyperglycemia which is the most prominent clinical symptom of diabetes may affect tumorigenesis via hyperinsulinemia or a chronic inflammatory state [3]. Chronic hyperglycemia may lead to the production of reactive oxygen species (ROS) and bioaccumulation of advanced glycation end products (AGEs) [14,18-20]. Receptor for AGEs (RAGE), which causes the activation of the nuclear transcription factor NF-κB and the signal transducer and activator of transcription (STAT) 3, and release of inflammatory cytokines such as interleukin 6 and tumor necrosis factor (TNF)-α [18,20,21]. In addition, inflammation-induced ROS can damage cellular components such as DNA, proteins and lipids, all of which can directly or indirectly contribute to malignant cell transformation [19,20]. Alternatively, chronic hyperglycemia may result in carcinogenesis via chronic inflammation [22,23].

There are several limitations of the present study. First, the cancer incidences were small so we could not acquire incidence data for individual cancer types. Since the responses

were founded on doctor's diagnosis, the statistics were compiled using data from authentic sources. Despite these limitations, this was a large-scale prospective study of a cohort. Our study is novel because unlike the majority of other studies, we examined the association between HbA1c and cancer, and not diabetes or cardiovascular diseases. Furthermore, as commented previously, the HbA1c is an integrated indicator of average blood glucose concentrations over a period of 6–8 weeks [24], and HbA1c level is more robust than the fasting glucose level as an independent biomarker [9,25].

In conclusion, the novel finding of this study was that a 39.4% increase in HbA1c was causally related to a 3.03-fold increase in the risk of all cancers. This result implied that HbA1c may have a pivotal role in predicting cancer incidence prior to diabetes diagnosis. In other words, our results suggest HbA1c as a causal risk factor for all cancers in the general Korean population. Considering that there has been a gradual increase in the incidence of all-site cancers and diabetes in Korea [26,27], our findings may contribute to predicting cancer incidence and to lowering the risk of cancer before diabetes diagnosis in the general population.

ACKNOWLEDGEMENTS

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