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A simple screening score to predict diabetes in cancer patients

A Korean nationwide population-based cohort study

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Abstract

Many cancer patients develop diabetes, which may result in reduction of chemotherapy effectiveness and increased infection risk and cardiovascular mortality. Diabetes may also increase the risks of chemotherapy-related toxicity and post-operative mortality, or represent an obstacle to optimal cancer treatment. However, the clinical predictors of diabetes in cancer patients remain largely unknown. Therefore, the aim of our study was to evaluate the risk factors for developing diabetes and construct a nomogram to predict diabetes in cancer patients.

We investigated patients from a national sample cohort obtained from the Korea National Health Insurance Service (KNHIS), which included 2% of the Korean population. Patients who had undergone routine medical evaluation by the KNHIS between 2004 and 2008 and been hospitalized due to cancer (ICD-10 codes C00–97) during the past 3 years were included. After excluding patients with type 2 diabetes and missing data, 10,899 patients were enrolled and followed-up until 2013. A total of 7630 (70%) patients were assigned as the training cohort and used to construct the nomogram which was based on a multivariable logistic regression model. The remaining patients (n = 3269) were used as the validation cohort.

The incidence rate of diabetes was 12.1 per 1000 person-years over a mean follow-up of 6.6 ± 1.8 years. Significant risk factors for developing diabetes were age, sex, obesity, fasting plasma glucose, hypertension, and hypercholesterolmia. A nomogram was constructed using these variables and internally validated. The area under the curve was 0.70 (95% confidence interval, .666-.730, $P < .0001$) and the calibration plot showed agreement between the actual and nomogram-predicted diabetes probabilities.

The nomogram developed in this study is easy to use and convenient for identifying cancer patients at high-risk for type 2 diabetes, enabling early type 2 diabetes screening and management.

Abbreviations: BMI = body mass index, CI = confidence interval, ICD-10 = international classification of diseases, tenth revision, IL-6 = interleukin-6, KNHIS = Korea National Health Insurance Service, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, NHI = national health insurance, OR = odd ratio, ROC = receiver operating characteristic, TNF-α = tumor necrosis factor alpha.

Keywords: cancer, diabetes mellitus, nomogram, prediction model, risk factor modeling, screening tool

1. Introduction

Both cancer and diabetes are common diseases that are increasing worldwide, have major global impacts on public health, and require substantial medical investments and expenditures.[1] In the United States, the overall cancer incidence has been reported as 454.8 per 100,000 person-years based on the US National Cancer Institute report, with the incidence rates steadily increasing.[2] In a comparable report from the Korea National Cancer Institute Center, the cancer incidence was reported as 445.7 per 100,000 person-years in 2013, and the age-adjusted incidence was found to have increased 3.21% annually from 1999.[3] However, the overall cancer death rate has decreased due to advances in the early detection and treatment strategies.[2,3]

Similarly, the global population of diabetes patients has also increased. The World Health Organization reported that the global prevalence of diabetes increased from 4.7% in 1980 to 8.5% in 2014.[4] In a comparable report from Korea, the prevalence of diabetes was found to have steadily increased from 5.6% in 2006 to 13.7% in 2014.[5]

The increasing population of those who have lived with and beyond cancer, combined with the rapid rise in diabetes incidence, suggests that increasing proportions of cancer patients will be diagnosed with and treated for diabetes. Although many

Editor: Jianxun Ding.

This study was supported by the National Research Foundation of Korea (grant number NRF-2015R1C1A1A02036408).

The authors have no conflicts of interests to disclose.

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How to cite this article: Kim JS, Ko SH, Baeg MK, Han KD. A simple screening score to predict diabetes in cancer patients: A Korean nationwide population-based cohort study. Medicine 2019;98:51(e18354).

Received: 11 April 2019 / Received in final form: 24 October 2019 / Accepted: 13 November 2019

http://dx.doi.org/10.1097/MD.0000000000018354

patients have diabetes long before their cancer diagnosis, many develop diabetes because of their cancer or its treatment.[6–11] Importantly, several studies and meta-analyses have reported that cancer patients with diabetes have an increased mortality compared to those without diabetes.[12–14] Diabetes might reduce the chemotherapy effectiveness and increase the risks of infections and cardiovascular mortality.[15,16] Moreover, diabetes might increase the risks of chemotherapy-related toxicity and post-operative mortality, or represent an obstacle to optimal cancer treatment.[9,17]

Nevertheless, despite diabetes being an important risk factor for cancer mortality, the clinical predictors of diabetes in cancer patients remain largely unknown. These problems prompted us to find a method for quickly identifying cancer patients at a high risk of developing diabetes as early as possible. The purpose of this study was to investigate the predictive factors for diabetes, and to develop a nomogram using these factors as a means to predict diabetes in cancer patients.

2. Methods

2.1. Data source and subjects

The Korea National Health Insurance Service (KNHIS) is the only insurer and nonprofit organization managed by the government in Korea. The National Health Insurance (NHI) is a health insurance program that covers approximately 97% of the Korean population, and is managed by the KNHIS. The present study data were drawn from a national sample cohort of 1,025,340 individuals, equivalent to approximately 2% of the Korean population and based on the NHI claims database. The database provides diagnostic codes in the International Classification of Diseases, Tenth revision (ICD-10) format. Additional details regarding the study design and methods of the national sample cohort have been comprehensively described elsewhere.[18]

The inclusion criteria were patients with cancer who

(1) had undergone one biennial medical evaluation provided by the KNHIS between 2004 and 2008 and
(2) had been hospitalized due to cancer (ICD-10 codes C00–97) during the past 3 years.

We excluded patients who

(1) had fasting plasma glucose over 7.0 mmol/L, or had taken antidiabetic medication due to a diagnosis of diabetes (ICD-10 codes E11–14),[19] and who
(2) had missing records for analysis.

All enrolled patients were followed-up until 2013.

Approval for this study was waived by the institutional review board of Chung-Ang University Hospital. As the data consisted of de-identified secondary data released for research purposes, the need for participant consent was waived.

2.2. Measurements

The medical evaluations from 2004 to 2008 provided by the KNHIS included measurements of weight, height, and blood pressure, and laboratory tests, such as the fasting plasma glucose, cholesterol, and cholesterol levels. Anthropometric measurements were taken by specially trained examiners. Self-reporting questionnaires included past medical histories and health behaviors such as smoking, drinking, and exercise habits. Laboratory samples were properly collected and analyzed under quality control by the Korean Association of Laboratory Quality Control.

2.3. Definitions

Body mass index (BMI) was calculated by dividing the weight by the square height (kg/m^2), and BMI $\geq$ 25 kg/m^2 was categorized as obesity according to the World Health Organization.[20,21] Ever smokers were defined as those who had smoked 100 cigarettes or more in their lifetime. Based on the drinking frequency, the patients were classified as nondrinkers, moderate drinkers ($\leq$2 times per week), or heavy drinkers ($\geq$3 times per week). Diabetes was defined as those who had taken anti-diabetic medication, with the presence of the diabetes diagnosis codes (ICD-10 codes E11–14).[19] Hypertension was defined as systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or any use of antihypertensive medication due to diagnosed hypertension (ICD-10 codes I10–15). Hypertension was further divided into 2 subgroups, stage I hypertension (systolic blood pressure 140–159 mmHg and/or diastolic blood pressure 90–99 mmHg) or stage II hypertension (systolic blood pressure $\geq$160 mmHg and/or diastolic blood pressure $\geq$100 mmHg). Hypercholesterolmia was defined as the ICD-10 code E78 and current use of cholesterol-lowering drugs or fasting cholesterol levels $\geq$6.2 mmol/L.

2.4. Statistical analysis

All statistical analyses were performed with SAS for Windows (version 9.3; SAS institute, Cary, NC), and 2-sided *P* values of less than .05 were considered statistically significant. Data are presented as the means ± standard deviation or as frequencies and percentage. The Pearson's chi-square test was used for analysis of categorical variables. The incidence rates of diabetes were calculated as the number of cases per 1000 person-years of follow-up. Logistic regression models were used to test potential predictors of diabetes and calculate multivariate-adjusted odd ratios (ORs). Seventy percent of all eligible patients were randomly selected for the training cohort and used to develop a nomogram for the prediction of diabetes. The other 30% were assigned to the validation cohort, which was used for internal validation. The nomogram was built based on the results of the logistic regression to predict the occurrence of diabetes. A calibration plot was derived to evaluate the relationship between the actual probability and predicted probability and was depicted graphically. The discriminative ability of the model was evaluated by the area under the receiver operating characteristic (ROC) curve with its 95% confidence interval (CI). Internal validation was performed for the predictive performance of the model. The 7630 patients in the training cohort were divided into quintiles according to the predictive risk based on their nomogram score. For each quintile the actual probability of diabetes was compared with the predicted probability of diabetes. The incidence of diabetes was evaluated according to the quintiles. In addition, to investigate whether there were differences by cancer types, further analysis was performed according to pancreatic cancer, hepatobiliary cancers and other cancers.

2.5. Subject involvement

Subjects were recruited from a national database cohort and had given their written consent to being included in this cohort.

However, as this data was retrospectively analyzed, the subjects were not involved in the development of the research question and outcome measures or the design of this study. The results of this study will be made available to the subjects in the KNHIS database upon publication.

3. Results

3.1. Patient characteristics

For this study, 14,432 patients were eligible, out of whom 3533 patients were excluded (2135 had diabetes and 1398 had missing data for variables included in the analysis). The training cohort included 7630 patients (3661 men and 3969 women) and the validation cohort included 3269 patients (1576 men and 1693 women). For both cohorts, the mean follow-up was 6.6 years (± 1.8 years), and there was no significant difference between these 2 cohorts (Table 1).

The demographic and clinical characteristics of the cancer patients according to the diabetes occurrence are summarized in Table 2. The incidence of diabetes in the training cohort was 12.1 per 1000 person-years and the incidence of diabetes was higher in men (14.3 per 1000 person-years) than in women (10.0 per 1000 person-years) during the follow up period. Patients with diabetes were more frequently male (56.6% vs 47.2%, $P < .0001$) and elderly (40.8% vs 29.0%, $P < .0001$) than those without diabetes. Patients with diabetes also had significantly higher rates of obesity (42.2% vs 28.0%, $P < .0001$), hypertension (54.3% vs 35.3%, $P < .0001$), hypercholesterolmia (24.4% vs 16.0%, $P < .0001$), and high fasting plasma glucose (50.1% vs 24.4%, $P < .0001$). There were no differences in the exercise habits between patients with and without diabetes.

3.2. Predictive nomogram for the probability of diabetes in cancer patients

Table 3 shows the predictor selection results. In the age- and sex-adjusted logistic regression analysis, older age, male sex, obesity, hypertension, hypercholesterolmia, and fasting plasma glucose had predictive value for diabetes. However, smoking and drinking were not associated with the development of diabetes. Multivariable analysis showed that the variables significantly associated with occurrence of diabetes were age (OR 1.36; 95% CI, 1.152–1.609; $P < .0001$), male sex (OR 1.31; 95% CI, 1.113–1.538; $P < .0001$), obesity (OR 1.54; 95% CI, 1.304–1.817; $P < .0001$), fasting plasma glucose (OR 2.58; 95% CI, 2.194–3.027; $P < .0001$), hypertension (OR 1.56; 95% CI, 1.314–1.840; $P < .0001$), and hypercholesterolmia (OR 1.39; 95% CI, 1.145–1.674; $P < .0001$). When hypertension was analyzed by subgroups such as stage I hypertension or stage II hypertension, there were no significant differences.

Based on these results, we developed a nomogram that visually showed the multivariate impact of each variable on the risk of diabetes (Fig. 1). This nomogram included age, sex, obesity, fasting plasma glucose, hypertension, and hypercholesterolmia. Of these factors, fasting plasma glucose was the most influential, while hypertension represented the second most influential variable. Each value of these variables was assigned a point, and the sum of these points was converted to a probability of diabetes in the lowest scale.

The calibration plots are shown in Figure 2. The predictive performance of the model was assessed by internal validation. A ROC curve was drawn to assess the predictive ability of the

Table 1

Basic characteristics for the patients in the training and validation cohorts.

Characteristics	Training cohort	Validation cohort	P
Total no. of patients	7630	3269	
Age ≥ 65 yr (%)	2283 (29.9)	1030 (31.5)	.099
Male sex (%)	3661 (48.0)	1576 (48.2)	.827
Ever smoker (%)	1620 (21.2)	683 (20.9)	.691
Drinking (%)			.810
No	5400 (70.8)	2333 (71.4)	
Moderate	1653 (21.7)	691 (21.1)	
Heavy	577 (7.6)	245 (7.5)	
Regular exercise (%)	948 (12.42)	386 (11.81)	.368
Obesity (%)	2224 (29.1)	894 (27.3)	.057
Hypertension (%)	2807 (36.8)	1235 (37.8)	.327
Hypercholesterolmia (%)	1272 (16.7)	535 (16.4)	.695
Fasting plasma glucose ≥5.6 mmol/L (%)	2015 (26.4)	899 (27.5)	.238

Table 2

Clinical characteristics of the cancer patients according to the diabetes occurrence in the training cohort.

Characteristics	DM (−)	DM (+)	P
Total no. of patients	7,019	611	
Age ≥ 65 yr (%)	2,034 (29.0)	249 (40.8)	<.0001
Male sex (%)	3,315 (47.2)	346 (56.6)	<.0001
Ever smoker (%)	1,465 (20.9)	155 (25.4)	.009
Drinking (%)			.020
No	4,960 (70.7)	440 (72.0)	
Moderate	1,542 (22.0)	111 (18.2)	
Heavy	517 (7.4)	60 (9.8)	
Regular exercise (%)	3,238 (46.1)	279 (45.7)	.820
Obesity (%)	1,966 (28.0)	258 (42.2)	<.0001
Hypertension (%)	2,475 (35.3)	332 (54.3)	<.0001
Hypercholesterolmia (%)	1,123 (16.0)	149 (24.4)	<.0001
Fasting plasma glucose ≥ 5.6 mmol/L (%)	1,709 (24.4)	306 (50.1)	<.0001

Data are presented as n (%).

Table 3

Logistic regression for potential risk factors of diabetes development among cancer patients.

	Age- and sex- adjusted		Multivariate adjusted*	
Characteristics	OR (95% CI)	P	OR (95% CI)	P
Age ≥ 65 yr	1.60 (1.360–1.882)	<.0001	1.36 (1.152–1.609)	<.0001
Male sex	1.32 (1.123–1.550)	<.0001	1.31 (1.113–1.538)	.001
Ever smoker	1.20 (0.974–1.465)	.090		
Drinking				
No	1	.340		
Moderate	0.89 (0.715–1.108)			
Heavy	1.12 (0.844–1.483)			
Obesity	1.89 (1.611–2.224)	<.0001	1.54 (1.304–1.817)	<.0001
FPG ≥ 5.6 mmol/L	2.72 (2.317–3.191)	<.0001	2.58 (2.194–3.027)	<.0001
Hypertension	1.74 (1.471–2.053)	<.0001	1.56 (1.314–1.840)	<.0001
Hypercholesterolemia	1.62 (1.344–1.952)	<.0001	1.39 (1.145–1.674)	<.0001

CI = confidence interval, FPG = Fasting plasma glucose, OR = odds ratio.

* Adjusted for age, male sex, obesity, fasting plasma glucose, hypertension, and hypercholesterolemia.

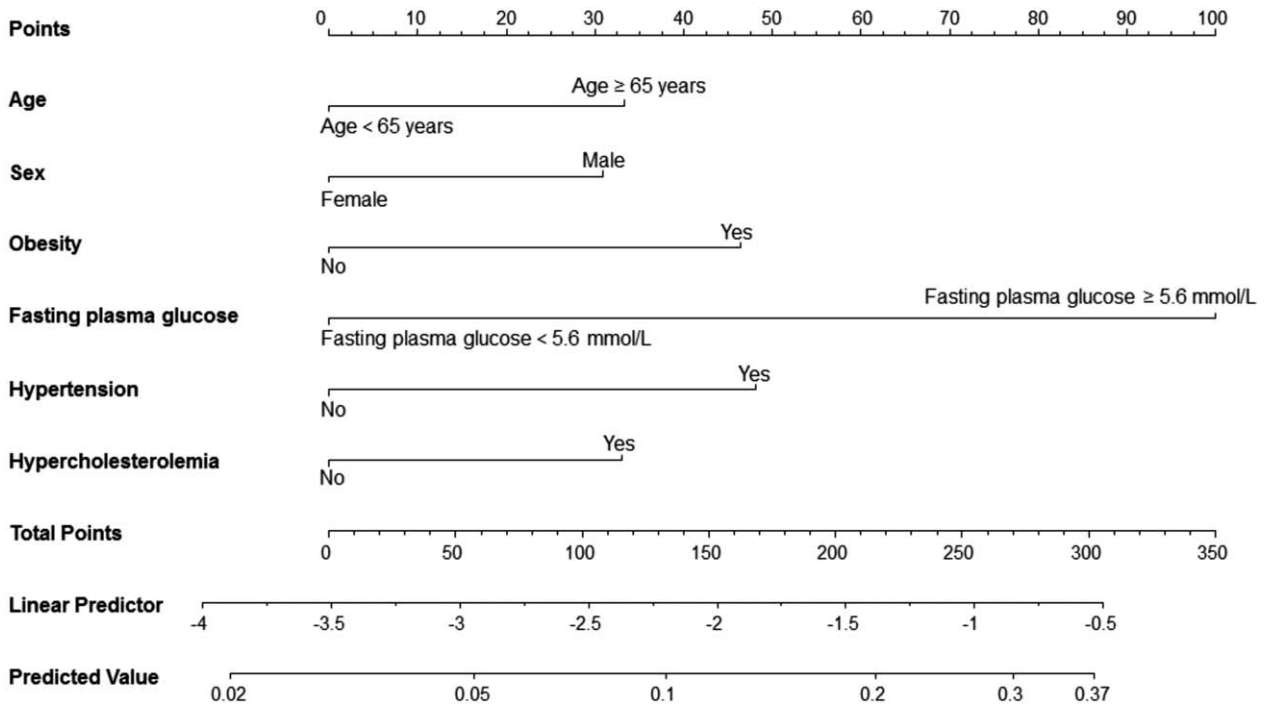

Figure 1. Nomogram to predict the probability of diabetes in cancer patients. Each variable value is allocated a score, which is determined by drawing a vertical line to the points scale. The sum of these scores is located on the total points scale, and a vertical line is drawn downward to the predicted value scale to determine the probability of diabetes in cancer patients.

nomogram. The area under the ROC curve was 0.70 (95% CI, 0.666–0.730, $P < .0001$; data not shown).

To assess the accuracy of the nomogram, the actual probability of diabetes in the training cohort was compared with the predictive probability of diabetes in the validation cohort for each quintile. There were no statistical significant differences between the predicted and actual probabilities of diabetes in any risk interval. The incidence rate of diabetes for the predictive risk score based on the individual nomogram score by quintile are presented in Figure 3. In both training and validation cohorts, the incidence rate of diabetes was highest in the 5th quintile (80% to 100%) of the predictive score (27.3 and 26.6 per 1000 person-years, respectively). The lowest incidence rate of occurred in the 1st quintile (< 20%) and the incidence rate of diabetes increased linearly according to predictive score quintiles.

When cancer types were analyzed separately, the risk factors for diabetes remained similar. However, risk of diabetes was significantly higher in pancreatic cancer compared to other cancers. (OR 1.74; 95% CI, 1.258–2.397; $P = .01$). In regard to specific types of cancers, in pancreas cancer, both obesity (OR 2.16; 95% CI, 1.125–4.157; $P = .02$) and fasting plasma glucose (OR 2.81; 95% CI, 1.492–5.300; $P = .001$) resulted in a significant increase in diabetes risk. In case of hepatic cancer, fasting plasma glucose showed a greater association with diabetes risk (OR 3.10; 95% CI, 1.807–5.309; $P < .0001$).

4. Discussion

In this study, we identified independent predictive factors and developed a nomogram based on these factors to predict cancer patients at high risk of developing diabetes. The nomogram included age, sex, obesity, fasting plasma glucose, hypertension, and hypercholesterolmia as significant variables. To establish a simple risk score model, we used only categorized variables, and the resulting nomogram is easy to use and convenient for identifying high-risk patients, consequently allowing them to be referred for additional testing or careful follow-up. To our knowledge, this is the first population-based study to develop a nomogram to predict the diabetes risk in cancer patients. Recently, increasing epidemiological evidence has suggested co-occurrence of cancer and diabetes, which is more frequent than would be expected.[1,22,23] In the present study, diabetes occurred in 12.1 per 1000 cancer patients during the follow up period and the risk of developing diabetes in highest risk group was over 2 times the risk of the total group. This incidence rate was higher than the diabetes incidence in the general Korean population, which has been reported as 9.5 to 9.8 per 1000 person-years.[24] In addition, this discrepancy between cancer patients and the general population should increase considering the decreasing trend in the annual incidence of diabetes in the general Korean population after 2004.[24,25]

Early detection and management of diabetes in cancer patients is important, as diabetes has been associated with reduced quality of life, decreased survival, and increased cancer mortality.[16,26–28] These findings may be due to therapy-related factors such as changes in chemotherapy brought on by diabetic complications, poorer response to the cancer treatment, chemotherapy-related toxicity, and/or increased intra- or post-operative mortality.[17,26,27,29] Other possible mechanisms include the increased risk of infection and increased cardiovascular morbidity and mortality in patients with diabetes.[16,29] However, despite this clinical importance, most research efforts are currently focused on cancer-directed treatments to reduce cancer-related mortality, and non-cancer comorbid conditions such as diabetes have been underestimated.[22,30] A recent study from the United States found that cancer patients received less diabetes management

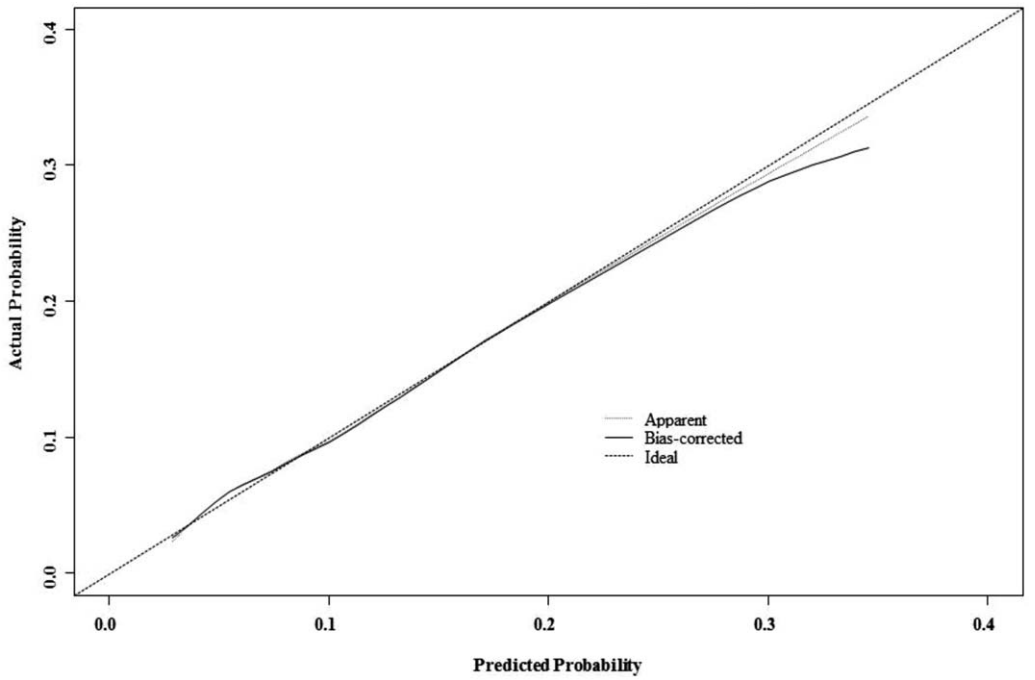

Figure 2. Calibration plot of the nomogram for predicting diabetes in cancer patients. The nomogram-predicted probability of diabetes is plotted on the *x*-axis, and the *y*-axis represents the actual rate of diabetes. The 45° line on the plot shows the ideal nomogram, in which the predicted and actual probabilities are identical. The dotted line represents the apparent accuracy of the nomogram and the solid line indicates the bias-corrected line.

after the cancer diagnosis than before the diagnosis,[31] and these results are similar to those of a recent cross-sectional study that reported that cancer patients have a higher prevalence of diabetes than the general population, but that they do not have significantly greater diabetes management.[32] A nomogram such as that developed herein may simplify the detection of cancer patients at higher risk of diabetes and improve the perception and management thereof.

Diabetes occurrence in cancer patients may be increased either by the cancer itself or as a complication of the cancer treatment. Breast, liver, and pancreas cancers have all been associated with increased risks of diabetes,[6,33,34] which is partially corroborated by our study results, which found that diabetes risk was significantly increased in pancreas cancer patients. Several studies have also reported that various anticancer therapies increase the diabetes risk, which may vary depending on the cancer type and

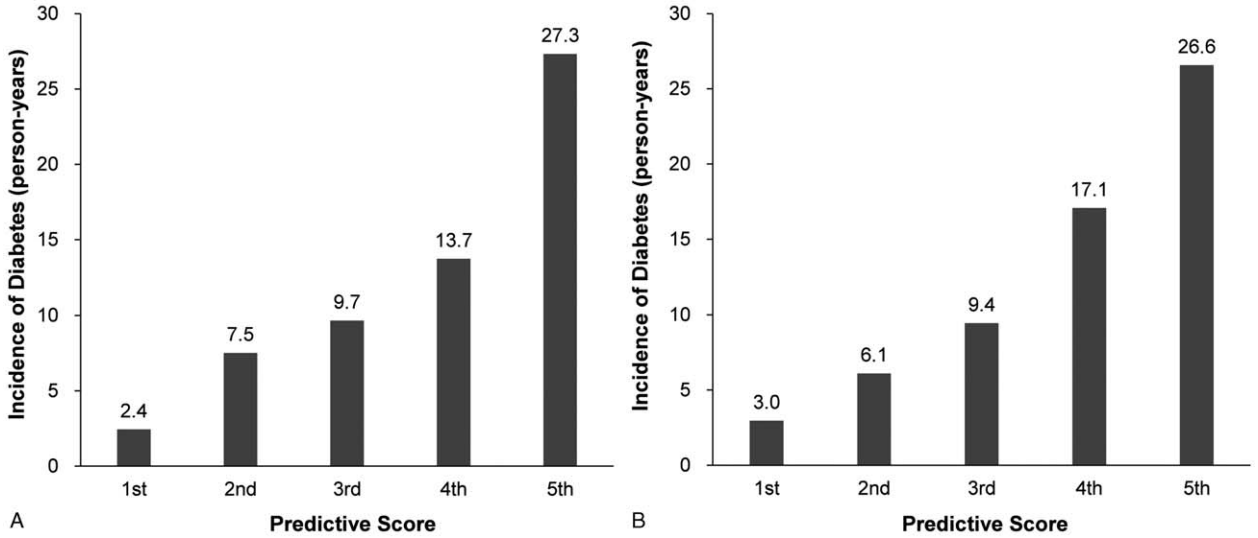

Figure 3. Diabetes in cancer patients according to the predictive score (A) Training cohort (B) Validation cohort. The *x*-axis represents the quintiles of the predictive risk score based on the nomogram score and the *y*-axis represents the incidence of diabetes in each quintile. In both the training and validation cohorts, the incidence rate was highest in the 5th quintile (80%–100%) and lowest in the 1st quintile (<20%), respectively. The incidence rate of diabetes increased linearly as the predictive score increased and there were no differences between the 2 cohorts.

specific therapy.[7–11] For example, secondary diabetes has been reported in approximately 10% of patients who received 5-fluorouracil-based chemotherapy for colorectal cancer.[11] Other studies have reported that hyperglycemia can be caused by the mammalian target of rapamycin inhibitor everolimus, aromatase inhibitors, or L-asparaginase.[8,9,35] The pathophysiology behind chemotherapy-induced hyperglycemia and diabetes has not been well-elucidated. Acute or chronic damage by chemotherapy agents may result in injured pancreatic β-cells, increased insulin resistance, decreased β-cell function, and reduced β-cell mass.[9–11] In addition, glucocorticoid-induced hyperglycemia may be another factor. Glucocorticoids are used as part of chemotherapy regimens in hematologic malignancies or as anti-emetics to reduce edema or help in cancer pain control[26]; these agents induce hyperglycemia by promoting hepatic gluconeogenesis, increasing insulin resistance by decreasing glucose uptake and utilization in the adipose tissues and skeletal muscle, and by altering pancreatic β-cell function.[36] Similarly, although the underlying pathophysiology responsible for the relationships between cancer and diabetes has not been clarified, there are some potential candidates. Chronic inflammation is a possible mechanism linking cancer and diabetes. Chronic inflammation is characterized by increased free fatty acids, inflammatory cytokine production, and chemoattraction of immune cells such as macrophages.[37] In turn, inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1, and cyclooxygenase-2 can contribute to the development and progression of cancer, as well as promote insulin resistance through several mechanisms.[37–42] For example, IL-6 may inhibit apoptosis and induce proliferation of pre-neoplastic cells and induce insulin resistance through its interaction with β-cell function and the insulin signaling pathway.[37,40,42] Free fatty acids activate carcinogenesis signaling molecules, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and promote insulin resistance and diabetes,[43] while TNF-α has been reported to contribute to cancer progression via NF-κB and insulin resistance by downregulation of insulin receptors and glucose transporters.[37] In turn, activation of NF-κB is associated with insulin resistance and expression of genes involved in cell proliferation, metastasis, and apoptosis.[41,43] Another putative mechanism linking cancer with diabetes might be the shared predisposing risk factors such as obesity.[23] Obesity is associated with chronic systemic inflammation, as adipose tissues are known to produce inflammatory mediators such as IL-6, interleukin-1 β, TNF-α, and monocyte chemoattractant protein-1.[37] In addition, enlarged adipocytes lose effective oxygen diffusion, which results in hypoxia, production of inflammatory cytokines, macrophage infiltration, and insulin resistance.[37]

There are some limitations to this study that need to be addressed. Most importantly, this study is limited by the subject population, as only Korean cancer patients were included in this study. Although internal validation demonstrated good performance, external validation is required for the application of our nomogram to clinical practice. However, to our knowledge, this is the first study to investigate diabetes occurrence in cancer patients with a long follow-up period, which might limit external validation of our nomogram. Second, we could not evaluate the differences in the risk factors between cancer patients and the general population. This is because advanced cancer patients experience cancer cachexia, which is reported to be related with increased insulin resistance, impaired glucose tolerance and diabetes.[44] However, parameters for cancer cachexia cannot be assessed in the Korean National Health and Nutrition Examination Survey, limiting comparison between cancer patients and the general population. Third, hypertension and dyslipidemia were defined not only by blood pressure or cholesterol levels but also by medication use. Almost 50% of patients had taken medications, we were unable to fully investigate the effect of hypertension or hypercholesterolemia subgroups in the diabetes risk of cancer patients.

Nevertheless, this study also has several strengths. First, this nomogram is based on information that is readily available in routine clinical practice, which allows diabetes screening without adding prohibitive time or cost. Second, this study is population-based, thus reducing potential biases and allowing generalization to the Korean population, as per the design of KNHIS. Third, we used ICD-10 codes of the claims data in the registry source to avoid recall bias. Fourth, cancer patients were followed for an average of 6.6 years, which is a sufficiently long period for diabetes development.

In conclusion, considering the higher proportion of diabetes in cancer patients compared to the general population as well as the unfavorable effects of diabetes on cancer mortality, elucidating the predictive factors of diabetes in this population may be clinically significant. For optimal outcomes in cancer patients, both the cancer and diabetes must be appropriately addressed. However, there are currently no cancer guidelines that include screening or preventive interventions for diabetes. Our proposed nomogram can be used to select patients at high risk for diabetes and consequently recommend them to undergo appropriate diabetes screening. In this study, old age, male sex, obesity, high fasting plasma glucose, hypertension, and hypercholesterolmia were found to be predictive factors for diabetes. More precise models for prediction of various comorbidities, including diabetes, should be designed for life-long cancer survivors, and new guidelines should be implemented based on these models.

Author contributions

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Funding acquisition: Ji-Su Kim.
Investigation: Sun-Hye Ko.
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Supervision: Sun-Hye Ko.
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