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Original Article

Survival of macrovascular disease, chronic kidney disease, chronic respiratory disease, cancer and smoking in patients with type 2 diabetes: BioBank Japan cohort

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ABSTRACT

Background: The number of patients with diabetes is increasing worldwide. Macrovascular disease, chronic kidney disease, chronic respiratory disease, cancer and smoking frequently accompany type 2 diabetes. Few data are available related to mortality of Asians with diabetes associated with these serious comorbidities. The present study aimed to quantify the excess mortality risks of type 2 diabetic patients with comorbidities.

Methods: We analysed the available records of 30,834 Japanese patients with type 2 diabetes from the BioBank Japan Project between 2003 and 2007. Men and women were followed up for median 8.03 and 8.30 years, respectively. We applied Cox proportional hazard model and Kaplan–Meier estimates for survival curves to evaluate mortality in diabetic patients with or without macrovascular disease, chronic respiratory disease, chronic kidney disease, cancer and smoking.

Results: Adjusted hazard ratios (HRs) for mortality were 1.39 (95% CI, 1.09–1.78) for male sex, 2.01 (95% CI, 1.78–2.26) per 10-year increment of age. Adjusted HRs of primary interest were 1.77 (95% CI, 1.42–2.22), macrovascular disease; 1.58 (95% CI, 1.08–2.31), chronic respiratory disease; 2.03 (95% CI, 1.67–2.47), chronic kidney disease; 1.16 (95% CI, 0.86–1.56), cancer; and 1.74 (95% CI, 1.30–2.31), current smoking.

Conclusions: Diabetic patients with a past or current history of chronic kidney, macrovascular or respiratory diseases or smoking habit have exhibited the highest risk of mortality. Data were limited to those of survivors of comorbidities but we propose the need to improve comorbidities and terminate cigarette smoking for better prognosis in patients with diabetes.

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Introduction

The prevalence of type 2 diabetes and its complications is a global problem. Caucasian and Asian patients with diabetes have an approximately two-fold increased risk of mortality compared with healthy individuals.[1] Therefore, in Asian countries where the prevalence of obesity are rapidly increasing,[2] significant increases in the rate of death from diabetes require urgent attention.

Diabetes contributes to death caused by arterial sclerotic disease[3] and cancer.[4] Stroke, acute myocardial infarction (MI) and chronic kidney disease represent major complications of American patients with diabetes.[5] In European and North American countries, patients with diabetes are at a higher risk of death caused by vascular disease, followed by cancer and other causes.[4] Cancer and diabetes cause each other,[6] and middle-aged to aged patients with diabetes may likely have experienced cancer.[7] Furthermore, renal disease, often accompanying artery calcification, leads to cardiovascular mortality,[8] and in patients with diabetes, renal comorbidity is a significant risk factor for death.[9] Chronic obstructive pulmonary disease, usually caused by cigarette smoking, also frequently accompanies diabetes and leads to high mortality.[10]

Improvements in the treatment of vascular diseases, cancer and chronic kidney and respiratory diseases should be preventing deaths directly caused by diabetes, indicating that the survival of patients with diabetes will increase. However, to our knowledge, no data are currently available in Asian countries that associate the mortality of diabetic patients with comorbidities. This study aimed to determine the contributions of comorbidities and cardiovascular risk factors to the risk of death in Japanese patients with diabetes. For this purpose, we also compared the survival curves of patients with diabetes with or without major comorbidities.

Methods

Participants

Between fiscal years 2003 and 2007, the BioBank Japan Project registered 200,000 patients with 47 diseases treated at 12 institutions.[11] The study profiles are published elsewhere.[12–14] The project follows 39,697 patients with diabetes treated at 66 hospitals. We collected serum samples and information from patients' medical records. We also collected annual information on survival, mortality and causes of death from patients' medical records, the residence registry and the Vital Statistics Act.[15] The ages of participants were mainly ≥19 years.

To assess the influence of comorbidities and cardiovascular risk factors on mortality of patients with type 2 diabetes, we eliminated the data of those with diabetes other than type 2 (other endocrinological or metabolic diseases, systemic infectious diseases, other cardiac diseases for the use of steroid and amyotrophic lateral sclerosis).[16] In other words, we did not analyse those with mitochondrial diabetes, maturity-onset diabetes of the young (MODY), hyper- or hypo-thyroidism, Hashimoto's thyroiditis, pheochromocytoma, Cushing disease or syndrome, acromegaly, amyloidosis, tuberculosis, atypical mycobacteriosis, systemic lupus erythematosus, rheumatoid arthritis, juvenile rheumatoid arthritis, malignant rheumatoid arthritis, dermatomyositis, polymyositis, systemic sclerosis, steroid use, myocarditis, dilated cardiomyopathy or hypertrophic cardiomyopathy.

Measurements

We identified the comorbidities as follows: 1. History of macrovascular disease included acute myocardial infarction, stable or unstable angina pectoris, heart failure, cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage, cerebral arterial aneurysm, aortic aneurysm and peripheral artery disease (arteriosclerosis obliterans). 2. In the present study, comorbid chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at registration, although the guideline for clinical practice require this low level that persists continuously for ≥3 months.[17] Furthermore, stage-3 diabetic nephropathy (overt nephropathy, macroalbuminuria ≥300 mg/g Cr or persistent proteinuria ≥0.5 g/g Cr), stage 4 (kidney failure, eGFR <30 mL/min/1.73 m^2) or stage 5 (any status of continued dialysis therapy) were included as comorbid chronic kidney disease.[18] 3. History of chronic respiratory disease included asthma, chronic obstructive pulmonary disease, interstitial pneumonia, pulmonary fibrosis and pneumoconiosis. 4. History of cancer included that of any organ. Serum glycated haemoglobin A1c (HbA1c) levels measured in the scale of The Japanese Diabetes Society (JDS) between 2003 and 2007 years were converted to those in the National Glycohemoglobin Standardization Program (NGSP) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).[19,20]

Statistical analysis

We analysed the data to determine the distributions of sex, HbA1c levels, fasting plasma glucose and diabetic complications. We presented the mean (standard deviation [SD]) values of age, HbA1c, body mass index (BMI), blood pressure and plasma cholesterol levels and the median (interquartile range) of the follow-up period. For primary outcomes, we used the Cox proportional hazard model[21] to calculate crude and multivariable-adjusted hazard ratios (HRs) in the model with explanatory variables of sex, age, serum HbA1c levels, systolic blood pressure (SBP), serum low-

Table 1
Baseline characteristics of patients with type 2 diabetic in Biobank Japan cohort.

Characteristics	Men	Women
Number (%)	19,830 (64.3)	11,004 (35.7)
Age, years	63.4 (11.0)	64.3 (11.2)
Body mass index, kg/m^2	24.1 (3.7)	24.7 (4.4)
Glycated haemoglobin A1c, % and mmol/mol	7.4 (1.4) and 57.1 (15.4)	7.5 (1.4) and 58.8 (15.5)
Systolic blood pressure, mm Hg	133.6 (17.2)	135.0 (17.6)
Diastolic blood pressure, mm Hg	77.5 (10.9)	75.6 (10.9)
Smoking, never/ex-/current, no.	5038/8282/6510	8832/990/1182
Currently drinking, no. (%)	10,057 (52.5)	1530 (14.3)
Glycated haemoglobin, no. (%)		
<6.0% (<42 mmol/mol)	7314 (36.9)	3879 (35.3)
6.0–6.4% (42–47 mmol/mol)	2304 (11.6)	1097 (10.0)
6.5–6.9% (48–52 mmol/mol)	2842 (14.3)	1556 (14.1)
7.0–7.9% (53–63 mmol/mol)	3804 (19.2)	2235 (20.3)
8.0–8.9% (64–74 mmol/mol)	2018 (10.2)	1230 (11.2)
≥9.0% (≥75 mmol/mol)	1548 (7.8)	1007 (9.2)
Fasting plasma glucose, no. (%)		
<126 mg/dL (<7.0 mmol/L)	1136 (10.4)	763 (12.3)
≥126 mg/dL (≥7.0 mmol/L)	9829 (89.6)	5430 (87.7)
Vascular complications, no. (%)		
None	7638 (38.5)	4778 (43.4)
Macrovascular disease	7368 (37.2)	3152 (28.6)
Nephropathy	1039 (5.2)	578 (5.3)
Retinopathy	1550 (7.8)	1090 (9.9)
Neuropathy	2235 (11.3)	1406 (12.8)
Comorbidity and past histories, no. (%)		
Chronic kidney disease	6236 (31.5)	3588 (32.6)
History of cancer	1910 (9.6)	949 (8.6)
History of chronic respiratory disease	805 (4.1)	568 (5.2)
Follow-up period from baseline, years, median (interquartile range)	8.03 (5.84–9.67)	8.30 (6.47–9.88)

The data are presented as mean (SD) or number (%) unless stated otherwise.

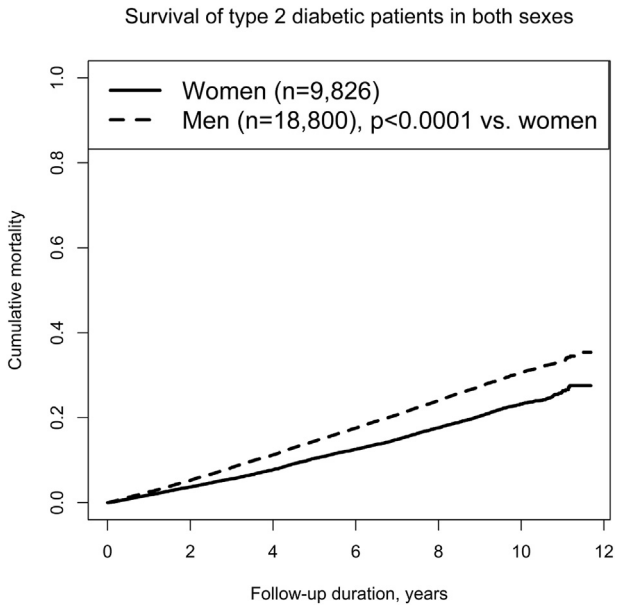

Fig. 1. Survival curves of Japanese patients with type 2 diabetes according to sex.

density lipoprotein cholesterol levels, histories of macrovascular disease, chronic respiratory disease and cancer, comorbid chronic kidney disease and smoking status. No multicollinearities were detected in terms of variance inflation factors < 1.5[22] among the explanatory variables of the multivariate analysis. We depicted Kaplan–Meier estimates for survival curves[23] to analyse the associations of sex, histories of macrovascular disease, chronic respiratory disease and cancer, comorbid chronic kidney disease and smoking status. We used the log-rank test[24] to assess the significance of the differences between survival curves. The statistical analyses were performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC, USA). R statistical software (version 2.15.3, R Project for Statistical Computing, Vienna, Austria) was used to generate Kaplan–Meier estimates. All reported p values were 2-sided, and $p < 0.05$ indicates a significant difference.

Ethical considerations

The ethics committees of the Institute of Medical Science, The University of Tokyo, RIKEN Center for Integrative Medical Sciences and 12 cooperating medical institutions approved the protocol of this study in accordance with the ethical guidelines and regulations of the Declaration of Helsinki. The Japanese guidelines permit the use of data from medical examinations and information without consent if the data are anonymous. Hence, informed consent was not required for the present investigation.

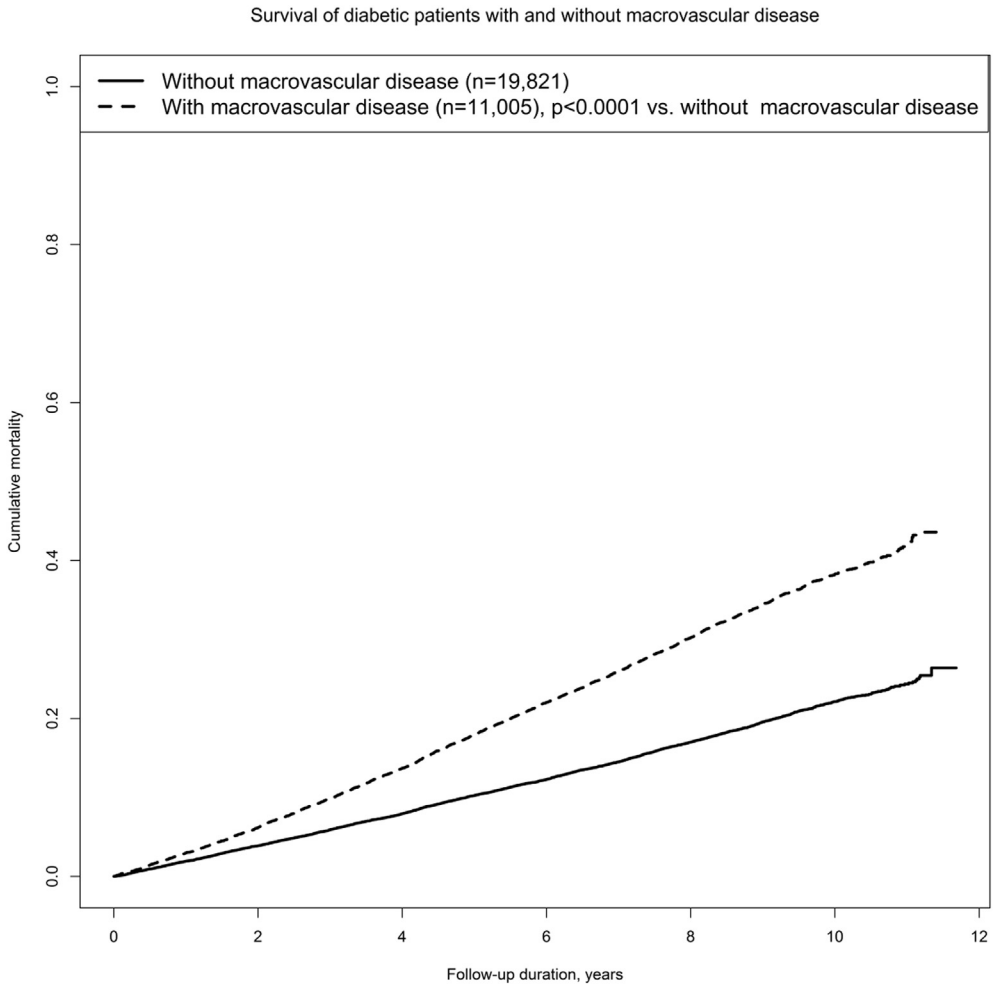

Fig. 2. Survival curves of Japanese patients with type 2 diabetes with and without a history of macrovascular disease.

Results

Patients

The study comprised 19,830 men (age range, 19–95 years) and 11,004 women (age range, 20–98 years) with type 2 diabetes. Table 1 presents the means (SDs) of age, BMI, HbA1c, blood pressure and the distributions of smoking and drinking status, glycaemic control, macro- and microvascular complications, histories of cancer and respiratory disease, comorbid chronic kidney disease at the baseline and follow-up period. The mean serum HbA1c levels were 7.4% (SD, 1.4) and 57.1 mmol/mol (SD, 15.4) for men and 7.5% (SD, 1.4) and 58.8 mmol/mol (SD, 15.5) for women. The mean ages of men and women were early sixties with mean BMIs of 24–25. At the baseline, 36.9% of men and 35.3% of women had HbA1c <6.0% (42 mmol/mol), and 61.5%, and 56.6% of the men and women, respectively, had complication of macro- or microvascular diseases.

Association of patients' characteristics and survival

Figs. 1–6 present estimated survival curves according to sex, histories of macrovascular disease, chronic respiratory disease and cancer and comorbidities of chronic kidney disease and smoking status. The median survival was short for those with a history of smoking, macrovascular disease, chronic respiratory disease or cancer or comorbidity of chronic kidney disease compared with those without the comorbidities. Table 2 presents crude and adjusted HRs of the explanatory variables associated with mortality. A 10-year incremental increase in age was related to mortality with an adjusted HR = 2.01 (95% confidence interval [95% CI], 1.78–2.26). An HbA1c level = 1% and 10 mm Hg systolic blood pressure were significantly related to mortality (adjusted HRs = 1.11 [95% CI, 1.03–1.19] and 1.11 [95% CI, 1.05–1.18], respectively). The adjusted HRs of patients with histories of macrovascular disease, cancer and chronic respiratory disease and comorbid chronic kidney disease, respectively, were as follows: 1.77 (95% CI, 1.42–2.22), 1.16 (95% CI, 0.86–1.56), 1.58 (95% CI, 1.08–2.31) and 2.03 (95% CI, 1.67–2.47).

Discussion

Here we show that comorbid chronic kidney disease had the most significant influence on survival of patients with type 2 diabetes, followed by a history of macrovascular disease and cigarette smoking. The estimated survival curves show the excess risks of mortality associated with comorbidities of interest.

Interpretations in the context of previous studies

The present data illuminate the excess risk of death of patients with diabetes associated with sex, age, various comorbidities and smoking (current or in the past). The results agree with those of a

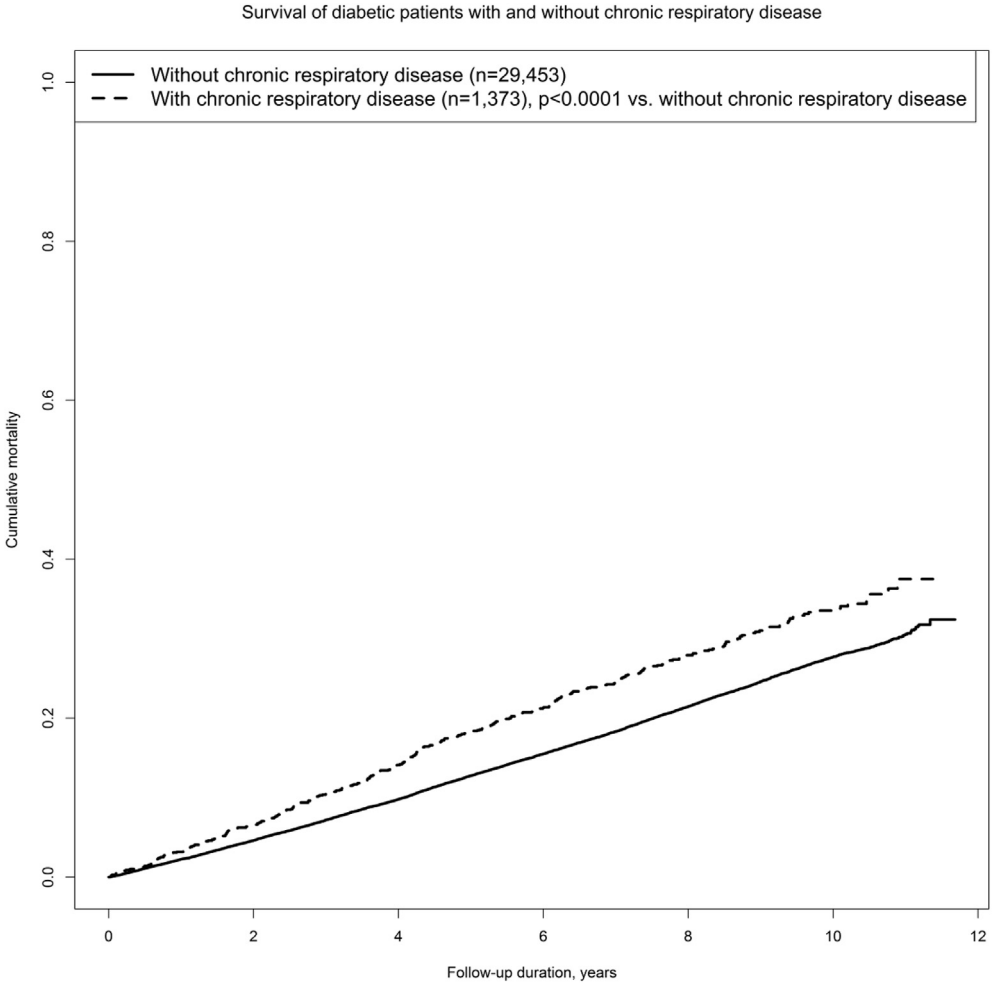

Fig. 3. Survival curves of Japanese patients with type 2 diabetes with and without a history of chronic respiratory disease.

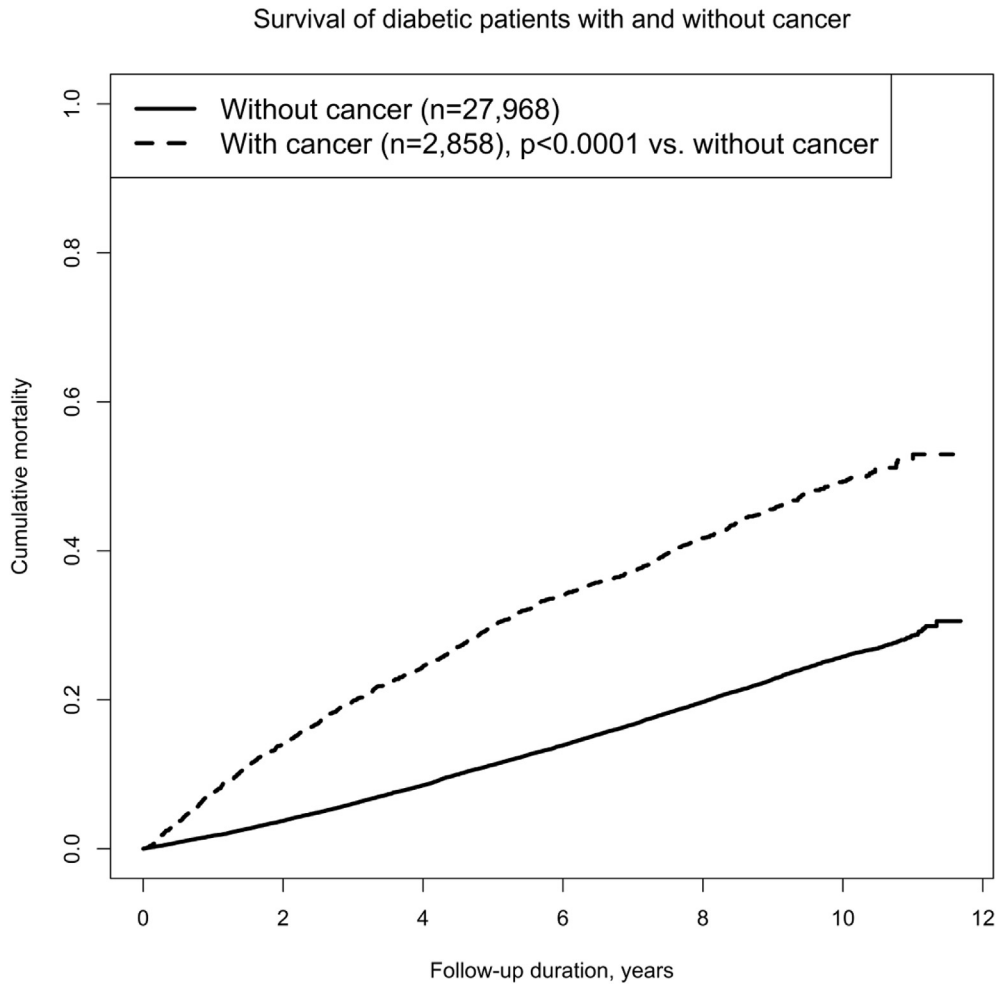

Fig. 4. Survival curves of Japanese patients with type 2 diabetes with and without a history of cancer.

previous study in North America,[25] indicating that for patients with diabetes, chronic kidney disease confers the highest risk of death among the risk factors listed in Table 2. Moreover, from literature, a lower glomerular filtration rate (GFR) contributes to a higher rate of all-cause mortality.[26] The relatively low risk of death (HR = 1.16 [95% CI, 0.86–1.56]) of patients with a history of cancer may be explained by survivor bias[27] and the use of biguanide metformin. Patients at the onset of cancer ought to have a high risk of mortality. A subset of the studied patients with a history of cancer may have survived from cancer and, at the baseline, may have a lower risk of cancer mortality. Additionally, a Danish study reports a reduced HR of 0.43 (95% CI, 0.23–0.80) for cancer mortality in patients with type 2 diabetes who were treated with biguanide metformin.[28] The agent may be reportedly anti-cancerous by decreased insulin-stimulated proliferation[29] and might decrease mortality risk in the present patients with a history of cancer.

Surprisingly, in appearance, chronic respiratory disease did not largely influence on the natural history of mortality (Fig. 3). This observation is because the patients were considered survivors from long disease duration of chronic respiratory disease, and patients with severe respiratory disease should have died at the baseline (survivor bias).[27] The risk of Japanese patients with respiratory disease should be determined using prospective cohort data for patients starting from the onset of chronic respiratory disease. Overall, we need to interpret that survivor bias should attenuate the differences as outcomes between patients with and without each comorbidity. In addition, because we preliminarily excluded the influence of steroid use, the adjusted HRs in Table 2 could be attenuated with the data of patients without severe chronic respiratory disease.

A history of macrovascular disease represented a large excess risk of death for 1.77 HR (95% CI, 1.42–2.22). This result is consistent with the results for American patients with adjusted HRs of 1.5 (95% CI, 1.1–2.0), 1.7 (95% CI, 1.2–2.3) and 2.4 (95% CI, 1.7–3.4) for nondiabetic previous MI, diabetic-first MI and diabetic previous MI groups, respectively, as compared with nondiabetic participants with no previous MI.[30] The significantly higher HR should alert patients to adhere to treatment prescribed by a physician and self-treatment. Male sex and age at baseline, unmodifiable risk factors, also exhibited excess mortality risk upon the patients in our data. The United Kingdom Prospective Diabetes Study (UKPDS), including a 4-year follow-up, reports 13% and 11% relative-risk increases in mortality associated with a 1% increase in serum HbA1c levels and a 10-mm Hg increase in SBP, respectively.[31] These data agree with ours as follows: median 8–9 year follow-up with 11% and 11% excess HR associated with a 1% increase in serum HbA1c levels and 10-mm Hg increase in SBP, respectively (Table 2).

The impacts of current and former smoking on survival curve are different than those on adjusted HR for mortality (Fig. 6 and Table 2). For this discrepancy, we consider that patients with serious comorbidities and at high risk of death who must have

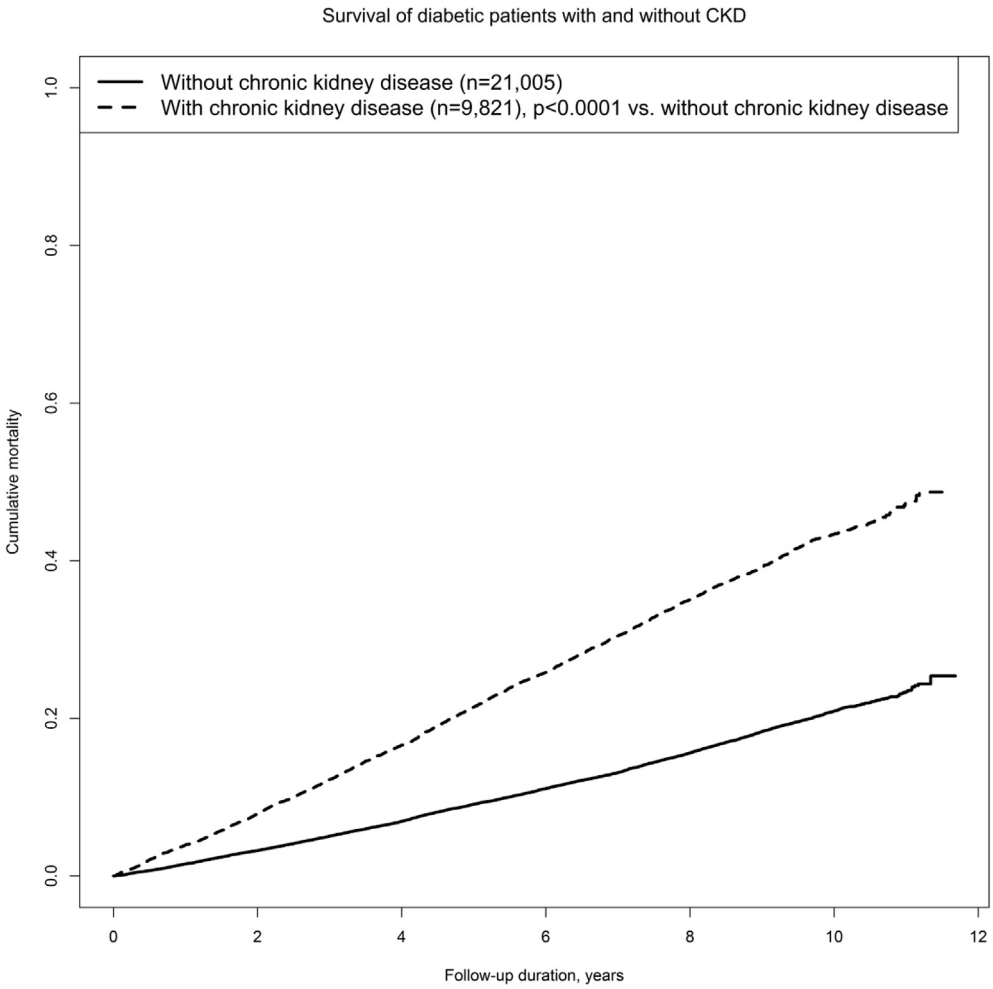

Fig. 5. Survival curves of Japanese patients with type 2 diabetes with and without chronic kidney disease.

stopped smoking cigarettes to improve their chances for survival were included in the ex-smoker group at the baseline, and the patients who 'could' continue to smoke represented a lower mortality risk in the crude survival curve. This observation and inference suggests that smoking cessation would extend life expectancy of patients with diabetes. In contrast, when adjusted for all the other risks, the higher HRs of current smokers compared with ex-smokers are medically reasonable. In the United States, approximately 17% of deaths can be attributed to current smoking in the general population.[32] The 1.74 HR (95% CI, 1.30–2.31) of current smokers among Japanese patients with diabetes should not be overlooked, and clinicians should firmly encourage patients to stop smoking because it is a modifiable risk factor.

Practical implications

Kidney disease accelerates atherosclerosis and therefore increases mortality,[33] contributing to the shorter survival of patients with diabetic nephropathy. A nationwide survey conducted in Japan demonstrates that lower eGFR levels and higher albuminuria linearly increased the incidence of cardiovascular events.[34] Conversely, a reduction in microalbuminuria in Japanese patients with diabetes reportedly results in a reduced cardiovascular risk.[35] The high HR with chronic kidney disease in our data should encourage diabetic patients to preserve renal function.

Cigarette smoking increases the mortality risk of patients with diabetes.[36] A randomised trial demonstrates that cessation of smoking decreases mortality in a general population.[37] The high HR for current smokers in the present study encourages patients with diabetes to stop smoking for longer survival expectancy. We believe that our data reported here that quantify mortality associated with comorbidities of patients with diabetes will be useful for clinicians to determine the priorities of treatments. In particular, we warn current smokers that this modifiable habit will impose approximately the same excess risk of death as 10-year increment of age and a history of macrovascular, chronic respiratory and chronic kidney diseases. Therefore, current smoking virtually ages patients by ten years, thus shortening life expectancy.

Limitations and strengths

We introduce here several aspects that strengthen the results. First, physicians diagnosed all diseases included in the BioBank Japan Project, providing internal validation. Second, >30,000 of the analysed patients with diabetes represent one of the highest numbers among the studied populations of East Asian countries. Third, the availability of detailed medical information allowed us to analyse various comorbidities together.

We note several limitations that may influence generalising the results to clinical practice. The primary limitation is that patients were enrolled during mid-course of disease, and therefore, they

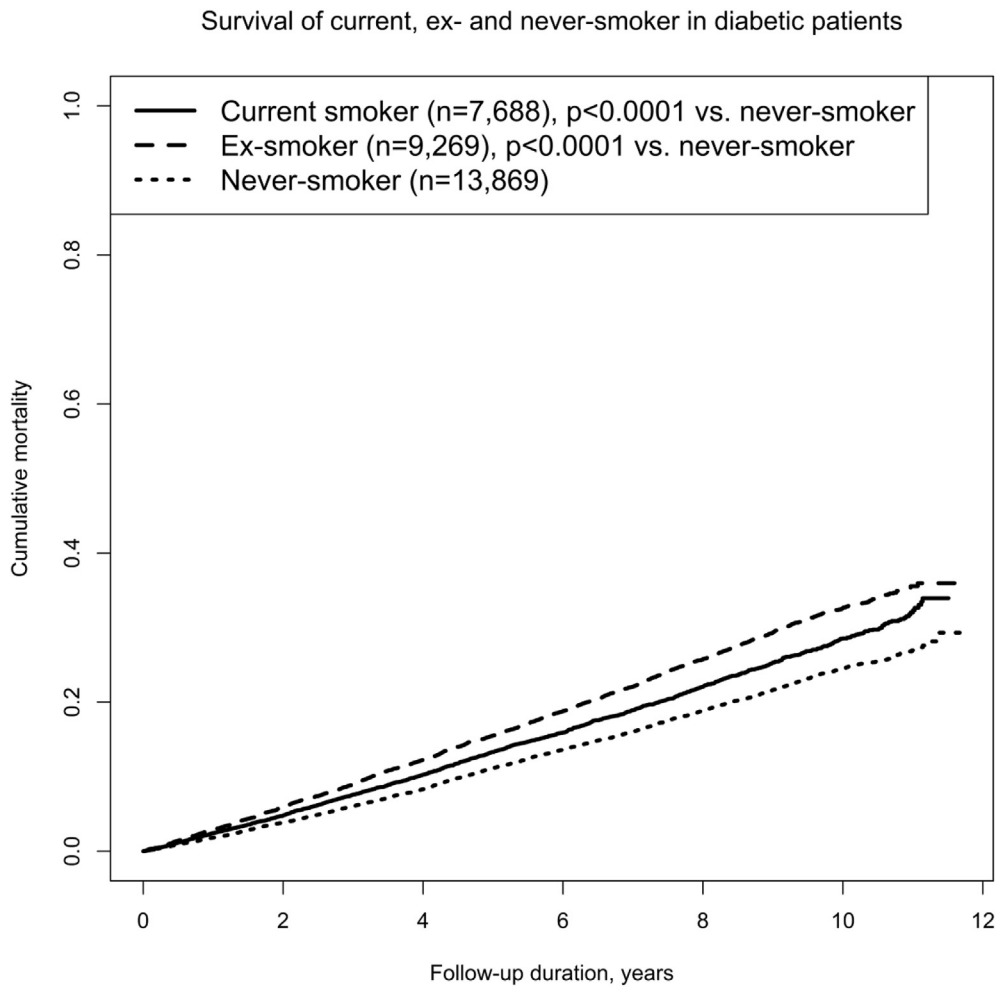

Fig. 6. Survival curves of current, ex- and non-smokers among Japanese patients with type 2 diabetes.

were not observed from onset of diabetes. Hence, the disease duration and the therapeutic regimens of the patients may have varied before enrolment. Although multivariable adjustment of the baseline age should attenuate this bias, the estimated survival curves and HRs should be carefully interpreted. Next, the chronological order of onsets of diabetes and comorbidities were unknown. This limitation resulted in the impossibility of causal inference linking comorbidities for exposure and death for outcome. In other words, we could not design the study to answer to the question of whether prevention of diabetic vascular comorbidities reduces the mortality. Third, the registration of diabetic patients in medium-to-large hospitals may have biased diabetes cases toward those of moderate to severe status, and the data may not represent Japanese patients with diabetes. Therefore, comparisons of mortality risks of patients with mild diabetes in primary care clinics are required to validate the data. Another limitation is the follow-up of a median 8–9 years. Because the effects of uncontrolled serum glucose and lipid levels and blood pressure[38] on

Table 2
Hazard ratios (95% confidence intervals) of risk factors for mortality of patients with type 2 diabetes.

Risk factors	Crude analysis[a]	p value	Multivariable analysis[a]	p value
Sex, men	1.40 (1.33–1.47)	p < 0.0001	1.39 (1.09–1.78)	p = 0.0081
Age per 10 years	1.97 (1.92–2.02)	p < 0.0001	2.01 (1.78–2.26)	p < 0.0001
HbA1c per 1%	0.97 (0.95–0.99)	p = 0.071	1.11 (1.03–1.19)	p = 0.0063
Systolic hypertension per 10 mm Hg	1.06 (1.04–1.07)	p < 0.0001	1.11 (1.05–1.18)	p = 0.0002
Low-density lipoprotein per 10 mg/dL	0.96 (0.94–0.98)	p = 0.0005	0.98 (0.95–1.01)	p = 0.14
History of macrovascular disease	1.92 (1.83–2.01)	p < 0.0001	1.77 (1.42–2.22)	p < 0.0001
History of cancer	2.48 (2.33–2.64)	p < 0.0001	1.16 (0.86–1.56)	p = 0.35
History of chronic respiratory disease	1.34 (1.21–1.48)	p < 0.0001	1.58 (1.08–2.31)	p = 0.019
Chronic kidney disease	2.48 (2.36–2.59)	p < 0.0001	2.03 (1.67–2.47)	p < 0.0001
Non-smoker	Ref		Ref	
Ex-smoker	1.42 (1.35–1.50)	p < 0.0001	1.24 (0.97–1.59)	p = 0.081
Current smoker	1.20 (1.13–1.28)	p < 0.0001	1.74 (1.30–2.31)	p = 0.0002

[a] Hazard ratios were estimated in crude or multivariable Cox proportional hazard model. In the multivariable analysis, no multicollinearity was detected in terms of variance inflation factors < 1.5.[22]

mortality would accelerate with time,[39] relatively fewer death events during the follow-up period may present smaller HRs. Last, analyses with more detailed information on variables such as diet, physical activity and socioeconomic status, should be considered as well.

Conclusions

Comorbid chronic kidney disease has exhibited the highest risk of mortality risk, followed by macrovascular disease, current smoking and chronic respiratory disease in patients with type 2 diabetes. The results indicate that patients with diabetes should preserve their renal, macrovascular and respiratory functions and terminate cigarette smoking, thus expecting better prognosis on their survival.

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Author contributions

MK and ZY conceived the study. MK, ZY and HY designed the study. HY performed statistical analysis and wrote the manuscript. AN, TN, YK and MH researched the data. All authors contributed to the discussion and reviewed and edited the manuscript. MK and ZY are the guarantors of this work, had full access to all the data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

None declared.

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Appendix

Members of medical institutions cooperating on the BioBank Japan Project who co-authored this paper include Hiromasa Harada, Sunao Matsubayashi, Rieko Komi and Kazuo Misumi (Tokushukai Hospitals); Shiro Minami, Hitoshi Sugihara and Eitaro Kodani (Nippon Medical School); Akio Kanazawa, Hiromasa Gotoh and Hidenori Haruna (Juntendo University); Satoshi Asai, Mitsuhiko Moriyama and Yasuo Takahashi (Nihon University); Tomoaki Fujioka and Wataru Obara (Iwate Medical University); Seijiro Mori and Hideki Ito (Tokyo Metropolitan Institute of Gerontology); Satoshi Nagayama and Yoshio Miki (The Cancer Institute Hospital of JFCR); Akihide Masumoto and Akira Yamada (Aso Iizuka Hospital); Yasuko Nishizawa and Ken Kodama (Osaka Medical Center for Cancer and Cardiovascular Diseases); Satoshi Ugi and Shinichi Araki (Shiga University of Medical Science); Yukihiro Koretsune and Hideki Taki (National Hospital Organization, Osaka National Hospital) and Takayuki Nakagawa (Fukujuji Hospital).

References

1. Asia Pacific Cohort Studies Collaboration. The effects of diabetes on the risks of major cardiovascular diseases and death in the Asia-Pacific region. *Diabetes Care*. 2003;26:360–366.
2. Yoon K-H, Lee J-H, Kim J-W, et al. Epidemic obesity and type 2 diabetes in Asia. *Lancet*. 2006;368:1681–1688.
3. Pyörälä K, Laakso M, Uusitupa M. Diabetes and atherosclerosis: an epidemiologic view. *Diabet Metab Rev*. 1987;3:463–524.
4. Seshasai SRK, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364:829.
5. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990–2010. *N Engl J Med*. 2014;370:1514–1523.
6. Noto H, Tsujimoto T, Noda M. Significantly increased risk of cancer in diabetes mellitus patients: a meta-analysis of epidemiological evidence in Asians and non-Asians. *J Diabetes Investig*. 2012;3:24–33.
7. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *CA-Cancer J Clin*. 2010;60:207–221.
8. Goodman WG, Goldin J, Kuizon BD, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med*. 2000;342:1478–1483.
9. Tancredi M, Rosengren A, Svensson A-M, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373:1720–1732.
10. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Resp J*. 2008;32:962–969.
11. Nakamura Y. The BioBank Japan Project. *Clin Adv Hematol Oncol*. 2007;5:696–697.
12. Nagai A, Hirata M, Muto K, et al. Overview of the BioBank Japan Project: study design and profiles. *J Epidemiol*. 2017;27:S2–S8.
13. Hirata M, Kamatani Y, Nagai A, et al. Cross-sectional analysis of BioBank Japan clinical data: a large cohort of 200,000 patients with 47 common diseases. *J Epidemiol*. 2017;27:S9–S21.
14. Hirata M, Nagai A, Kamatani Y, et al. Overview of BioBank Japan follow-up data in 32 diseases. *J Epidemiol*. 2017;27:S22–S28.
15. Ministry of Internal Affairs and Communications of Japan. *Statistics Act*; 2007. http://www.japaneselawtranslation.go.jp/law/detail/?vm=04&re=01&id=148. Accessed 12 December 2016.
16. Seino Y, Nanjo K, Tajima N, et al. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Invest*. 2010;1:212–228.
17. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011;80:17–28.
18. Haneda M, Utsunomiya K, Koya D, et al. A new classification of diabetic nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. *J Diabet Invest*. 2015;6:242–246.
19. Umemoto M, Raneva V, Tominaga M, et al. Relationship between NGSP and JDS HbA1c numbers. *Diabetol Int*. 2015;6:77–81.
20. Tajima N, Noda M, Origasa H, et al. Evidence-based practice guideline for the treatment for diabetes in Japan 2013. *Diabetol Int*. 2015;6:151–187.
21. Cox D. Regression models and life tables (with discussion). *J Roy Stat Soc*. 1972;34:187–220.
22. Lawlor DA, Benfield L, Logue J, et al. Association between general and central adiposity in childhood, and change in these, with cardiovascular risk factors in adolescence: prospective cohort study. *Br Med J*. 2010;341. c6224.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457–481.
24. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep Part 1*. 1966;50:163–170.
25. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis*. 1998;32:S112–S119.
26. Weiner DE, Tighiouart H, Amin MG, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol*. 2004;15:1307–1315.
27. Richardson D, Wing S, Steenland K, McKelvey W. Time-related aspects of the healthy worker survivor effect. *Ann Epidemiol*. 2004;14:633–639.
28. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ. Metformin associated with lower cancer mortality in type 2 diabetes ZODIAC-16. *Diabetes Care*. 2010;33:322–326.

29. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. *Endocr-Relat Cancer*. 2009;16:1103–1123.
30. Mukamal KJ, Nesto RW, Cohen MC, et al. Impact of diabetes on long-term survival after acute myocardial Infarction comparability of risk with prior myocardial infarction. *Diabetes Care*. 2001;24:1422–1427.
31. Leal J, Gray AM, Clarke PM. Development of life-expectancy tables for people with type 2 diabetes. *Eur Heart J*. 2009;30:834–839.
32. Carter BD, Abnet CC, Feskanich D, et al. Smoking and mortality—beyond established causes. *N Engl J Med*. 2015;372:631–640.
33. Chiu Y-W, Adler SG, Budoff MJ, Takasu J, Ashai J, Mehrotra R. Coronary artery calcification and mortality in diabetic patients with proteinuria. *Kidney Int*. 2010;77:1107–1114.
34. Yokoyama H, Araki S, Haneda M, et al. Chronic kidney disease categories and renal–cardiovascular outcomes in type 2 diabetes without prevalent cardiovascular disease: a prospective cohort study (JDDM25). *Diabetologia*. 2012;55:1911–1918.
35. S-i Araki, Haneda M, Koya D, et al. Reduction in microalbuminuria as an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes. *Diabetes*. 2007;56:1727–1730.
36. Stamler J, Vaccaro O, Neaton JD, Wentworth D, for the Multiple Risk Factor Intervention Trial Research Group. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434–444, 37.
37. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med*. 2005;142:233–239.
38. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903–1913.
39. Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008;358:580–591.