ARTICLE

Association between type 2 diabetes and risk of cancer mortality: a pooled analysis of over 771,000 individuals in the Asia Cohort Consortium

Yu Chen [1,2] · Fen Wu [1,2] · Eiko Saito [3,4] · Yingsong Lin [5] · Minkyo Song [6] · Hung N. Luu [7,8] ·
Prakash C. Gupta [9] · Norie Sawada [4] · Akiko Tamakoshi [10] · Xiao-Ou Shu [7] ·
Woon-Puay Koh [11,12] · Yong-Bing Xiang [13] · Yasutake Tomata [14] · Kemmyo Sugiyama [14] ·
Sue K. Park [15] · Keitaro Matsuo [16,17] · Chisato Nagata [18] · Yumi Sugawara [14] ·
You-Lin Qiao [19] · San-Lin You [20,21] · Renwei Wang [22] · Myung-Hee Shin [23] ·
Wen-Harn Pan [24] · Mangesh S. Pednekar [9] · Shoichiro Tsugane [4] · Hui Cai [7] ·
Jian-Min Yuan [25,26] · Yu-Tang Gao [13] · Ichiro Tsuji [14] · Seiki Kanemura [14] ·
Hidemi Ito [17,27] · Keiko Wada [18] · Yoon-Ok Ahn [15] · Keun-Young Yoo [28] ·
Habibul Ahsan [29] · Kee Seng Chia [12] · Paolo Boffetta [30] · Wei Zheng [7] · Manami Inoue [3,4] ·
Daehee Kang [15,31,32] · John D. Potter [33,34,35]

Abstract

Aims/hypothesis The aims of the study were to evaluate the association between type 2 diabetes and the risk of death from any cancer and specific cancers in East and South Asians.

Methods Pooled analyses were conducted of 19 prospective population-based cohorts included in the Asia Cohort Consortium, comprising data from 658,611 East Asians and 112,686 South Asians. HRs were used to compare individuals

✉ Yu Chen
   yu.chen@nyumc.org

[1] Department of Population Health, New York University School of Medicine, 650 First Avenue, Room 510, New York, NY 10016, USA

[2] Department of Environmental Medicine, New York University School of Medicine, Tuxedo Park, NY 10987, USA

[3] AXA Department of Health and Human Security, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

[4] Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan

[5] Department of Public Health, Aichi Medical University School of Medicine, Nagakute, Japan

[6] Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[7] Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN, USA

[8] Department of Epidemiology and Biostatistics, College of Public Health, University of South Florida, Tampa, FL, USA

[9] Healis Sekhsaria Institute for Public Health, Navi Mumbai, India

[10] Graduate School of Medicine, Hokkaido University, Sapporo, Japan

[11] Duke-NUS Medical School Singapore, Singapore, Republic of Singapore

[12] Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Republic of Singapore

[13] Shanghai Cancer Institute, Shanghai Jiaotong University, Shanghai, People's Republic of China

[14] Tohoku University Graduate School of Medicine, Miyagi Prefecture, Japan

[15] Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, South Korea

[16] Division of Molecular Medicine, Aichi Cancer Center Research Institute, Nagoya, Japan

[17] Department of Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan

with diabetes at baseline with those without diabetes for the risk of death from any cancer and from site-specific cancers, including cancers of the oesophagus, stomach, colorectum, colon, rectum, liver, bile duct, pancreas, lung, breast, endometrium, cervix, ovary, prostate, bladder, kidney and thyroid, as well as lymphoma and leukaemia.

Results During a mean follow-up of 12.7 years, 37,343 cancer deaths (36,667 in East Asians and 676 in South Asians) were identified. Baseline diabetes status was statistically significantly associated with an increased risk of death from any cancer (HR 1.26; 95% CI 1.21, 1.31). Significant positive associations with diabetes were observed for cancers of the colorectum (HR 1.41; 95% CI 1.26, 1.57), liver (HR 2.05; 95% CI 1.77, 2.38), bile duct (HR 1.41; 95% CI 1.04, 1.92), gallbladder (HR 1.33; 95% CI 1.10, 1.61), pancreas (HR 1.53; 95% CI 1.32, 1.77), breast (HR 1.72; 95% CI 1.34, 2.19), endometrium (HR 2.73; 95% CI 1.53, 4.85), ovary (HR 1.60; 95% CI 1.06, 2.42), prostate (HR 1.41; 95% CI 1.09, 1.82), kidney (HR 1.84; 95% CI 1.28, 2.64) and thyroid (HR 1.99; 95% CI 1.03, 3.86), as well as lymphoma (HR 1.39; 95% CI 1.04, 1.86). Diabetes was not statistically significantly

associated with the risk of death from leukaemia and cancers of the bladder, cervix, oesophagus, stomach and lung. *Conclusions/interpretation* Diabetes was associated with a 26% increased risk of death from any cancer in Asians. The pattern of associations with specific cancers suggests the need for better control (prevention, detection, management) of the growing epidemic of diabetes (as well as obesity), in order to reduce cancer mortality.

Keywords Asia Cohort Consortium · Asians · Cancer mortality · Meta-analysis · Type 2 diabetes

Abbreviations
ACC   Asia ohort Consortium
CPS II   Cancer Prevention Study II
CVD   Cardiovascular disease
ERFC   Emerging risk factors collaboration

[18]   Graduate School of Medicine, Gifu University, Gifu, Japan

[19]   Cancer Foundation of China, Beijing, People's Republic of China

[20]   School of Medicine, Fu-Jen Catholic University, Taipei, Taiwan

[21]   Big Data Research Centre, Fu-Jen Catholic University, Taipei, Taiwan

[22]   University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA

[23]   Department of Social and Preventive Medicine, Sungkyunkwan University School of Medicine, Seoul, South Korea

[24]   Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan

[25]   Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA

[26]   Division of Cancer Control and Population Science, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA

[27]   Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan

[28]   Armed Forces Capital Hospital, Seoul National University College of Medicine, Seoul, South Korea

[29]   Department of Public Health Sciences, University of Chicago, Chicago, IL, USA

[30]   Icahn School of Medicine at Mount Sinai, New York, NY, USA

[31]   Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, South Korea

[32]   Cancer Research Institute, Seoul National University, Seoul, South Korea

[33]   Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[34]   Centre for Public Health Research, Massey University, Wellington, New Zealand

[35]   Department of Epidemiology, University of Washington, Seattle, WA, USA

Introduction

There is emerging evidence of a link between type 2 diabetes and an increased risk of developing cancer and death from cancer. A meta-analysis estimated that diabetes was associated with a 17% and 21% increased risk of developing any cancer and death from any cancer, respectively [1]. However, most studies of the association between diabetes and cancer risk have been conducted in Western populations [2]. Epidemiological studies have documented consistent increases in the prevalence of diabetes across Asia [3, 4]. Some evidence suggests that, at any given BMI, Asians are more susceptible to insulin resistance and have a higher prevalence of diabetes in comparison with whites [5]. The risk of diabetes-related complications and comorbidities may be different in Asians and whites. Some evidence also suggests that cancer risk associated with diabetes is higher in Asians than in non-Asians [1]; however, the data are inconclusive. Given the increasing prevalence of diabetes and diabetes risk factors in Asian populations [3, 4], it is important to understand the effect of diabetes on cancer in Asians.

Several prospective studies of diabetes and site-specific cancer risk have been conducted in individual cohorts in East Asians. However, the majority of the studies have examined risk for one or only a few cancer sites [6–10], included a small number of patients with diabetes [11, 12], or failed to control for important potential confounding variables such as BMI or obesity [6–8, 12, 13]. Asia is heterogeneous, with higher cancer mortality found in East Asian countries such as China, Japan and South Korea (125–164 per 100,000 in men and 65–82 per 100,000 in women) than in South Asian countries such as Bangladesh and India (70–90 per 100,000 in

men and 60–72 per 100,000 in women) [14]. However, no prospective cohort studies have investigated the influence of diabetes on cancer in South Asians. Large prospective studies on the association between diabetes and cancer at specific organ sites in Asian populations are therefore needed.

We conducted a pooled analysis to evaluate the association between baseline diabetes and risk of death from all cancers and site-specific cancers, in 19 Asian prospective cohorts in the Asia Cohort Consortium (ACC).

Methods

ACC Details of the ACC, an international collaboration committed to the study of the aetiology of diseases in Asian populations, have been presented elsewhere [15, 16]. Cohorts were identified through a systematic search of the literature in early 2008, followed by a survey that was sent to each

cohort to assess data availability [16]. The ACC includes more than 20 cohorts representing Japan, China, South Korea, India, Taiwan, Bangladesh and Singapore. Cohort studies that were included in the present study are listed in Table 1. Several of these cohorts have examined the association between diabetes and cancer risk [9, 17, 18]. Our study was approved by the institutional review board of the Fred Hutchinson Cancer Research Center (Seattle, WA, USA) and by the ethics committees of each individual cohort study.

Data manipulation Relevant data from each of the participating cohorts were transferred and harmonised at the ACC coordinating centre at the Fred Hutchinson Cancer Research Center. Harmonisation involved several rounds of discussions to ensure that variables were correctly interpreted and extracted. Data were checked for illogical or missing values, and queries were sent back for clarification. The distributions of individual variables were explored to identify false or

Table 1 Selected characteristics of participating cohorts

Cohort	No. of participants	Enrolment period	Mean follow-up (years)	Mean age at baseline (years)	Male sex (%)	Ever smokers (%)		Diabetes at baseline (%)	No. of cancer deaths
						Men	Women		
East Asians	658,611	1984-2006	13.9	54.5	48.2	72.5	7.1	5.1	36,667
China (mainland)									
Linxian	29,464	1984-1987	18.5	51.9	44.6	67.1	0.2	0.1	2087
SCS	18,092	1986-1989	16.3	55.3	100.0	57.3	—	1.3	1974
SMHS	61,466	2001-2006	8.3	55.3	100.0	69.6	—	6.3	1977
SWHS	74,935	1996-2000	13.8	52.6	0.0	—	2.8	4.4	2682
Taiwan									
CBCSP	23,755	1991-1992	15.2	47.3	50.3	56.5	1.0	2.5	1012
CVDFACTS	5156	1990-1993	14.9	47.6	44.1	54.2	1.7	3.5	219
Singapore									
SCHS	63,257	1993-1999	11.5	56.5	44.2	58.0	8.8	9.0	3887
South Korea									
KMCC	13,143	1993-2004	13.5	54.9	40.0	79.6	9.3	4.7	833
Seoul Male	13,833	1992-1993	15.6	49.2	100.0	77.3	—	2.9	495
Japan									
3 Pref. Aichi	23,111	1985	11.7	54.8	47.0	83.3	15.0	4.7	1119
JPHC1	43,051	1990-1992	21.0	49.6	47.9	75.9	7.5	4.0	2933
JPHC2	56,535	1992-1995	17.7	54.3	47.4	75.8	7.8	5.7	4737
3 Pref. Miyagi	31,345	1984	11.5	57.3	44.6	77.4	12.6	5.7	1884
Miyagi	47,604	1990	16.2	52.1	48.0	81.7	11.3	4.3	2367
Ohsaki	51,250	1994	10.7	60.5	47.9	81.6	11.2	6.7	2886
JACC	75,485	1988-1990	12.8	57.0	42.0	78.9	6.3	5.5	3988
Takayama	27,129	1992	13.5	56.1	45.3	83.4	17.5	5.3	1587
South Asians	112,686	1991-2002	5.8	50.3	65.7	35.3	1.4	2.4	676
India									
MCS	101,262	1991-1997	5.0	51.8	68.3	32.5	0.4	2.4	552
Bangladesh									
HEALS	11,424	2000-2002	12.4	37.0	42.5	74.2	6.2	2.1	124
Total	771,297	1984-2006	12.7	53.9	50.8	65.3	6.5	4.7	37,343

3 Pref. Aichi, Three-Prefecture Cohort Study Aichi; 3 Pref. Miyagi, Three-Prefecture Cohort Study Miyagi; CBCSP, Community-Based Cancer Screening Program; CVDFACTS, Cardiovascular Disease Risk Factors Two-Township Study; HEALS, Health Effects of Arsenic Longitudinal Study; JACC, Japan Collaborative Cohort Study; JPHC, Japan Public Health Center-Based Prospective Study; KMCC, Korea Multicenter Cancer Cohort Study; Seoul Male, Seoul Male Cohort Study; Linxian, Linxian General Population Trial Cohort Study; MCS, Mumbai Cohort Study; Miyagi, Miyagi Cohort Study; Ohsaki, Ohsaki National Health Insurance Beneficiaries Cohort Study; SCHS, Singapore Chinese Health Study; SCS, Shanghai Cohort Study; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; Takayama, Takayama Study

implausible values. All personal identifiers were removed, but study-specific ID numbers were retained to facilitate referral of all queries back to the individual cohort.

Diabetes and outcome data The 19 participating cohorts included a total of 847,009 individuals. Self-reported data on diabetes at baseline were collected from all cohorts. Available data on other indicators of diabetes in some of the cohorts support the overall validity of these self-reported data. For instance, in the Bangladeshi cohort, glycosuria was measured in 11,122 (95%) members, and 62% of participants who tested positive for glycosuria also self-reported as having been diagnosed with diabetes by a physician, while 99.1% of those who tested negative reported no such history [19]. The result is comparable with that from high-income countries such as Japan, where the sensitivity and specificity of the questionnaire for diabetic hyperglycaemia were 46% and 98%, respectively [15, 20].

All the participating cohorts were required to have available baseline data on diabetes status (self-reported), BMI (measured or self-reported), cigarette-smoking status, age, sex, follow-up time, vital status and cause of death (ICD-9 [www.icd9data.com/2007/Volume1] or ICD-10 [www.who.int/classifications/icd/en/]). In the present analysis, we excluded participants with data missing on age ($n = 528$), baseline diabetes ($n = 73,178$) and vital status ($n = 2775$), and those for whom data on follow-up duration were invalid or missing ($n = 2947$). After these exclusions, 771,297 participants remained (391,619 men and 379,678 women). Information on the types of diabetes (i.e. type 1 or type 2) was not available; however, given that type 1 diabetes accounts for less than 3% of total diabetes in Asia [21] and that we included adult cohorts only, we assume the large majority would have had type 2 diabetes. Additional data were available from selected cohorts on alcohol drinking (17 cohorts), education (14 cohorts), urban/rural residence (18 cohorts), duration of diabetes (six cohorts), and diabetes treatment (four cohorts).

Cancer death was ascertained from the underlying causes of death recorded on death certificates or death records in East Asian cohorts and in the Mumbai cohort. A validated verbal autopsy questionnaire was used in the Bangladesh cohort [22]. Outcomes of interest included: death from any cancer and cancers of the oesophagus, stomach, colorectum, colon, rectum, liver, bile duct, pancreas, lung, breast, endometrium, cervix, ovary, prostate, bladder, kidney and thyroid, as well as lymphoma and leukaemia (electronic supplementary material [ESM] Table 1). Cancers of interest were selected based on prior literature on the association between diabetes and the risk of death from cancer [2, 23].

Statistical analyses To examine the relationship between diabetes and the risk of death from cancer, we estimated HRs and 95% CIs based on Cox proportional hazards regression models that combined studies in a meta-analysis of individual participant data [24, 25]. The assumption of proportional hazards was examined by testing the cross-product terms between covariate variables and log function of survival time within individual cohorts; p values for all the terms were >0.10. In all analyses, the effect of diabetes on the risk of death from cancer was taken to be cohort-specific, assuming that the log-HR associated with diabetes had a fixed-effect component in each cohort that was common to all cohorts and a cohort-specific random effect that was normally distributed with mean zero.

Potential confounders included baseline age, sex, cigarette smoking (never/ever), BMI, alcohol consumption (never/ever), educational attainment (no formal education, primary, secondary, trade/technical, university degree, postgraduate degree, other) and urban residence. Likelihood-based methods were used to test for heterogeneity across studies or geographic regions by comparing models with and without interactions between cohort or geographic region and baseline diabetes status. Stratified analyses were conducted by sex. To evaluate the potential effect of reverse causation, analyses excluded person-years and deaths with fewer than 3 years of follow-up.

For any cancer and cancers with sufficient number of deaths among those with diabetes ($n > 70$) that were also associated with diabetes status in the main analyses, including colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer and breast cancer, we further performed stratified analyses among East Asians (China, Taiwan, Singapore, South Korea and Japan) and South Asians (Bangladesh and India); by baseline age (<60 or ≥60 years, the median among cancer deaths in the combined East and South Asians); by baseline smoking status (never/ever); by baseline alcohol consumption status (never/ever); and by baseline BMI (22.8 kg/m^2, the median among cancer deaths), to evaluate whether the influence of diabetes was similar in different subgroups. In cohorts with the available information, sensitivity analyses were also conducted to: (1) further control for baseline status of hypertension or cardiovascular disease (CVD); (2) further control for baseline status of cancer; (3) exclude studies that were initially clinical trials; and (4) exclude prevalent cases of CVD and cancer at baseline. In a subgroup of six cohorts ($n = 243,214$) with data on age at first diagnosis of diabetes, diabetes duration at baseline was calculated as the difference between age at first diagnosis and age at enrolment. We conducted analyses to estimate HRs, comparing those with different diabetes duration (<5 or ≥5 years) with those without diabetes at baseline. A separate model was also conducted including only the diabetes cases to compare the risk of death from cancer by diabetes duration (<5 vs ≥5 years) and to estimate the p values of the comparisons. Similar analyses were conducted in a subgroup of four cohorts ($n = 198,440$) with data on current treatment of diabetes (yes/no). All statistical analyses were conducted using SAS, version 9.4 (SAS

Institute, Cary, NC, USA) or Stata, version 14.0 (StataCorp LP, College Station, TX, USA). All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

After exclusions, the study comprised a total of 771,297 participants from 19 cohorts (Table 1), including 658,611 East Asians and 112,686 South Asians. The participants were, on average, 53.9 years old at baseline and had a mean follow-up of 12.7 years. Across all studies, 50.8% were men and 65.3% of men were ever smokers. The diabetes prevalence was lowest in the Linxian General Population Trial Cohort Study in China (0.1%) and highest in the Singapore Chinese Health Study (9.0%). Overall, diabetes was statistically significantly associated with a higher risk of death from any cancer and from cancers of the colorectum, colon and rectum separately, liver, bile duct, gallbladder, pancreas, breast, endometrium,

ovary, prostate, kidney and thyroid, as well as lymphoma (Table 2). The association was strongest for cancers of the liver, endometrium and thyroid. After excluding the first 3 years of follow-up, the associations between diabetes and the risk of death from any cancer and site-specific cancers were not materially changed.

The pattern of the associations between diabetes and cancer mortality in men was similar to that seen overall (Fig. 1). The risk of death from lymphoma, oesophageal cancer and stomach cancer associated with diabetes was greater in women than in men. There was evidence of effect modification by sex for lymphoma ($p_{\text{interaction}} < 0.01$) and stomach cancer ($p_{\text{interaction}} = 0.02$). The positive association between diabetes and any cancer was similar in East and South Asians, although the estimate in South Asians did not reach statistical significance, possibly owing to the small number of deaths in participants with diabetes (Fig. 2). Excluding participants with a history of cancer, hypertension or CVD, and additional adjustment for these conditions did not change the strength of the

Table 2 Association between diabetes at baseline and site-specific cancer mortality in Asia

Type of cancer	All participants			Excluding first 3 years of follow-up		
	Deaths (n) with diabetes	Deaths (n) without diabetes	HR (95% CI)[a]	Deaths (n) with diabetes	Deaths (n) without diabetes	HR (95% CI)[a]
Any cancer	2694	34,649	1.26 (1.21, 1.31)	2229	30,023	1.25 (1.20, 1.31)
Oesophagus	71	1302	1.09 (0.85, 1.38)	57	1134	1.07 (0.81, 1.42)
Stomach	342	5974	1.08 (0.95, 1.23)	285	5126	1.11 (0.96, 1.29)
Colorectum	360	3834	1.41 (1.26, 1.57)	294	3372	1.36 (1.20, 1.53)
Colon	248	2433	1.50 (1.30, 1.73)	205	2147	1.47 (1.25, 1.72)
Rectum	112	1401	1.30 (1.07, 1.58)	89	1225	1.23 (0.99, 1.54)
Liver	434	3318	2.05 (1.77, 2.38)	347	2812	2.02 (1.74, 2.35)
Bile duct[b]	45	528	1.41 (1.04, 1.92)	40	487	1.42 (1.02, 1.96)
Gallbladder	121	1493	1.33 (1.10, 1.61)	102	1305	1.35 (1.10, 1.66)
Pancreas	208	2225	1.53 (1.32, 1.77)	178	1951	1.57 (1.34, 1.83)
Lung	463	7401	0.98 (0.89, 1.09)	381	6510	0.96 (0.86, 1.07)
Breast[c]	75	950	1.72 (1.34, 2.19)	62	786	1.95 (1.49, 2.56)
Endometrium[c]	15	143	2.73 (1.53, 4.85)	10	132	2.09 (1.05, 4.12)
Cervix[c]	17	257	1.70 (0.90, 3.23)	12	214	1.82 (0.80, 4.13)
Ovary[c]	26	396	1.60 (1.06, 2.42)	23	323	1.85 (1.19, 2.88)
Prostate[d]	66	692	1.41 (1.09, 1.82)	57	630	1.37 (1.03, 1.82)
Bladder	38	468	1.38 (0.90, 2.10)	32	427	1.45 (0.90, 2.34)
Kidney	51	514	1.84 (1.28, 2.64)	44	450	1.89 (1.34, 2.68)
Thyroid	11	137	1.99 (1.03, 3.86)	10	124	1.97 (1.00, 3.90)
Lymphoma	69	841	1.39 (1.04, 1.86)	62	729	1.51 (1.11, 2.04)
Leukaemia	52	790	1.30 (0.90, 1.88)	47	666	1.47 (1.00, 2.16)

[a] HRs were adjusted for sex, baseline age, BMI, cigarette smoking, alcohol consumption, educational attainment and urban residence

[b] Data were available only from the Seoul Male Cohort Study, Three-Prefecture Cohort Study Aichi, Japan Public Health Center-Based Prospective Study 1 and 2, Miyagi Cohort Study, Three-Prefecture Cohort Study Miyagi and the Ohsaki National Health Insurance Beneficiaries Cohort Study

[c] Among women only

[d] Among men only

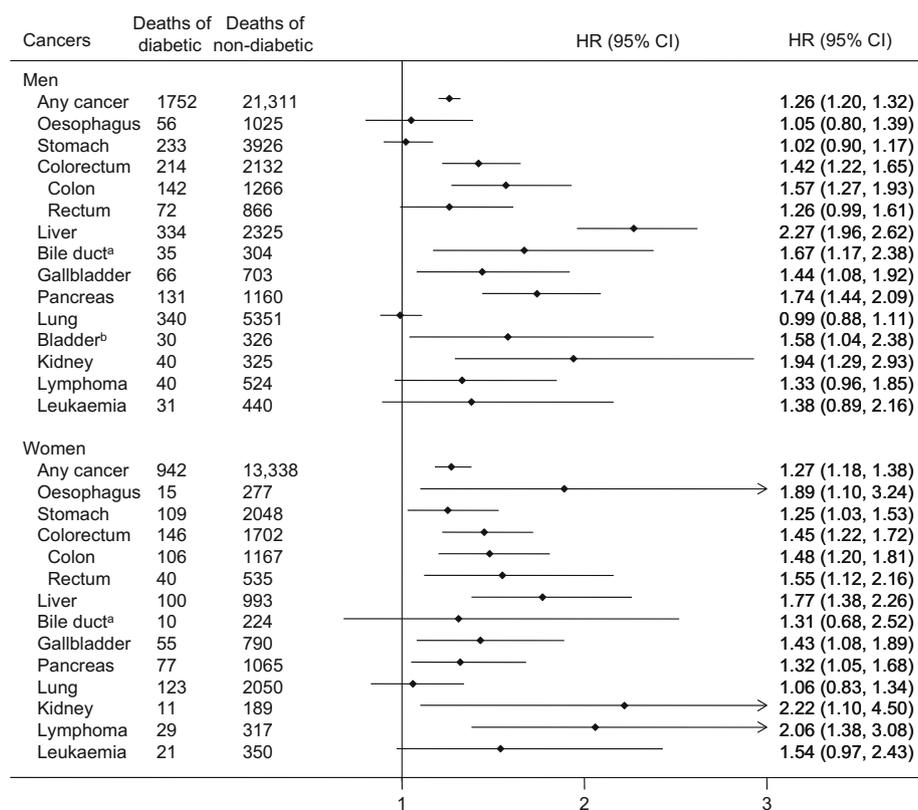**Fig. 1** Association between diabetes at baseline and site-specific cancer mortality in Asia by sex. HRs were adjusted for sex, baseline age, BMI, cigarette smoking, alcohol consumption, educational attainment and urban residence. [a]Data were available only from the Seoul Male Cohort Study, Three-Prefecture Cohort Study Aichi, Japan Public Health Center-Based Prospective Study 1 and 2, Miyagi Cohort Study, Three-Prefecture Cohort Study Miyagi and Ohsaki National Health Insurance Beneficiaries Cohort Study. [b]Results are not shown among women because there were fewer than ten cancer deaths among participants with diabetes at baseline

Cancers	Deaths of diabetic	Deaths of non-diabetic	HR (95% CI)
Men			
Any cancer	1752	21,311	1.26 (1.20, 1.32)
Oesophagus	56	1025	1.05 (0.80, 1.39)
Stomach	233	3926	1.02 (0.90, 1.17)
Colorectum	214	2132	1.42 (1.22, 1.65)
Colon	142	1266	1.57 (1.27, 1.93)
Rectum	72	866	1.26 (0.99, 1.61)
Liver	334	2325	2.27 (1.96, 2.62)
Bile duct[a]	35	304	1.67 (1.17, 2.38)
Gallbladder	66	703	1.44 (1.08, 1.92)
Pancreas	131	1160	1.74 (1.44, 2.09)
Lung	340	5351	0.99 (0.88, 1.11)
Bladder[b]	30	326	1.58 (1.04, 2.38)
Kidney	40	325	1.94 (1.29, 2.93)
Lymphoma	40	524	1.33 (0.96, 1.85)
Leukaemia	31	440	1.38 (0.89, 2.16)
Women			
Any cancer	942	13,338	1.27 (1.18, 1.38)
Oesophagus	15	277	1.89 (1.10, 3.24)
Stomach	109	2048	1.25 (1.03, 1.53)
Colorectum	146	1702	1.45 (1.22, 1.72)
Colon	106	1167	1.48 (1.20, 1.81)
Rectum	40	535	1.55 (1.12, 2.16)
Liver	100	993	1.77 (1.38, 2.26)
Bile duct[a]	10	224	1.31 (0.68, 2.52)
Gallbladder	55	790	1.43 (1.08, 1.89)
Pancreas	77	1065	1.32 (1.05, 1.68)
Lung	123	2050	1.06 (0.83, 1.34)
Kidney	11	189	2.22 (1.10, 4.50)
Lymphoma	29	317	2.06 (1.38, 3.08)
Leukaemia	21	350	1.54 (0.97, 2.43)

association appreciably. A greater risk of death from any cancer was associated with diabetes among individuals who were <60 years at baseline than among individuals ≥60 years ($p_{interaction} < 0.01$). For colorectal cancer, the HRs were similar across all subgroups (Fig. 2). Similarly, a stronger association between diabetes and the risk of death from liver cancer and gallbladder cancer was observed in individuals <60 years compared with those ≥60 years ($p_{interaction} < 0.01$). For pancreatic cancer, the risk of death associated with diabetes was stronger in individuals <60 years and in those with a BMI <22.8 kg/m^2 compared with the HRs observed in the respective counterparts; the interaction of diabetes with age and BMI was statistically significant ($p_{interaction} = 0.02$ and 0.03, respectively). The positive association between diabetes and death from breast cancer remained robust with additional control for the influence of baseline cancer, hypertension or CVD, and among never smokers and never drinkers. The association was stronger in those with a lower BMI compared with those with a higher BMI, although the interaction was not statistically significant.

We further explored the relationship of duration and treatment of diabetes with the risk of death from cancer in cohorts with available data. Analyses were done for cancers with ten or more deaths among diabetic participants. With the exception of breast cancer, among diabetic participants the associations between diabetes of ≥5 years' duration at baseline and the risk of death from any cancer and colorectal cancer, liver

cancer or pancreatic cancer were weaker than those related to diabetes of <5 years' duration; however, none of the differences in estimates was statistically significant (ESM Table 2). In cohorts with data on current treatment, participants currently treated for diabetes, compared with those not currently treated, tended to have a greater risk of death from any cancer and cancers of the liver, gallbladder and pancreas; however, the risk difference reached statistical significance for death from any cancer only ($p = 0.03$; ESM Table 3). Results from sensitivity analyses excluding studies that were initially clinical trials (Linxian General Population Trial Cohort Study) were essentially the same (data not shown).

Discussion

In this pooled analysis of 19 Asian cohorts including more than 771,000 participants followed for up to 21 years, diabetes was associated with a 26% increase in the risk of death from any cancer. Specifically, diabetes was related to an increased risk of death from colorectal cancer, liver cancer, bile duct cancer, gallbladder cancer, pancreatic cancer, breast cancer, endometrial cancer, ovarian cancer, prostate cancer, kidney cancer, thyroid cancer and lymphoma. The positive associations for any cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer and breast cancer remained across different strata of BMI, smoking status and alcohol
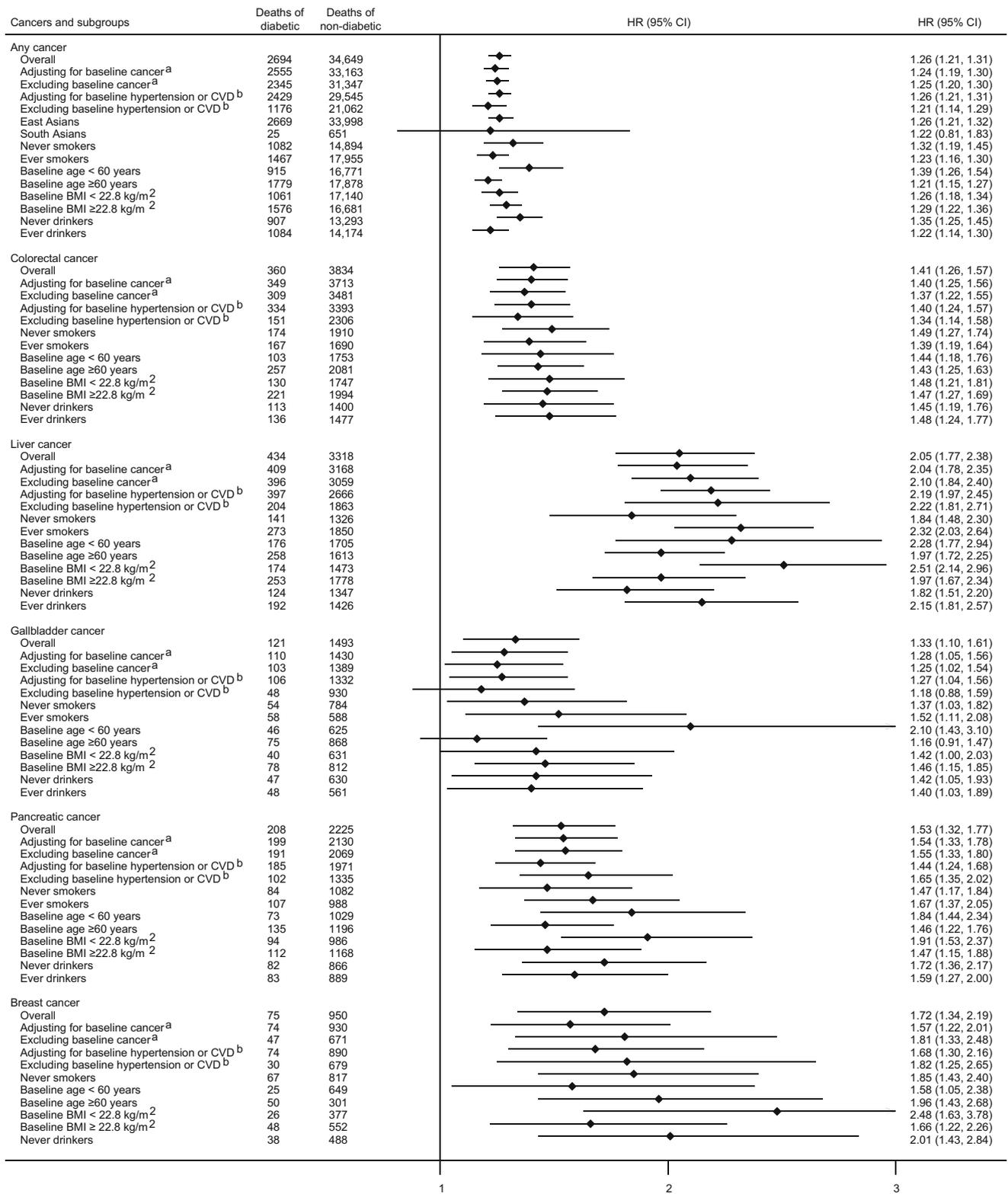
Cancers and subgroups	Deaths of diabetic	Deaths of non-diabetic	HR (95% CI)	HR (95% CI)
Any cancer				
Overall	2694	34,649		1.26 (1.21, 1.31)
Adjusting for baseline cancer [a]	2555	33,163		1.24 (1.19, 1.30)
Excluding baseline cancer [a]	2345	31,347		1.25 (1.20, 1.30)
Adjusting for baseline hypertension or CVD [b]	2429	29,545		1.26 (1.21, 1.31)
Excluding baseline hypertension or CVD [b]	1176	21,062		1.21 (1.14, 1.29)
East Asians	2669	33,998		1.26 (1.21, 1.32)
South Asians	25	651		1.22 (0.81, 1.83)
Never smokers	1082	14,894		1.32 (1.19, 1.45)
Ever smokers	1467	17,955		1.23 (1.16, 1.30)
Baseline age < 60 years	915	16,771		1.39 (1.26, 1.54)
Baseline age ≥60 years	1779	17,878		1.21 (1.15, 1.27)
Baseline BMI < 22.8 kg/m^2	1061	17,140		1.26 (1.18, 1.34)
Baseline BMI ≥22.8 kg/m^2	1576	16,681		1.29 (1.22, 1.36)
Never drinkers	907	13,293		1.35 (1.25, 1.45)
Ever drinkers	1084	14,174		1.22 (1.14, 1.30)
Colorectal cancer				
Overall	360	3834		1.41 (1.26, 1.57)
Adjusting for baseline cancer [a]	349	3713		1.40 (1.25, 1.56)
Excluding baseline cancer [a]	309	3481		1.37 (1.22, 1.55)
Adjusting for baseline hypertension or CVD [b]	334	3393		1.40 (1.24, 1.57)
Excluding baseline hypertension or CVD [b]	151	2306		1.34 (1.14, 1.58)
Never smokers	174	1910		1.49 (1.27, 1.74)
Ever smokers	167	1690		1.39 (1.19, 1.64)
Baseline age < 60 years	103	1753		1.44 (1.18, 1.76)
Baseline age ≥60 years	257	2081		1.43 (1.25, 1.63)
Baseline BMI < 22.8 kg/m^2	130	1747		1.48 (1.21, 1.81)
Baseline BMI ≥22.8 kg/m^2	221	1994		1.47 (1.27, 1.69)
Never drinkers	113	1400		1.45 (1.19, 1.76)
Ever drinkers	136	1477		1.48 (1.24, 1.77)
Liver cancer				
Overall	434	3318		2.05 (1.77, 2.38)
Adjusting for baseline cancer [a]	409	3168		2.04 (1.78, 2.35)
Excluding baseline cancer [a]	396	3059		2.10 (1.84, 2.40)
Adjusting for baseline hypertension or CVD [b]	397	2666		2.19 (1.97, 2.45)
Excluding baseline hypertension or CVD [b]	204	1863		2.22 (1.81, 2.71)
Never smokers	141	1326		1.84 (1.48, 2.30)
Ever smokers	273	1850		2.32 (2.03, 2.64)
Baseline age < 60 years	176	1705		2.28 (1.77, 2.94)
Baseline age ≥60 years	258	1613		1.97 (1.72, 2.25)
Baseline BMI < 22.8 kg/m^2	174	1473		2.51 (2.14, 2.96)
Baseline BMI ≥22.8 kg/m^2	253	1778		1.97 (1.67, 2.34)
Never drinkers	124	1347		1.82 (1.51, 2.20)
Ever drinkers	192	1426		2.15 (1.81, 2.57)
Gallbladder cancer				
Overall	121	1493		1.33 (1.10, 1.61)
Adjusting for baseline cancer [a]	110	1430		1.28 (1.05, 1.56)
Excluding baseline cancer [a]	103	1389		1.25 (1.02, 1.54)
Adjusting for baseline hypertension or CVD [b]	106	1332		1.27 (1.04, 1.56)
Excluding baseline hypertension or CVD [b]	48	930		1.18 (0.88, 1.59)
Never smokers	54	784		1.37 (1.03, 1.82)
Ever smokers	58	588		1.52 (1.11, 2.08)
Baseline age < 60 years	46	625		2.10 (1.43, 3.10)
Baseline age ≥60 years	75	868		1.16 (0.91, 1.47)
Baseline BMI < 22.8 kg/m^2	40	631		1.42 (1.00, 2.03)
Baseline BMI ≥22.8 kg/m^2	78	812		1.46 (1.15, 1.85)
Never drinkers	47	630		1.42 (1.05, 1.93)
Ever drinkers	48	561		1.40 (1.03, 1.89)
Pancreatic cancer				
Overall	208	2225		1.53 (1.32, 1.77)
Adjusting for baseline cancer [a]	199	2130		1.54 (1.33, 1.78)
Excluding baseline cancer [a]	191	2069		1.55 (1.33, 1.80)
Adjusting for baseline hypertension or CVD [b]	185	1971		1.44 (1.24, 1.68)
Excluding baseline hypertension or CVD [b]	102	1335		1.65 (1.35, 2.02)
Never smokers	84	1082		1.47 (1.17, 1.84)
Ever smokers	107	988		1.67 (1.37, 2.05)
Baseline age < 60 years	73	1029		1.84 (1.44, 2.34)
Baseline age ≥60 years	135	1196		1.46 (1.22, 1.76)
Baseline BMI < 22.8 kg/m^2	94	986		1.91 (1.53, 2.37)
Baseline BMI ≥22.8 kg/m^2	112	1168		1.47 (1.15, 1.88)
Never drinkers	82	866		1.72 (1.36, 2.17)
Ever drinkers	83	889		1.59 (1.27, 2.00)
Breast cancer				
Overall	75	950		1.72 (1.34, 2.19)
Adjusting for baseline cancer [a]	74	930		1.57 (1.22, 2.01)
Excluding baseline cancer [a]	47	671		1.81 (1.33, 2.48)
Adjusting for baseline hypertension or CVD [b]	74	890		1.68 (1.30, 2.16)
Excluding baseline hypertension or CVD [b]	30	679		1.82 (1.25, 2.65)
Never smokers	67	817		1.85 (1.43, 2.40)
Baseline age < 60 years	25	649		1.58 (1.05, 2.38)
Baseline age ≥60 years	50	301		1.96 (1.43, 2.68)
Baseline BMI < 22.8 kg/m^2	26	377		2.48 (1.63, 3.78)
Baseline BMI ≥ 22.8 kg/m^2	48	552		1.66 (1.22, 2.26)
Never drinkers	38	488		2.01 (1.43, 2.84)

Fig. 2 Subgroup analyses for the association between diabetes at baseline and mortality from any cancer, colorectal cancer, liver cancer, gallbladder cancer, pancreatic cancer and breast cancer. HRs were adjusted for sex, baseline age, BMI, cigarette smoking, alcohol consumption, educational attainment and urban residence. Results for breast cancer among ever smokers and ever drinkers are not presented because there were fewer than ten deaths among participants with diabetes at baseline. [a]Analyses excluded people with missing information on history of cancer and data from the Seoul Male Cohort Study and Mumbai Cohort Study, which did not have data on previous diagnoses of cancer. [b]Analyses excluded people with missing information on history of CVD or hypertension and data from the Mumbai Cohort Study

drinking status. Consistently stronger associations were seen in individuals <60 years at enrolment than in their older counterparts for liver cancer, gallbladder cancer and pancreatic cancer.

Several studies have addressed the association of diabetes with the risk of death from any cancer. A pooled analysis of 97 prospective cohorts in 820,900 whites from the Emerging Risk Factors Collaboration (ERFC) reported an HR of 1.25 (95% CI 1.19, 1.31) for death from any cancer in people with diabetes compared with those without diabetes [26]. In a prospective cohort of one million US adults in Cancer Prevention Study II (CPS II), diabetes was associated with increases in the risk of death from any cancer of 7% and 11% in men and women, respectively [27]. A meta-analysis reported a summary relative risk of death from any cancer associated with diabetes of 1.32 (95% CI 1.20, 1.45) based on three studies in Asians, and 1.16 (95% CI 1.01, 1.34) based on 14 studies in non-Asians [1]. In the present pooled analysis of Asians, we report an HR of 1.26 (95% CI 1.21, 1.31) for death from any cancer associated with diabetes. In CPS II, diabetes was positively related to death from cancers of the colon, liver or intrahepatic bile duct, pancreas, breast, endometrium, prostate (reduced risk) and bladder (in men only) [27]. The ERFC study reported that diabetes was moderately associated with death from cancers of the colorectum, liver, pancreas, breast, ovary, lung and bladder [26]. Our observed cancer-specific associations are largely consistent with these reports from two large studies in cohorts from Western countries on digestive cancers (including cancers of the colorectum, liver, bile duct, gallbladder and pancreas), as well as breast cancer. These data together suggest that the influence of diabetes on the risk of death from overall cancer, digestive cancers and breast cancer is largely similar in Asians and in developed Western countries.

The moderate associations between diabetes and the risk of death from liver and pancreatic cancer observed in our analyses are consistent with previous studies [2, 28]. A recent meta-analysis of 25 prospective studies of Asians and whites reported a twofold higher risk of liver cancer associated with diabetes, after controlling for alcohol intake, cirrhosis and viral hepatitis B or C infection [29]. However, reverse causation has been suspected, as mechanistic studies found that pancreatic cancer causes paraneoplastic beta cell dysfunction by shedding exosomes containing adrenomedullin and CA19-9 into circulation that inhibit insulin secretion [30]. In our subgroup analyses, although we observed that diabetes of short duration was more strongly related to the risk of cancer compared with diabetes of long duration, the difference was not statistically significant and the risk associated with diabetes of long duration remained elevated. A recent meta-analysis of 36 cohort studies reported that summary relative risks of pancreatic cancer remained elevated when excluding diabetes of short duration [31], suggesting that reverse causation does not account for all the association. The higher risk of liver cancer and pancreatic cancer in diabetes could potentially be related to exposure of these organs to particularly elevated insulin in

people with diabetes, particularly if the tumour cells remain sensitive to insulin [23, 32]. In the present study, a stronger association seen in younger participants for liver, gallbladder and pancreatic cancer also supports metabolic dysfunction (more predominant in the early years of diabetes because of insulin resistance [33]) as being involved in the association between diabetes and these cancers. Taken together, given the magnitude of the associations and the consistent data across studies and different populations, diabetes control should be considered in cancer prevention for these cancers in Asians, especially for liver cancer, which has a high incidence in Asians.

Available data on the association between diabetes and colorectal cancer mortality are limited but are generally consistent with our findings [26, 34]. In addition to hyperinsulinaemia, hypothesised mechanisms include the slower bowel transit time and the elevated faecal bile acid concentrations related to diabetes [32]. We also found that diabetes was related to a 30–40% increased risk of death from gallbladder cancer and bile duct cancer, consistent with previous meta-analyses in whites and Asians [35, 36]. Aside from hyperinsulinaemia and resultant high levels of insulin-like growth factors, possible explanations for the increased risk include the propensity of diabetic individuals to develop gallstones [37], and increased production of biliary cholesterol and lithogenic bile salts as a result of insulin resistance, which also directly promotes the formation of gallstones [38].

We observed positive associations of diabetes with the risk of death from breast cancer, endometrial cancer, ovarian cancer, prostate cancer, kidney cancer, thyroid cancer and lymphoma. Hormone-related mechanisms, such as increases in bioavailable oestrogen, stimulation of endometrial stromal cells, increases in androgen synthesis and increases in endogenous sex steroids [23] due to increased circulating insulin, may underlie the associations for breast and other female cancers. Cumulative epidemiological evidence suggests an association between diabetes and breast cancer [34]. Genetic factors have emerged that potentially contribute to the associations with some female cancers [39, 40]. Data on ovarian cancer are less well established, possibly due to small sample sizes in existing studies, including the present analysis. Further large studies are needed to confirm and investigate effect modifiers for the influence of diabetes on less common hormone-related female cancers such as ovarian cancer in Asians.

Consistent with other prospective studies of cancer mortality in both whites [27, 41] and Asians [42], we did not observe an association between diabetes and the risk of lung cancer mortality. The association with mortality from oesophageal cancer and stomach cancer in whites and Asians has been generally null [26, 27, 42], except for a South Korean study, which found a positive association between diabetes and the risk of death from both cancers in men [28]. By contrast, we observed an increased risk of death from these two cancers

that was confined to women. The lack of consistency may be caused by the heterogeneous nature of these cancers (each has subtypes with different aetiologies). Future studies are needed to investigate associations by subtypes of cancer and to explore whether other sex-specific risk differences, such as in the pattern and extent of alcohol drinking, can explain the difference by sex. Evidence of the association between diabetes and kidney cancer, thyroid cancer and lymphoma has also been inconsistent, although meta-analyses have suggested positive associations between diabetes and these cancers [43–45]. Two cohort studies in Asians reported a statistically significant increase in the risk of thyroid cancer incidence or mortality among diabetic patients [10, 13]. We observed moderate associations for kidney (HR 1.84; 95% CI 1.28, 2.64) and thyroid (HR 1.99; 95% CI 1.03, 3.86) cancer in Asians, suggesting that the effects of diabetes on these cancers may be greater than those observed in whites. However, future larger studies that include information on subtypes of these cancers are needed to confirm the associations in Asians.

For prostate cancer, most of the studies that found an inverse association were conducted in whites [27, 46]. Studies in Asians generated inconsistent findings, and a meta-analysis of studies in Asians concluded that there was a positive association [47]. The influence of diabetes on prostate cancer in Asians and whites appears different, possibly due to differences in incidence rates, screening, diagnosis and treatment in the two populations. In addition, because the outcomes in this study are based on mortality data, they reflect the combined influence of diabetes on disease incidence and survival. Additional studies with incidence data in Asians are warranted, as such data are critical for prostate cancer, for which there is a greater difference between cancer incidence and cancer mortality, compared with other cancers such as liver and pancreatic cancers, which have a shorter survival time.

Major strengths of the present study included a large sample size of diverse Asian populations, allowing us to conduct several sensitivity analyses and stratified analyses by sex, age, smoking status and alcohol consumption. In addition, we had detailed data at the individual level from all cohorts for covariate adjustments and exploration of heterogeneity, avoiding some drawbacks of meta-analysis based on aggregate data from published results. In addition, we included a comprehensive list of causes of cancer death. A limitation of our study is the use of self-reported diabetes status and the lack of update on diabetes status during follow-up. This might have resulted in non-differential misclassification. In a subgroup analysis, we found that the association between treated diabetes and cancer was stronger than that between untreated diabetes and cancer, suggesting that the use of a more stringent definition of diabetes may reduce this misclassification. The use of self-reported information prevented us from distinguishing between type 1 and type 2 diabetes; however, type 2 diabetes accounts for more than 90% of diabetes [16, 48]. Certain

diabetes treatments have been reported to increase (e.g. exogenous insulin) or decrease (e.g. metformin) the risk of cancer [23, 49, 50], but our pooled analyses cannot address the influence of specific treatments, due to the lack of data. We had data on the absence and presence of current treatment only in a small subset of cohorts. Finally, we have limited sample sizes to evaluate the influence of diabetes on site-specific cancers in South Asians. Given that South Asian populations are undergoing an epidemiological transition, there is an emerging need for cohort studies to be conducted for cancer risk factors.

Conclusion We observed that diabetes was related to an increased risk of death from any cancer, colorectal cancer, liver cancer, bile duct cancer, gallbladder cancer, pancreatic cancer, breast cancer, endometrial cancer, ovarian cancer, prostate cancer, kidney cancer, thyroid cancer and lymphoma in Asians. The findings indicate a potential need for appropriate cancer screening among individuals with diabetes and a greater emphasis on lifestyle modifications related to cancer mortality not only in Western populations but also in Asians. We also found an increased risk associated with diabetes from other cancers, which requires future confirmation.

References

1. Noto H, Tsujimoto T, Noda M (2012) Significantly increased risk of cancer in diabetes mellitus patients: a meta-analysis of epidemiological evidence in Asians and non-Asians. J Diabetes Investig 3: 24–33

2. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP (2015) Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 350:g7607

3. Ramachandran A, Ma RC, Snehalatha C (2010) Diabetes in Asia. Lancet 375:408–418

4. Chan JC, Malik V, Jia W et al (2009) Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 301:2129–2140

5. Ma RC, Chan JC (2013) Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. Ann N Y Acad Sci 1281:64–91

6. Chen HF, Chen P, Li CY (2010) Risk of malignant neoplasms of liver and biliary tract in diabetic patients with different age and sex stratifications. Hepatology 52:155–163

7. Lee MY, Lin KD, Hsiao PJ, Shin SJ (2012) The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. Metab Clin Exp 61:242–249

8. Lin Y, Tamakoshi A, Kawamura T et al (2002) Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk. Int J Cancer 99:742–746

9. Seow A, Yuan JM, Koh WP, Lee HP, Yu MC (2006) Diabetes mellitus and risk of colorectal cancer in the Singapore Chinese Health Study. J Natl Cancer Inst 98:135–138

10. Tseng CH (2013) Diabetes and thyroid cancer mortality: a 12-year prospective follow-up of Taiwanese. Eur J Clin Invest 43:595–601

11. Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S (2006) Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. Arch Intern Med 166:1871–1877

12. Khan M, Mori M, Fujino Y et al (2006) Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. Asian Pac J Cancer Prev 7:253–259

13. Lo SF, Chang SN, Muo CH et al (2013) Modest increase in risk of specific types of cancer types in type 2 diabetes mellitus patients. Int J Cancer 132:182–188

14. Ferlay J, Shin HR, Bray F et al (2013) GLOBOCAN 2008 v1.2: Cancer incidence and mortality worldwide: IARC CancerBase No. 10. Lyon (France): IARC Press. Available at http://canceratlas. cancer.org/data/#?view=map, accessed 5 Jan 2010

15. Boffetta P, McLerran D, Chen Y et al (2011) Body mass index and diabetes in Asia: a cross-sectional pooled analysis of 900,000 individuals in the Asia cohort consortium. PLoS One 6:e19930

16. Chen Y, Copeland WK, Vedanthan R et al (2013) Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. BMJ 347:f5446

17. Sasazuki S, Charvat H, Hara A et al (2013) Diabetes mellitus and cancer risk: pooled analysis of eight cohort studies in Japan. Cancer Sci 104:1499–1507

18. Yang WS, Li HL, Xu HL et al (2016) Type 2 diabetes and the risk of non-Hodgkin's lymphoma: a report from two population-based cohort studies in China. Eur J Cancer Prev 25:149–154

19. Chen Y, Ahsan H, Slavkovich V et al (2010) No association between arsenic exposure from drinking water and diabetes mellitus: a cross-sectional study in Bangladesh. Environ Health Perspect 118: 1299–1305

20. Waki K, Noda M, Sasaki S et al (2005) Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I. Diabet Med 22:323–331

21. Cockram CS (2000) The epidemiology of diabetes mellitus in the Asia-Pacific region. Hong Kong Med J 6:43–52

22. Argos M, Parvez F, Rahman M et al (2014) Arsenic and lung disease mortality in Bangladeshi adults. Epidemiology 25:536–543

23. Giovannucci E, Harlan DM, Archer MC et al (2010) Diabetes and cancer: a consensus report. Diabetes Care 33:1674–1685

24. Smith C, Williamson PR, Marson AG (2005) An overview of methods and empirical comparison of aggregate data and individual patient data results for investigating heterogeneity in meta-anlaysis of time-to-event outcomes. J Eval Clin Pract 11:468–478

25. Riley R, Simmonds MC, Look MP (2007) Evidence synthesis combining individual patient data and aggregate data: a systematic review indentified current practice and possible methods. J Clin Epidemiol 60:431–439

26. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S et al (2011) Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 364:829–841

27. Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM (2012) Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care 35:1835–1844

28. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM (2005) Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293:194–202

29. Wang C, Wang X, Gong G et al (2012) Increased risk of hepatocellular carcinoma in patients with diabetes mellitus: a systematic review and meta-analysis of cohort studies. Int J Cancer 130:1639–1648

30. Javeed N, Sagar G, Dutta SK et al (2015) Pancreatic cancer-derived exosomes cause paraneoplastic beta-cell dysfunction. Clin Cancer Res 21:1722–1733

31. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M (2005) Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 92:2076–2083

32. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R (2009) Diabetes and cancer. Endocr Relat Cancer 16:1103–1123

33. Satija A, Spiegelman D, Giovannucci E, Hu FB (2015) Type 2 diabetes and risk of cancer. BMJ 350:g7707

34. De Bruijn KM, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CH (2013) Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. Br J Surg 100:1421–1429

35. Jing W, Jin G, Zhou X et al (2012) Diabetes mellitus and increased risk of cholangiocarcinoma: a meta-analysis. Eur J Cancer Prev 21:24–31

36. Ren HB, Yu T, Liu C, Li YQ (2011) Diabetes mellitus and increased risk of biliary tract cancer: systematic review and meta-analysis. Cancer Causes Control 22:837–847

37. Shebl FM, Andreotti G, Rashid A et al (2010) Diabetes in relation to biliary tract cancer and stones: a population-based study in Shanghai, China. Br J Cancer 103:115–119

38. Biddinger SB, Haas JT, Yu BB et al (2008) Hepatic insulin resistance directly promotes formation of cholesterol gallstones. Nat Med 14:778–782

39. Zhao Z, Wen W, Michailidou K et al (2016) Association of genetic susceptibility variants for type 2 diabetes with breast cancer risk in women of European ancestry. Cancer Causes Control 27:679–693

40. Nead KT, Sharp SJ, Thompson DJ et al (2015) Evidence of a causal association between insulinemia and endometrial cancer: a Mendelian randomization analysis. J Natl Cancer Inst 107:dvj178

41. Zhou XH, Qiao Q, Zethelius B et al (2010) Diabetes, prediabetes and cancer mortality. Diabetologia 53:1867–1876

42. Lam EK, Batty GD, Huxley RR et al (2011) Associations of diabetes mellitus with site-specific cancer mortality in the Asia-Pacific region. Ann Oncol 22:730–738

43. Bao C, Yang X, Xu W et al (2013) Diabetes mellitus and incidence and mortality of kidney cancer: a meta-analysis. J Diabetes Complicat 27:357–364

44. Mitri J, Castillo J, Pittas AG (2008) Diabetes and risk of Non-Hodgkin's lymphoma: a meta-analysis of observational studies. Diabetes Care 31:2391–2397

45. Schmid D, Behrens G, Jochem C, Keimling M, Leitzmann M (2013) Physical activity, diabetes, and risk of thyroid cancer: a systematic review and meta-analysis. Eur J Epidemiol 28:945–958

46. Kasper JS, Giovannucci E (2006) A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomark Prev 15:2056–2062

47. Long XJ, Lin S, Sun YN, Zheng ZF (2012) Diabetes mellitus and prostate cancer risk in Asian countries: a meta-analysis. Asian Pac J Cancer Prev 13:4097–4100

48. Deshpande AD, Harris-Hayes M, Schootman M (2008) Epidemiology of diabetes and diabetes-related complications. Phys Ther 88:1254–1264

49. Hemkens LG, Grouven U, Bender R et al (2009) Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: a cohort study. Diabetologia 52:1732–1744

50. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ (2010) Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care 33:322–326