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Associations of Diabetes Mellitus with Site-Specific Cancer Mortality in the Asia-Pacific Region

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Abstract

Background—Owing to the increasing prevalence of obesity and diabetes in Asia, and the paucity of studies, we examined the influence of raised blood glucose and diabetes on cancer mortality risk.

Methods—Thirty-six cohort Asian and Australasian studies provided 367,361 participants (74% from Asia); 6% had diabetes at baseline. Associations between diabetes and site-specific cancer mortality were estimated using time-dependent Cox models, stratified by study and sex, and adjusted for age.

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Results—During a median follow-up of 4.0 years, there were 5,992 deaths due to cancer (74% Asian; 41% female). Participants with diabetes had 23% greater risk of mortality from all-cause cancer compared with those without: hazard ratio (HR) 1.23 (95% CI 1.12, 1.35). Diabetes was associated with mortality due to cancer of the liver (HR 1.51, 95% CI 1.19, 1.91), pancreas (HR 1.78, 95% CI 1.20, 2.65), and, less strongly, colorectum (HR 1.32, 95% CI 0.98, 1.78). There was no evidence of sex- or region-specific differences in these associations. The population attributable fractions for cancer mortality due to diabetes were generally higher for Asia compared with non-Asian populations.

Conclusion—Diabetes is associated with increased mortality from selected cancers in Asian and non-Asian populations.

Keywords

Diabetes Mellitus; Cancer Mortality; Epidemiology; Asia-Pacific

INTRODUCTION

A substantial proportion of cancer deaths are attributed to unhealthy lifestyles and behaviours including poor diet [1], obesity [2], smoking [3], and alcohol [4]. Mortality rates for specific cancers are known to vary significantly by geographical region and country. Mortality from cancers of the colon and rectum, which are considered to be due in large part to poor diet and lifestyle, is higher for industrialised nations, such as Australia, North America, and Western Europe, as compared with many Asian countries. By comparison, mortality from liver cancer is far more common across Asia, and particularly China, than in the West, due mainly to the high prevalence of chronic hepatitis B and C infections that account for a large majority of all liver cancers worldwide [5].

Previous studies have reported that diabetes status is associated with a 20-30% increased risk of total cancer mortality [6-10]. A positive association between abnormal glucose tolerance and the risk of cancer mortality has also been demonstrated for Western countries [11-13]. With regard to site-specific cancer mortality, many studies have shown positive associations between diabetes and the risk of mortality from cancers of the pancreas, liver, colorectum, and prostate [12-19]. . Most of these studies were conducted in Western populations, with scarce results from Asia. Among the few Asian studies, positive associations between diabetes and cancers of the pancreas, liver, and colorectum, as well as non-Hodgkin lymphoma, have been reported [6, 8, 20-24]. Given increasing life expectancy and urbanization [25], the increasing prevalence of obesity [26], and the growing prevalence of diabetes in Asian populations [27, 28], more studies are needed to clarify the evidence of the possible effect of diabetes on cancer mortality in Asia.

The Asia Pacific Cohort Studies Collaboration (APCSC) is a large-scale collaborative project with previous reports on the relationship between diabetes and major causes of death [20-22, 29]. A systematic analysis of mortality from specific cancers in relation to diabetes and blood glucose in the APCSC has not yet been reported. The aims of the present study are two-fold. First, to examine associations between fasting blood glucose levels, diabetes, and site-specific cancer mortality for which sufficient numbers of fatal events were available

for analysis; and second, to estimate the population attributable fractions (PAFs) of cancer mortality due to diabetes within countries in the region. These give crude measures of the percentages of deaths that are expected to be due to diabetes, should there be a causal relationship [30].

MATERIAL AND METHODS

Participating studies

The APCSC is a pooled-analysis of individual data from cohort studies conducted in the Asia-Pacific region; details have been published elsewhere [31]. Studies were eligible for inclusion if the following criteria were met: study sample was drawn from the Asia-Pacific region; study was of a prospective cohort design; study had at least 5,000 person-years of follow-up. Studies were not eligible if entry was dependent on having a particular medical condition or risk factor. At a minimum, studies must have had data on date of birth or age, sex, blood pressure, and date or age of death. Outcome data included mortality from specific cancers. Cohorts were classified as Asian if study members were recruited from mainland China, Hong Kong, Japan, Korea, Singapore, South Korea, Taiwan, or Thailand; and as Australasian if from Australia or New Zealand. This classification largely represents a dichotomy by ethnicity into Asians and non-Asians.

Baseline assessment

Study participants' diabetes status were determined on the basis of self-reported history of diabetes, or by applying the World Health Organization (WHO) diagnostic criteria to blood glucose levels at baseline [32]. Diabetes status according to glucose levels was positive if fasting whole blood glucose was ≥ 6.1 mmol/L (110 mg/dL) or plasma glucose ≥ 7 mmol/L (126 mg/dL); or if non-fasting whole blood glucose was ≥ 10 mmol/L (180 mg/dL) or plasma glucose ≥ 11.1 mmol/L (200 mg/dL) (information on glucose-lowering medication not available). All data on cigarette smoking were self-reported as either current smoker or non-smoker at the time of study entry. Height and weight were ascertained from direct measurements; body mass index (BMI) was calculated as weight (kg) divided by height (m)squared. Systolic blood pressure was measured using a sphygmomanometer. Participants also reported alcohol use habits (current alcohol user/non-alcohol user), exercise habits ('none or almost none' as sedentary lifestyle/'any exercise' as active exercise), and educational attainment (none/at least primary school).

Outcomes

Cancer deaths were classified according to the ninth [33] or tenth [34] revision of the International Classification of Diseases (ICD): bladder (ICD-9; ICD-10: 188; C67); brain and central nervous system (191-192; C70-72); breast (174; C50); colon and rectum (153-154; C18-21); leukaemia (204-208; C91-95); liver (155, 197.7; C22, C78.7); lung (162; C33-34); Non-Hodgkin's lymphoma (200, 202; C82, C85); melanoma (172; C43); multiple myeloma (203; C90); ovary and uterus (179-183; C53-56); pancreas (157; C25); prostate (185; C61); kidney (189; C64); and stomach (151; C16). Malignancies of the upper aero-digestive tract (UADT) were analysed by combining cancers of the oropharynx, oesophagus, and larynx (ICD-9; ICD-10: 140-150, 161, C00-C15, C32).

Statistical analyses

Analyses were restricted to participants aged ≥ 20 years at the time of the baseline survey with complete data on diabetes status and site-specific cancer mortality. Cox proportional hazards regression models, stratified by study cohort and sex, and adjusted for age, were used to compute hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for those with and without diabetes, as well as for those with various fasting serum glucose levels. Further adjustments were made in multivariable models which included *a priori* potential confounding variables: BMI, height [35], education, smoking status, and alcohol use at baseline. Statistical significance of effect modification across groups defined by geographical area (Asia and Australasia) and sex were tested using the likelihood ratio test [30]. Differences between region and sex were tested for statistical significance using likelihood ratio tests. The PAFs for mortality from site-specific cancer mortality due to diabetes were calculated for each of the countries in the APCSC using previously published prevalence estimates of diabetes that were adjusted to a world standard population [36] by the formula [30]:

$$PAF = 100 \times prevalence \times (HR - 1) / [100 + prevalence \times (HR - 1)]$$

To explore the possibility of participants with a pre-existing malignancy (e.g. pancreatic cancer) at time of study entry contributing to the analyses, and potentially attenuating the diabetes-cancer relation (i.e. reverse causality), deaths from cancer in the first two years of follow-up were excluded ("left censored") in a sensitivity analysis. In doing so, we reasoned that most deaths due to sub-clinical malignancy at study entry would have occurred during the first two years.

Trends were explored through analyses of fasting serum glucose levels according to tertiles (< 4.8 mmol/L; 4.8-5.4 mmol/L; > 5.4 mmol/L). Trends were tested for statistical significance using likelihood ratio tests. All statistical analyses were performed using STATA version 10.1 for Windows (StataCorp, College Station, Texas).

RESULTS

A total of 44 studies involving 600,443 participants were recruited to the APCSC by the end of 2006 [31]. Figure 1 shows the selection process of the analytical sample for this study. Information on diabetes at baseline and site-specific cancer mortality was available from 36 of the 44 eligible studies involving 367,361 participants, of whom 41% were female, 74% were Asian, and 6.4% had type 2 diabetes mellitus at study entry (Table 1). A summary of the characteristics of the included studies are shown in Table 1. The median follow-up time was 4.0 years and the mean age of participants was 48 years. Participants from the Australasian cohorts were older than those from Asian cohorts. During mortality follow up, a total of 2,223,958 person-years of follow-up gave rise to 17,413 deaths of which 5,992 were ascribed to cancer (31% female, 51% Asian).

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Study baseline characteristics

Of the 367,361 participants, 23,560 (24% female, 80% Asian) were classified as having diabetes at baseline. Both Asian and Australasian participants with diabetes were older, had higher levels of BMI, systolic blood pressure, total cholesterol, and triglycerides in both Asia and Australasia. Those from either region with diabetes were also more likely to be male, physically inactive, and have lower levels of education.

Outcomes

The age-adjusted, sex and study stratified, HR for death from all cancers was 1.23 (95% CI: 1.12, 1.35) for individuals with diabetes compared with individuals without diabetes (Table 2). This remained largely unchanged after two year left-censoring (HR 1.19, 95% CI 1.06, 1.32). Additional adjustment for BMI, height, education, smoking, and alcohol use had no material effect on the magnitude of the diabetes-cancer association. Analysis of the diabetes-cancer association by sex and region showed no evidence of any difference (*p*-value for interaction > 0.1). For mortality from specific cancers, diabetes was associated with an increased risk of cancers of the liver (HR 1.51, 95% CI: 1.19, 1.91) and pancreas (HR 1.78, 95% CI: 1.20, 2.65), compared with those without diabetes (Table 2). These also persisted after two year left-censoring: HR 1.52 (95% CI: 1.15, 2.01) and 1.66 (95% CI: 1.04, 2.63), respectively. An increase in the risk of mortality from colorectal cancer was also observed both before and after left-censoring: HR 1.32 (95% CI: 0.98, 1.78) and HR 1.34 (95% CI: 0.96, 1.87), respectively.

Additional analyses were performed for diabetes at baseline among individuals with cancer mortality with at least 8 years of follow-up. Information on diabetes at baseline and site-specific cancer mortality was reduced to 15 of the 44 eligible studies involving 95,979 participants, of whom 53% were female, 30% were Asian, and 4.4% had type 2 diabetes mellitus at study entry (Table 1a). The new median follow-up time was 9.1 years and the mean age of participants was 50 years. During this longer mortality follow up, 3,135 deaths were ascribed to cancer.

The age-adjusted, sex and study stratified HR for death from all cancers was 1.31 (95% CI: 1.13, 1.51) for individuals with diabetes compared with individuals without diabetes (Table 2a). Additional adjustment for BMI, height, education, smoking, and alcohol use had no substantial effect on the magnitude of the diabetes-cancer association. For mortality from specific cancers, diabetes was associated with an increased risk of cancers of the colorectum (HR 1.50, 95% CI: 1.03, 2.18), liver (HR 2.14, 95% CI: 1.08, 4.25), and pancreas (HR 1.85, 95% CI: 1.03, 3.31) compared with those without diabetes (Table 2a). In addition, diabetes was associated with an increased risk of cancers of the stomach among those with longer follow-up period (HR 1.90, 95% CI: 1.17, 3.08).

Association between fasting serum glucose levels and mortality from cancer

Fasting serum glucose levels were available from 202,681 participants with a total of 1490 cancer deaths of whom 8% (16,439/202,682) were classified as having diabetes. Based on this smaller sub-sample, there were no significant linear associations between glucose levels and all-cause cancer mortality (p for trend = 0.39; Table 3) or with any of the site-specific

cancers. There was however, some evidence of a weak positive association with liver cancer (*p*-value for trend = 0.06) (Table 3). Analysis of trend in those who died from melanoma and multiple myeloma were not possible due to insufficient numbers.

Population attributable fractions of cancer mortality due to diabetes

Figure 2 shows the PAF of mortality from specific cancers that seem to have notable associations with diabetes in the APCSC: pancreas, liver, and colorectum. These PAFs differed substantially across the Asia-Pacific region, and were generally higher for Asia than Australasia (Figure 2). Overall, the PAF ranged from 3.1% to 7.3% for pancreatic cancer, 2.0% to 4.9% for liver cancer, and 1.3% to 3.1% for colorectal cancer.

DISCUSSION

To our knowledge, the present study is the first to systematically examine the associations between diabetes and mortality from specific cancers for the diverse populations of the Asia-Pacific region. The results from our large collaborative study indicate that individuals with diabetes have an approximately 20% greater risk of mortality from all-cause cancer compared with those without the condition. Specifically, diabetes is independently associated with mortality from pancreatic, liver and, possibly, colorectal cancer. These associations did not vary by region or by sex, and were adjusted for BMI, height, education, smoking, and alcohol use. The majority of cases of diabetes in this report are likely to be type 2 diabetes but an undetermined proportion may have diabetes secondary to pancreatic disease and some will have type 1 diabetes especially in the non-Asian cohorts.

We found a nearly 78% increased risk of death from pancreatic cancer for those with diabetes, which is comparable with other reports [6, 13, 14, 16, 20, 37], and a previous meta-analysis [38]. Other studies have also shown abnormal glucose metabolism to be associated with pancreatic cancer mortality [12, 37]. Though our findings suggest diabetes to be a risk factor for pancreatic cancer, the diabetic state is also a potential consequence of pancreatic malignancy [24, 38-41].

The earlier meta-analysis reported a 50% lower excess risk ratio of pancreatic cancer for individuals with greater than five year history of diabetes, compared with those with a shorter duration of diabetes [38]. Recent studies have also shown that onset of diabetes mellitus of less than two years of duration was more prevalent for patients with pancreatic cancer and, therefore, more likely to be induced by malignancy [24, 39]. Our finding of a 50% increased risk of liver cancer mortality for those with diabetes, compared with those without, is consistent with previous reports [6, 13-15, 42]. Our results also showed a marginally non-significant trend in risk of liver cancer mortality from fasting serum glucose levels (*p*-value for trend = 0.06). Previous studies [6, 14, 43-45] as well as a meta-analysis [46] have shown increased risk of colorectal cancer mortality for those with diabetes as suggested in the present study as a possible 30% increased risk of colorectal cancer mortality upon participants with diabetes.

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Plausible mechanisms

It has been suggested that the increased risk of cancer mortality for those with type 2 diabetes might reflect metabolic and hormonal changes of compensatory hyperinsulinemia, and elevated levels of insulin-like growth factors (IGFs) in response to reduced insulin sensitivity [8, 37, 47-49]. In this regard, IGF-1 has been shown to stimulate cellular proliferation in the pancreas, liver, and colon [48-50]. In addition, increased levels of circulating insulin may activate IGF-1 receptor and thereby promote cellular growth and cell cycle progression [8, 37, 47]. Glucose-lowering therapy, such as exogenous insulin, has been shown to increase cancer risk in a large retrospective cohort study [51]. In these diabetic patients, glucose lowering therapies with sulphonylurea drugs or insulin were associated with increased cancer risk, as compared to treatment with metformin. In the subjects on insulin, the hazard ratio for solid tumour incidence was 1.42 and for pancreatic cancers 4.63, these conditions occurring in < 2.0% and < 0.2% of cases respectively. These were a multiplicity of confounders and no causal association can be assumed [51]. The present study, however, did not have information regarding glucose-lowering medications and our reported results may misrepresent the strength of the overall diabetes-cancer association. Similar to the diabetes-pancreatic cancer association, plausible biological mechanisms for the diabetes-liver cancer association may also involve glucose lowering therapy. Donadon *et al* have reported an approximately three-fold increased risk of hepatocellular carcinoma for individuals with diabetes on insulin or sulphonylurea treatment [52]. Another putative pathway between diabetes and liver cancer is the occurrence of fatty liver disease. Non-alcoholic fatty liver disease can progress to non-alcoholic steatohepatitis, which may develop subsequently into irreversible cirrhosis, and ultimately hepatocellular carcinoma [53].

Strengths and limitations

The key strengths of the APCSC include its prospective design, its capacity to adjust for several possible confounders, and its large sample size, which allows reliable estimates of associations with deaths from rare cancers to be estimated.

One limitation is that information regarding duration of diabetes was not available. Instead, to explore the possibility of reverse causality, the data were two-year left-censored, with a negligible effect on the original estimates. Given the long latency period between diabetes onset and death from cancer, it is possible that left-censoring the data by two years was insufficient to fully eliminate the effects of reverse causality. In this study, the median follow-up time available for analysis was only four years duration so we were unable to explore this issue further. This relatively short median duration of follow-up might not capture mortality from specific cancers that have longer average survival periods. Information regarding cancer incidence, rather than mortality, would be more useful for assessing cancers with low fatality rates (such as prostate cancer) as a smaller proportion of incidence of such cancers would be included in an analysis of cancer mortality alone. There is certainly a distinction between whether diabetes may cause cancer and whether diabetes may increase individual risk of mortality once a particular cancer is acquired – the present study is limited to exploring the latter question as only cancer mortality data were collected.

We are, therefore, unable to determine to what extent the increased risk of cancer mortality represents an etiologic role for diabetes or an early manifestation or consequence of cancer.

Another limitation of this study is the diagnostic criteria used for diabetes. While some participants had provided self-reported history of diabetes, approximately two-thirds (65%) of the analytical sample had only laboratory measurements of blood glucose levels to identify their diabetes status. Sole reliance on records of blood glucose levels, without information on self-reported history of diabetes or medication history, might underestimate the true effect of diabetes on cancer mortality as the dataset does not preclude blood glucose levels within normal ranges to be the outcomes of glucose-lowering treatment. The effects of misclassification as such would be conservative and alter the observed effect towards null. However, misclassification of self-reported diabetes may also alter the observed effect away from null as certain participants who reported themselves as ‘non-diabetic’ may have elevated glucose levels if blood samples were not taken from them during the study. Moreover, the effects of glucose-lowering treatment on normalizing blood glucose levels, leading to a misclassification of someone with diabetes as non-diabetic, may be more pronounced among those with diabetes of longer duration, which may have a different relation with cancer mortality than diabetes of shorter duration; thereby making prediction of the direction of misclassification bias difficult. Lastly, some significant associations reported in the present study may be due to chance alone, given the large number of statistical tests performed for 17 specific cancer endpoints.

Our comparisons of glucose categories also have potential misclassification issues. Individuals in the normoglycaemic group could have had diabetes since, for those analyses, we were not able to identify individuals who were treated with glucose-lowering therapy. Such misclassifications will attenuate the dose response relationship between fasting serum glucose levels and liver cancer mortality reported in this study. Finally the possibility of residual confounding remains. We adjusted for BMI but not measures of central obesity which might be more strongly related to some cancers. In particular, heavy alcohol consumption is associated both with diabetes and with cancers of the liver and colorectum, but our measure of alcohol intake was crude and unable to differentiate between amount, type and duration of alcohol consumed.

CONCLUSIONS

The present study adds to the growing body of literature concerning the long-term co-morbidities of diabetes and provides insight into future patterns of diabetes-related cancer mortality. Our findings suggest diabetes is positively associated with cancer mortality for both Asian and Australasian populations. The relative effect of diabetes on the mortality risk from specific cancers for Asian populations is comparable to those for the largely Caucasian populations of Australasia. Given the increasing diabetes epidemic in both regions [54], and if the associations were causal, mortality from pancreatic, liver, and, possibly, colorectal cancers may be expected to rise, given that these cancers had the greatest percentage of deaths explained by diabetes. The large number of people living in Asia, particularly China, suggests this will be a public health problem of importance. Concerted interventions that target the control and reduction of type 2 diabetes in populations of the Asia-Pacific region

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may have considerable benefits on reducing mortality from cancer, in addition to that from other chronic illnesses.

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Abbreviations

APCSC	Asia Pacific Cohort Studies Collaboration
DM	Diabetes Mellitus
ICD	International Classification of Diseases
IFG	Impaired Fasting Glucose
PAF	Population Attributable Fractions

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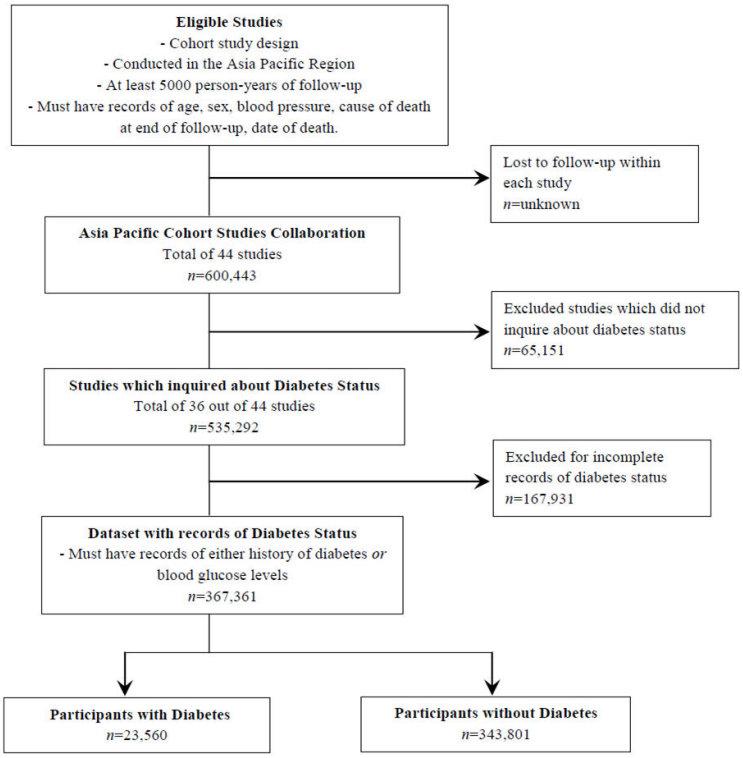

Figure 1. Selection of Analytical Sample

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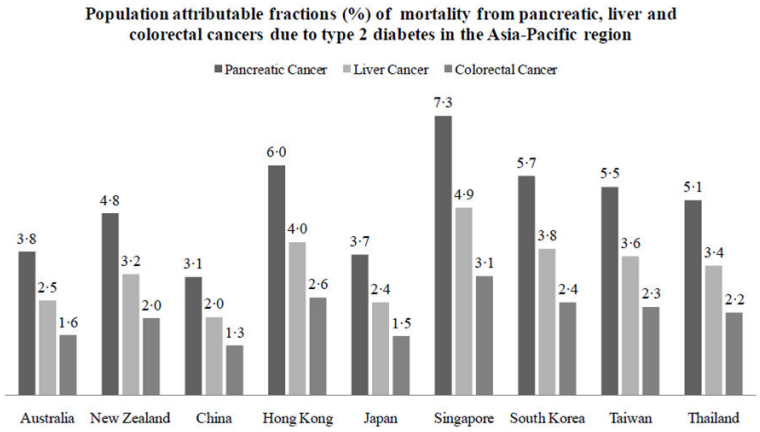

Figure 2. Estimated population attributable fractions for mortality from pancreatic, liver, and, colorectal cancers due to diabetes in the Asia-Pacific region

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Table 1

Summary Characteristics of Participating Studies* from the Asia Pacific Cohort Studies Collaboration (APCSC)

Cohort Name	Country	*n*	Median follow-up (years)	Range of follow-up (years)	Female (%)	Age (years) mean	SD	Diabetes Mellitus (%)	No. total cancer deaths
Australasia									
ALSA	Australia	1,557	4.9	0.04-9.04	47.7	78	6	8.2	68
ANHF	Australia	9,272	8.3	0.15-8.63	51.0	43	13	1.9	153
Busselton	Australia	5,976	23.5	0.51-35.50	52.2	46	17	3.5	602
Canberra	Australia	712	9.2	0.04-13.27	45.3	77	5	6.6	100
Fletcher Challenge	New Zealand	10,366	5.8	0.02-7.33	28.0	44	15	2.6	135
Melbourne	Australia	41,286	8.5	0.02-11.39	58.9	55	9	5.4	1112
Newcastle	Australia	3,462	4.7	0.10-10.25	50.0	53	11	3.5	83
Perth	Australia	10,222	14.4	0.12-19.56	48.3	45	13	2.1	310
WA AAA Screenees	Australia	12,203	3.2	0.03-4.71	0.0	72	4	11.6	400
Subtotal		***95,056***	***8.2***	***0.02-35.50***	***42.4***	***57***	***14***	***5.0***	***2963***
Asia									
Aito Town	Japan	1,717	15.2	0.73-16.96	56.7	51	9	2.7	62
Akabane	Japan	1,828	11.0	0.45-12.92	55.7	54	8	2.5	57
Anzhen	China	4,122	3.0	0.72-3.00	51.0	47	8	11.1	0
Beijing Aging	China	2,092	4.8	0.01-4.99	50.6	70	9	24.7	48
CISCH	China	2,162	3.3	0.24-3.90	51.0	44	7	2.4	3
Civil Service									
Workers	Japan	9,319	6.7	0.13-7.78	32.7	47	5	1.7	61
CVDFACTS	Taiwan	5,730	6.0	0.08-9.44	55.3	47	15	2.7	65
East Beijing	China	1,128	17.1	1.02-20.49	51.4	44	15	5.6	20
EGAT	Thailand	3,131	11.4	0.09-12.39	23.3	43	5	2.4	43
Fangshan	China	821	2.7	1.75-3.58	67.6	47	9	7.1	4
Guangzhou	China	5,796	7.9	1.17-13.55	34.2	44	7	10.5	35
Occupational									
Hong Kong	Hong Kong	2,953	2.5	0.04-5.04	57.1	79	7	8.6	127
Huashan	China	1,649	2.9	0.34-3.71	54.4	53	11	13.0	4
Kinmen	Taiwan	2,453	2.9	0.09-5.28	48.7	63	10	8.8	41
KMIC	South Korea	183,581	4.0	0.01-5.00	37.0	44	7	7.7	1236
Konan	Japan	1,226	6.4	0.02-10.42	55.4	52	16	12.6	26
Miyama	Japan	1,072	6.6	0.15-8.06	55.8	61	10	5.1	36
Ohasama	Japan	2,240	4.1	0.08-5.29	63.8	60	11	10.9	30
Saitama	Japan	3,624	11.0	0.06-12.00	62.2	55	12	1.7	147
Seven Cities Cohorts	China	10,731	2.7	0.04-11.50	54.5	54	12	1.2	174
Shibata	Japan	2,349	20.0	0.07-20.00	57.7	57	11	1.1	208
Shigaraki Town	Japan	3,757	4.4	0.07-6.44	59.5	57	14	7.2	55

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Cohort Name	Country	*n*	Median follow-up (years)	Range of follow-up (years)	Female (%)	Age (years) mean	SD	Diabetes Mellitus (%)	No. total cancer deaths
Shirakawa	Japan	4,640	17.5	0.13-20.51	54.3	48	12	0.9	165
Singapore Heart	Singapore	2,325	14.6	0.14-16.31	49.0	41	13	11.4	35
Singapore NHS92	Singapore	3,305	6.2	0.09-6.32	51.8	39	12	9.7	22
Tanno/Soubetsu	Japan	1,973	16.4	0.42-18.92	53.2	51	7	7.2	86
Yunnan	China	6,581	4.5	0.02-5.18	3.1	56	9	0.5	239
Subtotal		***272,305***	***4.0***	***0.01-20.51***	***49.9***	***47***	***10***	***6.9***	***3029***
Total		**367,361**	**4.0**	**0.01-35.50**	**41.3**	**48**	**12**	**6.4**	***5992***

ALSA = Australian Longitudinal Study of Aging; ANHF = Australian National Heart Foundation; WA AAA Screenees = Western Australian AAA Screenees; CISCH = Capital Iron and Steel Company Hospital; EGAT = Electricity Generating Authority of Thailand; KMIC = Korean Medical Insurance Corporation; NHS92 = National Health Study 1992; CVDFACTS = Cardiovascular Disease Risk Factors Two-Township Study

*Restricted to studies and participants with information on history of diabetes or blood glucose levels at baseline and site-specific cancer mortality.

Table 1a

Summary Characteristics of Asia Pacific Cohort Studies Collaboration (APCSC) Participating Studies* with follow-up of 8 years or greater.

Cohort Name	Country	*n*	Median follow-up (years)	Range of follow-up (years)	Female (%)	Age (years) mean	SD	Diabetes Mellitus (%)	No. total cancer deaths
Australasia									
ANHF	Australia	9,272	8.3	0.15-8.63	51.0	43	13	1.9	153
Busselton	Australia	5,976	23.5	0.51-35.50	52.2	46	17	3.5	602
Canberra	Australia	712	9.2	0.04-13.27	45.3	77	5	6.6	100
Melbourne	Australia	41,286	8.5	0.02-11.39	58.9	55	9	5.4	1112
Perth	Australia	10,222	14.4	0.12-19.56	48.3	45	13	2.1	310
Subtotal		***67,468***	***8.5***	***0.02-35.50***	***55.5***	***51***	***12***	***4.2***	***2277***
Asia									
Aito Town	Japan	1,717	15.2	0.73-16.96	56.7	51	9	2.7	62
Akabane	Japan	1,828	11.0	0.45-12.92	55.7	54	8	2.5	57
East Beijing	China	1,128	17.1	1.02-20.49	51.4	44	15	5.6	20
EGAT	Thailand	3,131	11.4	0.09-12.39	23.3	43	5	2.4	43
Guangzhou	China	5,796	7.9	1.17-13.55	34.2	44	7	10.5	35
Occupational									
Saitama	Japan	3,624	11.0	0.06-12.00	62.2	55	12	1.7	147
Shibata	Japan	2,349	20.0	0.07-20.00	57.7	57	11	1.1	208
Shirakawa	Japan	4,640	17.5	0.13-20.51	54.3	48	12	0.9	165
Singapore Heart	Singapore	2,325	14.6	0.14-16.31	49.0	41	13	11.4	35
Tanno/Soubetsu	Japan	1,973	16.4	0.42-18.92	53.2	51	7	7.2	86
Subtotal		***28,511***	***11.4***	***0.06-20.51***	***47.7***	***48***	***11***	***4.8***	***858***
Total		**95,979**	**9.1**	**0.02-35.50**	**53.2**	**50**	**12**	**4.4**	**3135**

ANHF = Australian National Heart Foundation; EGAT = Electricity Generating Authority of Thailand

*Restricted to studies with median follow-up of ≥ 8.0 years and participants with information on history of diabetes or blood glucose levels at baseline and site-specific cancer mortality.

Table 2
Hazard ratio for diabetes in relation to causes of mortality

Site-Specific Cancer Mortality	APCSC (*n*=367,361)	
	No .of deaths	§Hazard Ratio (95% CI)
Bladder	105	1.42 (0.70, 2.86)
Brain	168	0.96 (0.51, 1.79)
Breast	299	0.75 (0.39, 1.47)
Colorectum	596	1.32 (0.98, 1.78) **
Kidney	75	0.64 (0.23, 1.80)
Leukaemia	167	1.18 (0.67, 2.06)
Liver	561	1.51 (1.19, 1.91) *
Lung	1227	0.88 (0.69, 1.13)
Melanoma	82	1.60 (0.76, 3.37)
Multiple Myeloma	65	1.89 (0.80, 4.47)
Non-Hodgkin's Lymphoma	161	1.00 (0.55, 1.82)
Ovarian & Uterine	148	0.63 (0.23, 1.71)
Pancreas	254	1.78 (1.20, 2.65) *
Prostate	284	1.27 (0.84, 1.93)
Stomach	662	1.17 (0.89, 1.54)
Upper Aero-Digestive Tract	266	1.04 (0.67, 1.63)
All Cancers	5992	1.23 (1.12, 1.35)*

§Hazard ratios are age-adjusted, sex and study stratified.

*p-value < 0.01

**p-value = 0.07

Table 2a

Hazard ratio for diabetes in relation to causes of mortality for studies with follow-up of 8 years or greater

Site-Specific Cancer Mortality	[#]APCSC (*n*=95,979)	
	No .of deaths	[§]Hazard Ratio (95% CI)
Bladder	63	1.39 (0.55, 3.51)
Brain	103	0.98 (0.39, 2.43)
Breast	226	0.69 (0.30, 1.56)
Colorectum	404	1.50 (1.03, 2.18)*
Kidney	47	0.78 (0.19, 3.25)
Leukaemia	98	0.70 (0.25, 1.92)
Liver	93	2.14 (1.08, 4.25)*
Lung	493	1.15 (0.80, 1.67)
Melanoma	65	2.11 (0.94, 4.71)
Multiple Myeloma	47	2.21 (0.85, 5.76)
Non-Hodgkin's Lymphoma	86	0.97 (0.39, 2.44)
Ovarian & Uterine	106	0.75 (0.24, 2.39)
Pancreas	161	1.85 (1.03, 3.31)*
Prostate	205	1.32 (0.79, 2.22)
Stomach	291	1.90 (1.17, 3.08)**
Upper Aero-Digestive Tract	122	1.13 (0.52, 2.46)
All Cancers	3135	1.31 (1.13, 1.51)***

[#]Restricted to studies with median follow-up of ≥ 8.0 years and participants with information on history of diabetes or blood glucose levels at baseline and site-specific cancer mortality.

[§]Hazard ratios are age-adjusted, sex and study stratified.

*p-value < 0.05

**p-value = 0.01

***p-value< 0.0001

Table 3

Age-adjusted, sex and study stratified hazard ratios of cancer mortality with respect to fasting serum glucose levels in Asia Pacific Cohort Studies Collaboration (APCSC).

Site-Specific Cancer Mortality	Adjusted[§] Hazard Ratio (95% CI) Fasting Serum Blood Glucose Levels						*P-value for trend
	n	1st Tertile (< 4.8 mmol/L)	*n*	2nd Tertile (4.8-5.4 mmol/L)	*n*	3rd Tertile (> 5.4 mmol/L)	
Bladder	4	1.0 (ref)	4	0.73 (0.18, 2.97)	2	0.33 (0.06, 1.86)	0.20
Brain	13	1	17	1.25 (0.60,2.60)	10	0.84 (0.36, 1.96)	0.72
Breast	22	1	20	1.02 (0.55, 1.90)	7	0.67 (0.27, 1.65)	0.47
Colorectum	26	1	29	0.89 (0.52, 1.54)	19	0.64 (0.35, 1.20)	0.17
Kidney	5	1	3	0.46 (0.11, 1.95)	7	1.02 (0.31, 3.30)	0.86
Leukaemia	14	1	11	0.74 (0.33, 1.63)	10	0.78 (0.34, 1.79)	0.53
Liver	116	1	120	0.98 (0.76, 1.26)	152	1.26 (0.98, 1.61)	0.06
Lung	86	1	63	0.63 (0.45, 0.87)	74	0.75 (0.54, 1.03)	0.08
Non-Hodgkin's Lymphoma	10	1	9	0.82 (0.33, 2.04)	7	0.72 (0.26, 1.98)	0.52
Ovarian & Uterine	11	1	15	1.58 (0.71, 3.50)	7	1.39 (0.51, 3.77)	0.42
Pancreas	21	1	18	0.72 (0.38, 1.36)	21	0.87 (0.47, 1.63)	0.68
Prostate	6	1	6	0.45 (0.14, 1.43)	10	0.62 (0.22, 1.73)	0.52
Stomach	90	1	94	1.02 (0.76, 1.36)	91	1.06 (0.79, 1.44)	0.68
Upper Aero-Digestive Tract	25	1	25	0.87 (0.49, 1.51)	33	1.05 (0.62, 1.80)	0.81
All Cancers	487	1	473	0.90 (0.94, 1.28)	530	1.06 (0.93, 1.20)	0.39

*p-values from Likelihood Ratio Test

§Hazard ratios are age-adjusted, sex and study stratified.

**Hazard ratios & 95% CI cannot be estimated due to an insufficient number of events