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Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies

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ABSTRACT

Background: Diabetes mellitus (DM) is widely considered to be associated with risk of pancreatic cancer (PaC), however, whether DM is a cause or a consequence of PaC is still controversial. We examined this association by conducting a detailed meta-analysis of cohort studies.

Methods: Studies were identified by searching Medline and Embase through November 30, 2010. Summary relative risks (RRs) with their corresponding 95% confidence intervals (CIs) were calculated using a random-effects model.

Results: A total of thirty-five cohort studies were included in this meta-analysis. DM was associated with an increased risk of PaC (the summary RRs = 1.94; 95% CI, 1.66–2.27), with significant evidence of heterogeneity among these studies ($p < 0.001$, $I^2 = 93.6\%$). Subgroup analyses revealed that the increased risk of PaC was independent of geographic locations, sex, study design, alcohol consumption, body mass index (BMI) and smoking status. In addition, the relative risk of PaC was correlated negatively with the duration of DM, with the highest risk of PaC found among patients diagnosed within less than 1 year. There was no significant publication bias ($p = 0.136$ for Egger's regression asymmetry test).

Conclusions: Findings from this meta-analysis strongly support that diabetes is associated with an increased risk of PaC in both males and females and that DM is both an early manifestation and an etiologic factor of pancreatic cancer.

1. Introduction

Pancreatic cancer (PaC) carries a dismal prognosis with a 5-year survival rate of less than 5%, and for most patients, death occurs within 6 months after diagnosis of cancer.[1] Curative resection offers the only chance of cure, but at the time of diagnosis, only 10–20% patients are fortunate enough to undergo tumours resection. Most patients are present with locally advanced or metastatic disease and thus are not eligible for curative surgery.[2] To improve the survival rate of pancreatic cancer, therefore, identification of individuals at high risk for pancreatic cancer could have a marked impact on reducing morbidity and mortality. However, the aetiology of this disease remains largely elusive, except for age, cigarette

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smoking, overweight and a family history of pancreatic cancer.[3] Increasing age is strongly associated with the elevated risk of PaC, with less than 10% of cases occurring in individuals <50 years of age.[4] Cigarette smoking is the only generally accepted modifiable risk factor, but explains only 25–29% of pancreatic cancer incidence.

Diabetes mellitus (DM) is considered to be one of the major public health challenges in both industrialised and developing countries. A number of studies have found that DM may alter risk of a variety of cancers, including cancers of the breast,[5] pancreas,[6] and liver.[7] Several biological mechanisms have been indicated to explain the potentially causal relationship between DM and risk of cancer. It is suggested that abnormal metabolic, immunologic and hormonal characteristics of DM may promote cancer development. In addition, insulin resistance and subsequent hyperinsulinemia may up-regulate the production of insulin-like growth factor-1 (IGF-1), which may result in enhanced cell proliferation and promote cancer development.[8] Specially, associations between DM and the development of PaC have been well-established; at the time of diagnosis, nearly 80% of PaC patients have either impaired glucose tolerance or evident DM.[9] However, it is not yet determined whether diabetes is a predisposing factor or a possible consequence of tumour development, or both.[10]

A meta-analysis based on 36 studies (17 case control and 19 cohort studies) performed by Huxley et al. was published in 2005. The analysis included over 9,000 PaC patients and supported a causal association between type 2 DM and PaC.[11] In addition, the relative risk of PaC was correlated negatively with the duration of DM, with the highest risk of PaC found among patients diagnosed within the last 5 years. Since this meta-analysis was published, several other studies on the association of DM and pancreatic cancer have been published.[12–20]

To provide more precise estimates for DM and PaC risk, in the present study, we performed an updated meta-analysis of cohort studies. We also evaluated whether this association differs to various study characteristics.

2. Materials and methods

2.1. Literature search strategies

Literature search was conducted using Medline (from January 1, 1966) and Embase (from January 1, 1974) through November 30, 2010 by two independent investigators (Ben and Xu). The search strategy used medical subject heading (MeSH) terms and keywords: diabetes or diabetes mellitus or NIDDM; neoplasm(s) or cancer or adenocarcinoma; pancreas; and epidemiologic studies. We also reviewed the reference lists to identify additional relevant studies. No language restrictions were imposed.

2.2. Inclusion and exclusion criteria

Studies were included in the meta-analysis if (1) they had a cohort or nested case control design; (2) one of the exposure interests was DM; (3) one of the outcome of interests was pancreatic cancer and;(4) rate ratio, hazard ratio or standardised incidence/mortality rate (SIR/SMR) with their 95% CIs (or data to calculate them) were reported. Studies were excluded if they provided only an effect estimate with no means to calculate a CI. Articles or reports from non-peer-reviewed sources were not included in this meta-analysis. In the event of multiple publications from the same population or cohort, we included only data from the most recent report or the publication with the most control for confounders. By these criteria, three articles were excluded from our meta-analysis.[21–23] We excluded two cohort studies containing patients with potential type 1 diabetes, which was defined as DM onset at early age ($\leqslant$30 years).[24,25] We also excluded one cohort study which presented with the association of gestational diabetes and risk of PaC.[26]

2.3. Data extraction

We extracted the following data from each study: the first author's last name, publication year, year of the study conducted, country, sample size, participant characteristics (age and sex), methods of ascertainment of diabetes and outcome, the follow-up period, estimate effects with their 95% CIs, and covariates adjusted for in the analysis. When studies provided more than one RRs according to the duration of diabetes before PaC was diagnosed, we extracted and combined the RRs for individuals diagnosed with diabetes more than 1 year prior to the diagnosis of PaC.

If studies reported both incidence rate and mortality rate, we extracted the incidence rate, since mortality rate could be confounded by survival related factors. Two researchers independently performed the data extraction (Ben and Xu).

2.4. Statistical analysis

We included in this meta-analysis reporting different measures of relative risks: rate ratio, hazard ratio and SIR/SMR. In practice, these four measures of effect yield similar estimates of RR because the absolute risk of PaC is low.

The variance of the log RR from each study was calculated by converting the 95% confidence interval (CI) to its natural logarithm by taking the width of the CI and dividing by 3.92. If the variance was unavailable, p-Values or χ^2 value were used to estimate the CI. Summary relative risk estimates with corresponding 95% CIs were derived with the method of DerSimonian and Laird using the assumptions of a random-effects model, which accounts for heterogeneity among studies.[27]

We conducted analyses stratified by (a) geographic area, (b) sex, (c) alcohol consumption, (d) body mass index (BMI), (e) smoking status and, (f) study design. Only the studies based on rate ratio or hazard ratio were included for subgroup analysis. Studies that reported separate RRs for mutually exclusive categories of duration since diabetes was diagnosed (e.g. 1–4 years, 5–9 years, $\geqslant$10 years) were pooled separately to examine how the strength of the association varied with duration of diabetes.

To assess heterogeneity among studies, we used the Cochran Q and I^2 statistics. This was used to test whether the differences obtained between studies was due to chance. For the Q statistic, a p value < 0.10 was considered statistically significant for heterogeneity; for I^2, a value >50% is considered a measure of severe heterogeneity. Publication bias

Table 1 – Characteristics of 27 cohort studies of diabetes and pancreatic cancer based on rate ratio and hazard ratio.

Author/year/country	Year of study conducted	Source and no. of subjects	Demographics (age, mean years)	DM ascertainment	Duration of DM,yr	PaC ascertainment	No. of PaC	Follow up, years	RR (95% CI)	Adjustments
Whittemore/1983/USA[44]	1962–1978	Students, 50,000	Age:NA, Male:100%	Self-reported	>6	Death registry and autopsy	NA	NA	6.08(0.99–47.00)	Age
Hiatt/1988/USA[29]	1978–1984	Population, 122,894	Age:40.8%, Male:44.1%	Self-reported	>5	Medical records (pathology, 75%)	48	NA	4.50(1.20–16.70)	Age, sex, race, smoking, alcohol, coffee
Mills/1988/USA[30]	1973–1984	Adventists, 34,000	Age:>25, Male:NA	Self-reported	>1	Death registry	8	5.7	3.43(1.47–7.94)	Age, sex
Friedman/1993/USA[32]	1964–1988	Residents, 175,000	Age:54.6, Male:50.7%	Self-reported	>1	Medical records	NA	12.6	2.37(1.46–3.85)	Age, weight
Balkau/1993/France[31]	1968–1988	Working men, 6,988	Age:44–55, Male:100%	OGTT	>5	Medical records	312	17	4.7(1.3–16.0)	Age, smoking
Shibata/1994/USA[33]	1981–1990	Retirees, 13,976	Age:75(m);73.8(f), Male:about 1/3	Self-reported	⩽4	Medical records	65	7.2	3.63(1.22–10.80)	Age, sex, smoking
Gapstur/2000/USA[10]	1967–1995	Employees, 35,656	Age:40, Male:57.4%	Self-reported	NA	Death registry	NA	25	2.48(1.20–4.49)	Age
Ye/2001/Sweden[34]	1965–1997	Patients with a history of cholecystectomy, 268,312	Age:57.4, Male:32.5%	NA	>2	Cancer registry	1053	13	1.79(1.39–2.28)	Duration of follow up, age, and calendar year
Stolzenberg–Solomon/2002/Finland[36]	1985–1997	Smokers, 29,048	Age:50–69, Male:100%	Self-reported	>5	Medical records	172	10.2	2.23(1.08–4.60)	Age, smoking, activity, asthma, blood pressure
Lin/2002/Japan[35]	1988–1997	Inhabitants, 110,792	Age:57.3, Male:41.9%	Self-reported	>1	Death registry	225	8.1	2.10(1.20–10.90) (both), 2.12 (1.19–3.77)(m), 1.50 (0.73–3.12)(f)	Age, sex, smoking
Rulyak/2003/USA[38]	1996–2001	Familial pancreatic cancer kindreds, 251	Age:61, Male:NA	Self-reported	NA	Pathology, Medical records, Death registry	83	NA	2.1(0.40–10.9)	Age, smoking, sex, prior history of non-PC
Inoue/2003/Japan[37]	1988–1999	Population, 77,803	Age:60.5, Male:NA	Self-reported	>1	Cancer registry	200	NA	1.79 (1.08–2.97) (both), 2.07 (1.14–3.74)(m), 1.29 (0.46–3.56)(f)	Age, sex, family history of PaC, exercise, bowel habits, raw vegetable, alcohol
Batty/2004/UK[39]	1967–1995	Government employees, 18,006	Age:40–64, Male:100%	OGTT	NA	Death registry	114	NA	3.99 (1.44–11.00)	Age, employment, smoking, SBP, physical activity, disease history
Coughlin/2004/USA[40]	1982–1998	Inhabitants, 1,056,243	Age:57, Male:44%	Self-reported	>1	Death registry	4106	12.5	1.46(1.30–1.64)*(both), 1.48(1.27–1.73)(m), 1.44(1.21–1.72)(f)	Age, sex, race, education, family history, BMI, physical activity, smoking, alcohol, diet
Jee/2005/Korea[12]	1992–2002	Population, 1,298,385	Age:47, Male:64%	Self-reported and blood glucose levels	>1	Cancer registry and medial records	NA	10	1.73(1.49–2.01)*(both), 1.78 (1.50–2.11) (m), 1.56 (1.14–2.14)(f)	Age, age squared, smoking, alcohol
Larsson/2005/Sweden[13]	1987–2004	Population, 83,053	Male:55.3%, Age:62(f); 60(m)	Self-reported	>1	Cancer registry	136	6.6	1.97(1.10–3.53)	Age, education, physical activity, smoking, alcohol
Gupta/2006/USA[42]	1999–2004	Veterans health administration, 1,421,794	Age:>40, Male:92.5%	Disease registry	2–6	Cancer registry	2630	NA	1.73(1.42–2.12)	Age, sex, race
Ansary-Moghaddam/2006/Asia-Pacific Region[41]	1966–1999	Population, 182,173	Age:47, Male:65%	Self-reported and blood glucose levels	>5	Death registry	324	6.9	1.75(0.87–3.55)	Age, smoking, BMI
Inoue/2006/Japan[43]	1990–2003	Population, 97,771	Age:40–69, Male:47.6%	Self-reported	>5	Cancer registry	210	14	1.78(1.00–3.20)*(both), 1.97(1.01–3.88)(m), 1.32 (0.41–4.28)(f)	Age, study area, cerebrovascular disease, smoking, alcohol, BMI, physical activity, etc.
Khan/2006/Japan[14]	1988–1997	Population, 56,881	Age:40–70, Male:41%	Self-reported	>2	Cancer registry	123	18–20	1.5(0.72–3.12)*(both), 1.57(0.67–3.68)(m), 1.30(0.30–5.57)(f)	Age, BMI, smoking, alcohol
Luo/2007/Japan[15]	1990–2003	Population, 99,670	Age:62.8 (m); 65.8(f), Male:47.7%	Self-reported	>1	Death registry and histologically	224	11	2.22(1.35–3.64)*(both); 2.4(1.3–4.2)(m); 1.8(0.7–4.6)(f)	Smoking, BMI, physical activity; study area, age, alcohol, cholelithiasis
Ogunleye/2009/Scotland[19]	1993–2004	Population, 28,731	Age:62, Male:53%	Self-reported	>1	Cancer registry	51	3.9	2.85 (1.27–6.43)	NA
Arnold/2009/USA[16]	1984–2004	Population, 1,060,389	Median age:57, Male:43.2%	Self-reported	>2	Death registry	6243	20	1.25(1.07–1.47)*(both), 1.07(0.53–2.15)*(m), 1.26(1.07–1.47)*(f)	Family history of PaC, cholecystectomy, smoking, BMI.
Stevens/2009/England[20]	1996–2007	Population, 1.29×10^7	Age:55.7, Female:100%	Self-reported	>2	Cancer registry	1338	7.2	1.51 (1.13–2.03)	Age, region, socioeconomic status, smoking, BMI, height
El-Serag/2009/USA[17]	1988–2004	HCV-carriers, 718,687	Age:52, Male:97%	Medical records	NA	Cancer registry	617	2.3	1.24(1.03–1.49)	Age, sex, visit date, type of visit
Jamel/2009/USA[18]	1990–2000	Veterans, 1,115,044	Age:65, Male:98%	Medical records	>3	Cancer registry	NA	NA	3.22(3.03–3.42)	Age, ethnicity, smoking, BMI
Chodick/2010/Israel[45]	1999–2008	Population, 100,595	Age:61.6, Male:52.6%	Self-reported or blood glucose level	>5	Cancer registry	48	8	1.67(1.18–2.36)*(both), 1.89 (1.16–3.07)(m), 1.47(0.90–2.41)(f)	Age, region, BMI, cardiovascular diseases, etc.

RR, relative risk; CI, confidence interval; DM, diabetes mellitus; NA, data not applicable; BMI, body mass index; PaC, pancreatic cancer; OGTT, oral glucose tolerance test; p-ys, person-years; m, male; f, female.

* The RRs with 95% confidence intervals were derived by pooling the sex-specific RRs.

Table 2 – Characteristics of eight cohort studies of diabetes and pancreatic cancer based on standardised incidence/mortality ratio.

Author/ publication years(country)	Year of study conducted	No. of subjects	Demographics (age, mean years)	DM ascertainment	Duration of DM, years	PaC ascertainment	No. of PaC	Follow up, years	RR[a] (95% CI)	Adjustments
Kwssler/1970/ USA[47]	1930–1959	21,290	Age:40–59, Male:44%	Blood glucose test	>1	Death registry	78	10.2	1.80(1.26–2.59)[b](both), 1.47(1.03–2.10)[c](m), 2.13(1.62–2.81)[c](f)	Age, sex
Ragozzino/1982/ USA[48]	1945–1969	1,135	Age:61, Male:53%	Blood glucose levels	>1	Histological verification	5	8.6	2.6(0.9–6.1) (both), 2.70 (0.60–8.0)(m), 2.50 (0.30–9.5)(f)	Age, sex
Adami/1991/ Sweden[49]	1965–1984	51,008	Age:all years, Male:45.4%	Medical records	>1	Cancer registry	156	5.2	1.40(1.2–1.7)(both), 1.40(1.10–1.80)(m), 1.50 (1.20–1.80)(f)	Age, sex
Chow/1995/ Sweden[50]	1965–1989	134,096	Age:all age, Male:47.7%	Medical records	>1	Medical records	650	6.8 (M); 6.7(F)	1.93(1.78–2.08) (both), 1.88 (1.62–2.10)(m), 1.97(1.77–2.19)(f)	Age, sex, year of follow-up
Wideroff/1997/ Denmark[51]	1977–1989	109,581	Age:64(m); 69(f), Male:49%	Medical records	>1	Cancer registry	417	17	1.65(1.49–1.84)[b](both), 1.7(1.5–2.0)(m), 1.6(1.4–1.9)(f)	Age, sex, calendar year
Verlato/2003/ Italy[52]	1987–1996	7148	Age:67, Male:50%	Medical records	NA	mortality records	35	10	1.33 (0.93–1.85) (both), 0.90 (0.46–1.57) (m), 1.78 (1.13–2.67) (f)	Age, smoking, BMI,
Swerdlow/2005/ UK[53]	1972–2003	5066	Age:30–49, Male:58.1%	Self-reported	NA	Cancer registry	12	18	1.30 (0.67–2.27)	Age, sex, calendar year, residence
Hemminki/2010/ Sweden[46]	1964–2007	125,126	Age:>39, Male:NA	Medical records	>1	Cancer registry	566	15	3.57(3.28–3.88)	NA

CI, confidence interval; DM, diabetes mellitus; BMI, body mass index; NA, data not applicable; m, male; f, female; RR, relative risk.

[a] The measure of RR is a standardised incidence (or mortality) ratio.

[b] The RR and 95% CI were derived by pooling the sex-specific SIR/SMR.

[c] The RR and 95% CI were calculated from the data reported in the article.

was evaluated using the funnel plot and Egger's test, which is based on a regression model to determine funnel plot asymmetry.[28] For Egger's test, a p value of less than 0.10 was considered to be statistically significant publication bias. All statistical analyses were performed using STATA, version 11.0 (STATA, College Station, TX, USA).

3. Results

3.1. Search results

A total of thirty-five cohort studies, which met the inclusion and exclusion criteria, were used in this meta-analysis (Tables 1 and 2). Of these 35 studies, 27 studies employed incidence and/or mortality rates as the measurement of relative risk[10,12–20,29–45] (Table 1), and 8 cohort studies used SIR/SMR as the measurement of relative risk[46–53] (Table 2).

3.2. Characteristics in selected studies

The countries in which the studies were conducted were as follows: Japan ($n = 5$)[14,15,35,37,43]; the United States ($n = 14$),[10,16–18,29,30,32,33,38,40,42,44,47,48] Europe ($n = 13$)[13,19,20,31,34,36,39,46,49–53], Asia-Pacific Region ($n = 1$)[41]; Israel ($n = 1$)[45] and Korea ($n = 1$).[12]

The 27 cohort studies, which used incidence or mortality rate as the measurements of relative risk, comprised between 251 and 1,298,385 persons with a median follow-up period of 8.1 years (ranged 2.8–25 years). Most cohorts included in this meta analysis were apparently healthy population, and only three studies included a special population: familial pancreatic cancer kindreds,[38] patients with a history of cholecystectomy[34] and HCV-carriers.[17] Most of the studies included both men and women, and four studies consisted entirely of men[31,36,39,44] and 1 study consisted entirely of women.[20]

Eight studies comprising 454,450 persons (range: 1135–134,096) reported risk estimates of cohorts with T2DM.[46–53] After a median follow-up period of 10 years (ranged 5.2–18 years), 1919 patients were found to be afflicted with pancreatic cancer.

Among these 35 studies, only 4 studies did not demonstrate a significantly increased risk of pancreatic cancer in patients with diabetes,[38,48,52,53], and the rest 31 studies reported a significantly increased risk of PaC in diabetic individuals. DM was determined on the basis of a positive history ($n = 23$); the remaining were based on the following: fasting or postprandial glucose test($n = 4$)[31,39,47,48]; medical records ($n = 7$)[17,18,46,49–52]; not indicated clearly ($n = 1$).[34] Pancreatic cancer diagnosis was made by histological evaluation and/or medical records[12,15,29,31,38,44,48,50] in 8 studies; and cancer registry or death registry alone in the rest studies. Most researches provided the relative risks of duration of DM >1 year, except 6 studies, which did not provide these relative risks.[10,17,38,39,52,53] Potential confounders (at least for age) were controlled in most of the studies, except in 2 studies, the confounders adjusted for were not indicated clearly.[19,46]

3.3. DM and PaC risk

As shown in Fig. 1, the summary RR with 95% CI was 1.94(95% CI, 1.66–2.27) in a random-effects model for individuals with diabetes compared with individuals without diabetes or general population. Though there was significant heterogeneity among these studies ($p < 0.001$, $I^2 = 93.6\%$), all risks were above unity.

Fifteen studies provided results on cancer risk specific for both sexes, and three studies consisted entirely of men, one study consisted entirely of women. In stratified analysis by sex, diabetes was associated with an increased risk of PaC in both males and females [summary RRs(95%CI), 1.70(1.55–1.87) in males and 1.60(1.43–1.77) in females]. The difference in the summary RRs between males and females was not significant ($z = 0.84$, $p = 0.40$), (Table 3).

Next, we conducted subgroup meta-analyses by geographical area and study design (Table 3). The summary RRs were similar for studies conducted in Asia (summary RR, 1.76; 95%CI, 1.56–1.98; test for heterogeneity $Q = 1.22$, $p = 0.976$, $I^2 = 0\%$), or in America (summary RR, 2.12; 95%CI, 1.54–2.92; test for heterogeneity $Q = 289.66$, $p < 0.001$, $I^2 = 95.5\%$), or in Europe (summary RR, 1.92; 95%CI, 1.54–2.38; test for heterogeneity $Q = 7.61$, $p = 0.268$, $I^2 = 21.1\%$). In a random-effects model, the summary RRs with 95% CIs were 2.01(1.64–2.46) for

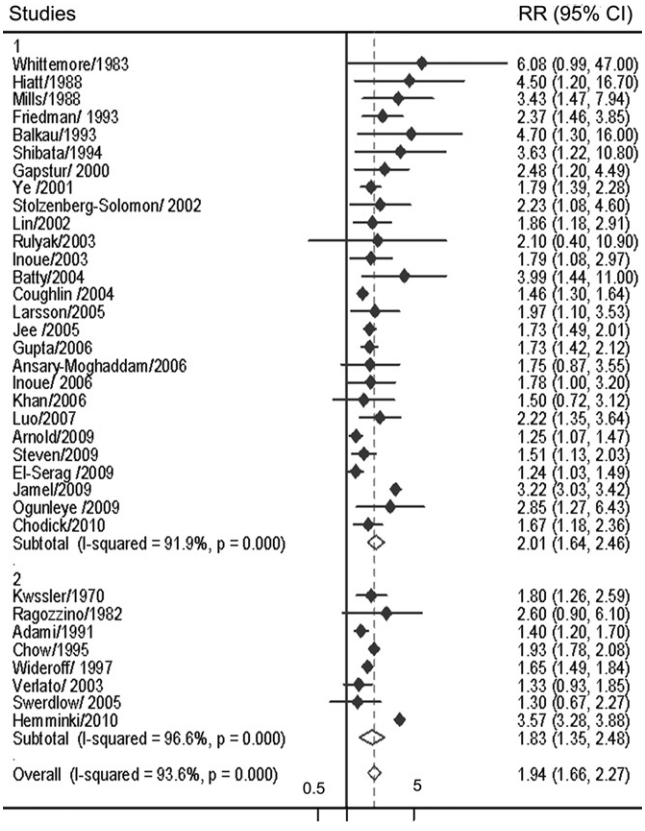

Fig. 1 – Relative risks for the association between diabetes and risk of pancreatic cancer. Studies are sub-grouped according to design. Diamonds represent study-specific relative risks or summary relative risks with 95% CIs; horizontal lines represent 95% confidence intervals (CIs). Test for heterogeneity among studies: $p < 0.001$, $I^2 = 93.6\%$. 1, cohort studies ($n = 27$) use incidence or mortality rate as the measurements of relative risk. 2, cohort studies ($n = 8$) use standardised incidence/mortality rate as the measurement of relative risk.

Table 3 – Subgroup analysis of relative risks for the association between diabetes and pancreatic cancer.

Subgroup	References	RR (95% CI)	Tests for heterogeneity		
			Q	P	I^2(%)
Geographical region[*]					
Europe	13,19,20,31,34,36,39	1.92(1.54–2.38)	7.61	0.268	21.1
USA	10,16–18,29,30,32,33,38,40,42,44	2.12(1.54–2.92)	289.66	<0.001	95.5
Asia	12,14,15,35,37,43,45	1.76(1.56–1.98)	1.22	0.976	0
Gender					
Male	12,14–16,31,35–37,39,40,43–45	1.70(1.55–1.87)	25.15	0.12	28.3
Female	12,14–16,20,35,37,40,43,45	1.60(1.43–1.77)	29.88	0.012	49.8
Study design					
DM–free as controls	10,12–15,17–20,29–46	2.01(1.64–2.46)	322.84	<0.001	91.9
Population as controls	46–53	1.83(1.35–2.48)	205.29	<0.001	96.6
Adjustment for smoking					
Yes	12–16,18,20,29,31,33,35–41,43	2.03(1.55–2.67)	262.1	<0.001	93.9
No	10,17,19,30,32,34,42,44,45	1.95(1.57–2.42)	243.62	<0.001	93.8
Adjustment for alcohol consumption					
Yes	12–15,29,37,40,43	1.64(1.46–1.85)	8.31	0.306	15.8
No	10,16–20,30–36,38,39,41,42,44,45	1.97(1.65–2.35)	456.1	<0.001	94.1
Adjustment for BMI					
Yes	14–16,18,40,41,43,45	1.73(1.19–2.52)	244.25	<0.001	96.7
No	10,12,13,17,19,20,29–39,42,44	2.01(1.69–2.38)	259.15	<0.001	90.0

Note: [*]One study[41] conducted in the Asia-pacific region were not included. RR, relative risk; CI, confidence interval; BMI, body mass index.

cohorts with diabetes compared with those without DM, and 1.83(1.35–2.48) for cohorts with T2DM compared with general population.

We also investigated the impact of confounding factors on the estimates of relative risk (Table 3). 18 studies were controlled for smoking, and the summary RR with 95% CI was similar between studies controlled for smoking and those without controlling for smoking [the summary RR(95% CI), 2.03(1.55–2.67) versus 1.95(1.57–2.42)].

When we restricted the meta-analysis to those studies controlled for BMI, the positive association between diabetes and risk of PaC remained (summary RR = 1.73, 95% CI = 1.19–2.52), with statistically significant heterogeneity among studies (Q = 244.25; $p < 0.001$, $I^2 = 96.7\%$). The association between DM and PaC risk was also similar between studies controlled for alcohol consumption and those not [summary RR(95% CI); 1.64(1.46–1.85) versus 1.97(1.65–2.35)]($z = -1.69$, $p = 0.091$).

3.4. *Duration of DM and PaC risk*

The temporal sequence between diabetes and pancreatic cancer has not always been clear. As shown in Table 4, duration of diabetes in four studies were similar across the studies: 1–4 years, 5–9 years and >10 years,[34,49–51] one study presented with RRs for duration of diabetes categorised for each year between the 1st and 6th year,[42] and three studies for less than 1 year.[34,42,49] Combining these studies according to diabetes duration, respectively, we found that individuals with the shorter duration of diabetes (1–4 years) had higher risk of developing pancreatic cancer than individuals who had duration of diabetes between 5years to 9 years [summary RR, 95%CI; 1.95(1.65–2.31) versus 1.49(1.05–2.12)] and more than 10 years (summary RR, 1.47; 95%CI, 0.94–2.31), but significantly lower than individuals who had diabetes less than 1 year (summary RR, 5.38; 95%CI,3.49–8.30; $z = 4.3$, $p < 0.001$). Fifteen studies presented with RRs for diabetes duration >1 year and 11 studies for duration >5 years, and the summary RRs(95%CI) were 1.96(1.60–2.40) and 1.83(1.38–2.43), respectively.

3.5. *DM and PaC risk in special population*

There were limited data on diabetes and risk of PaC in special populations, making formal statistical analyses impossible. In

Table 4 – Summary relative risks for the association between diabetes and pancreatic cancer according to diabetes duration.

Diabetes duration, years	No. of studies	References	Relative risk	95% Confidence interval
<1	3	34,42,49	5.38	3.49–8.30
1–4	5	34,42,49–51	1.95	1.65–2.31
5–9	4	34,49–51	1.49	1.05–2.12
⩾10	4	34,49–51	1.47	0.94–2.31
>1	14	12,15,30,32,34,35,37,40,46–51	1.96	1.60–2.40
>5	11	29,31,34,36,37,41,44,45,49–51	1.83	1.38–2.43

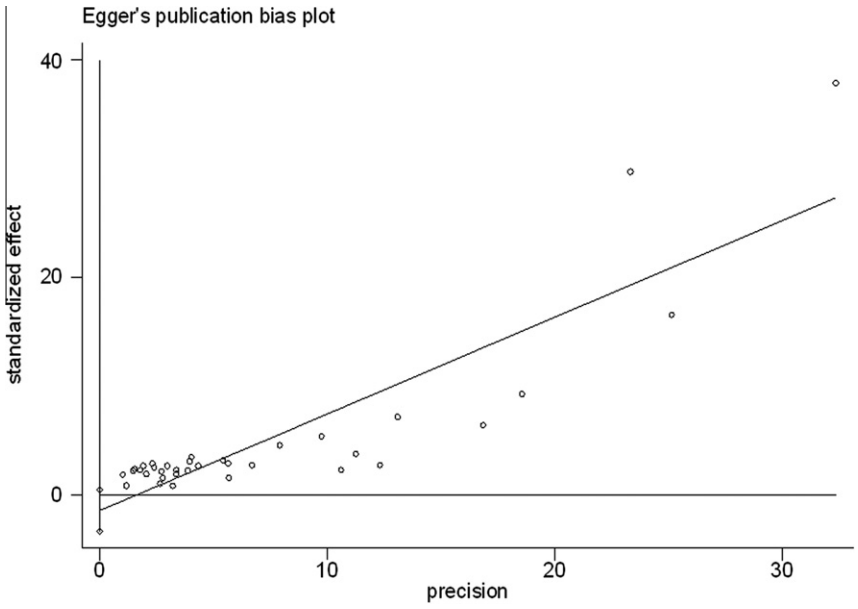

Fig. 2 – Funnel plot of cohort studies evaluating the association between diabetes and pancreatic cancer. Egger's regression asymmetry test (P = 0.136). Standardised effect was defined as the odds ratio divided by its standard error. Precision was defined as the inverse of the standard error.

1 study[38] that consisted of entirely familial pancreatic cancer kindreds, DM was not found to be significantly associated with risk of PaC (RR, 2. 1; 95%CI, 0.40–10.9). One research consisted entirely of patients with a history of cholecystectomy due to cholelithiasis.[34] These patients with a history of diabetes had an increased risk of PaC compared with those without a history of DM, with a RR and 95% CI of 1.79(1.39–2.28). Another one study consisted entirely of HCV-carriers,[17] these individuals with a history of DM had a higher risk of pancreatic cancer than those without DM [RR (95%CI), 1.24 (1.03–1.49)].

3.6. *Publication bias*

There was no funnel plot asymmetry for the association between DM and PaC risk. *p* value for Egger's regression asymmetry test was 0.136, suggesting a low probability of publication bias (Fig. 2).

4. Discussion

In this study, by methods of meta-analysis, we found that diabetic individuals have a nearly 2.0-fold increased risk of pancreatic cancer compared with non-diabetics or general population. The positive link was observed in both women and men, and was independent of alcohol consumption, BMI and smoking status. In addition, the relative risk of PaC was inversely associated with the duration of DM, with the highest risk of PaC found among patients with diabetes diagnosed less than 1 year.

The current, as well as previous, meta-analysis indicated that there was a moderately increased risk of pancreatic cancer among individuals with a shorter duration of diabetes (1–9 years) and an increased, but not statistically significant, rate of pancreatic cancer diagnosis was observed in individuals with the longer duration of diabetes (⩾10 years). Interestingly, the highest risk of pancreatic cancer was observed after duration of follow-up less than 1 year (summary RRs, 5.38; 95%CIs, 3.49–8.30). This supports the hypothesis that diabetes, at least in some cases, may be induced by pancreatic cancer and thus may be an early indicator of this cancer. If otherwise, the RR would be expected to increase, rather than decrease, with duration of diabetes.[11] This finding indicated that those with newly diagnosed diabetes should be highly alert to pancreatic cancer development. Chari et al. found that a marked and continuous increase in prevalence of DM was seen in PaC up to 36 months before the diagnosis of PaC,[54] so, hyperglycaemia may be an attractive biomarker for a high-risk group for pancreatic cancer screening.

Recent studies have suggested that pancreatic cancer-associated DM is likely to be a unique form of DM that is caused by the cancer. This is supported by the following findings: DM occurs with a high frequency and in close temporal association with the diagnosis of pancreatic cancer[54,55]; and DM improves after resection of the tumour of pancreas.[9,56,57] The mechanism by which pancreatic cancer leads to DM, however, is not clear. Several lines of evidence have indicated that the development of DM after pancreatic cancer does not depend on the destruction of pancreatic beta cells,[58,59] but rather, on the development of peripheral insulin resistance.[60] In vitro, blockage of insulin receptors and impaired insulin action and glucose transport, have been suggested to be involved in pancreatic cancer-associated insulin resistance.[61,62] In addition, pancreatic cancer cell-conditioned media (CM) was found to induce mice hyperglycaemia development.[58,59] Interestingly, a 2030 MW peptide in sera from pancreatic cancer patients or pancreatic cancer cell-CM was suggested to be a putative pancreatic cancer associated diabetogenic factor.[63]

On the other hand, individuals with a long duration of T2DM also have a significantly increased risk of pancreatic cancer, which supports a modest causal relationship between diabetes and pancreatic cancer. This is true especially when considering that it is unlikely that a malignancy with 1-year survival rate less than 20% can cause diabetes many years before its diagnosis.[64] T2DM is associated with insulin resistance, compensatory hyper-insulinemia and up-regulated level of IGF-1. Insulin is shown to have a direct, growth-promoting effect on pancreatic cancer cell lines in vitro, through binding to and activating the IGF-1 receptor, and stimulate growth in pancreatic cancer cells in an autocrine manner.[65] IGF-1 and IGF-1 receptor are highly expressed in pancreatic cancer cell lines, which can lead to decreased apoptosis and increased proliferation, invasion, and angiogenesis promotion.[66] In addition, researchers have found a graded dose-response association between pancreatic cancer risk and both fasting and postprandial glucose levels, which also support a causal relationship between the two variables.[10,12]

This study has several limitations which should be recognised. First, cohort studies, which are not affected by recall and selection biases, might be subject to detection bias because patients with diabetes are under increased medical surveillance and thus might be more likely to be diagnosed as pancreatic cancer. This bias may distort the true effects. Second, most of the studies did not distinguish between type 1 and type 2 diabetes (although we excluded two studies which included all patients with young-onset diabetes), which might attenuate any true relationship between diabetes and pancreatic cancer risk, as type-1 diabetes may not be related to pancreatic cancer risk.[67] However, it was likely that the majority of individuals with diabetes included in these studies were T2DM, because it is the most common form of diabetes particularly in older individuals. Third, confounding is also likely to be present because these two diseases share several risk factors, such as aging, smoking, alcohol consumption and obesity. However, the relationship between these two diseases risk only was marginally attenuated after adjustment for a wide range of potential confounders. Forth, all the included studies did not consider the role of anti-diabetic drugs in PC. For example, increasing researches have suggested metformin and thiazolidinediones could exert a protective role against the development and progression of PC.[68] Fifth, the methods of DM ascertainment is "self-reported" in a few studies, which may distort the true relationship between the two disease. Finally, as in any meta-analysis, the possibility of publication bias is of concern, because small studies with null results tend not to be published. Publication bias may have resulted in an overestimate of the relationship between DM and risk of pancreatic cancer. However, the results obtained from funnel plot analysis and formal statistical tests did not provide evidence for such a bias.

In summary, the results from this meta-analysis strongly support an association between diabetes and increased risks of pancreatic cancer in both women and men. Diabetes is both a possible risk factor and an early manifestation of pancreatic cancer. Future work should focus on identifying the potential mechanisms underlying pancreatic cancer–associated diabetes.

Conflict of interest statement

None declared.

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