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ASSOCIATION OF DIABETES MELLITUS WITH PANCREATIC CANCER AND PANCREATIC CANCER MORTALITY RATE. A META-ANALYSIS REVIEW STUDY

[1] Dr Ambreen Akhtar, [2]Dr Hunza Binte Ather,[3]Dr Nawal Ijaz

[1]WMO,RHC Phullarwan , Sargodha, [2]Ex WMO,THQ Hospital, Sabzazar, Lahore, [3]WMO,BHU Said Nagar, Gujranwala.

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Abstract:

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

Methods*: Studies were identified by searching Medline and Embase. By using a random effect model summary relative risk were calculated with 95% confidence interval.*

Results: *thirty-five cohort studies were selected in this meta-analysis. High risk of Pac (the summary RRs = 1.94; 95% CI, 1.66–2.27), with evidence of heterogeneity among these studies (p < 0.001, I 2 = 93.6%). 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.*

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. The death rate from pancreatic cancer was doubled in diabetics.*

Key words: *Diabetes mellitus pancreatic cancer, type 2 diabetes, mortality and pancreatic cancer.*

Corresponding author:

Dr. Ambreen Akhtar,

WMO,RHC Phullarwan , Sargodha.

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INTRODUCTION:

Diabetes mellitus and pancreatic cancer are known to be associated, but it is not known whether diabetes is a true risk factor, preceding development of the cancer, or if it is an early manifestation of the cancer. [1] 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. [2] Although cancer of the pancreas accounts for only 3% of all cancers worldwide its poor prognosis makes it the eighth major form of cancer-related death worldwide, causing more than 220 000 deaths annually. Apart from cigarette smoking, which has been estimated to cause about 30% of pancreatic cancers relatively little is known about the other chief determinants of the disease, although other lifestyle factors have been implicated, including obesity and type-II diabetes.[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.

Curative resection offers the only chance of cure, but at the time of diagnosis, only 10–20% patients are fortunate enough to undergo tumors resection. Most patients are present with locally advanced or metastatic disease and thus are not eligible for curative surgery. 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.

Diabetes mellitus (DM) is considered to be one of the major public health challenges in both industrialized 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 tumor development, or both. [10]

METHODOLOGY:

Data sources:

Relevant studies were identified through EMBASE, PUBMED and MEDLINE using a combined text word and MESH heading search strategy of pancreatic cancer (pancreas, tumor, malignancy) and type-II diabetes (NIDDM, diabetes, adult-onset diabetes). References from identified studies, as well as from the previous review, were also scanned to identify any other relevant studies.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they had a cohort or nested case control design; one of the exposure interests was DM; one of the outcome of interests was pancreatic cancer and; rate ratio, hazard ratio or standardized 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. 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 metaanalysis. [11-13] we excluded two cohort studies containing patients with potential type 1 diabetes, which was defined as DM onset at early age (630 years). We also excluded one cohort study which presented with the association of gestational diabetes and risk of PaC.

Study analysis:

Studies that reported separate ORs for mutually exclusive categories of duration since diabetes was diagnosed (e.g. 1 –4 years, 5 –9 years, 410 years) were pooled separately to examine how the strength of the association varied with duration of diabetes. Possible sources of heterogeneity were investigated by comparing the results for studies combined with respect to particular characteristics (e.g. sex, method of diagnosis of diabetes). All analyses were performed using STATA, version 8.

RESULTS AND DISCUSSION:

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. And 8 cohort studies used SIR/SMR as the measurement of relative risk.

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 and HCV-carriers. Most of the studies included both men and women, and four studies consisted entirely of men and 1 study consisted entirely of women. Eight studies comprising persons (range: 1135– 134,096) reported risk estimates of cohorts with T2DM. 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); medical records (n = 7); not indicated clearly (n = 1).

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.

Duration of DM and PaC risk:

The temporal sequence between diabetes and pancreatic cancer has not always been clear. 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 categorized for each year between the 1st and 6th year, and three studies for less than 1 year. 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.

Table 3. Eligible cohort for analysis, Cancer Prevention Study II, United States,

	No. of women		No. of men	
	Total	Pancreatic cancer deaths	Total	Pancreatic cancer deaths
Initial cohort	676,306	1,666	508,353	1,813
Exclusions				
Died within ®rst year of study	2,673	51	4,732	85
Missing race	3,271	6	2,397	7
Prevalent cancer	56,846	220	25,154	157
Analytic cohort	613,516	1,389	476,070	1,564
Diabetics	27,059	108	26,769	141

Mortality rate:

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)	93(1.78–2.08) (both), 1.88 (1.62–10)(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/ UK53	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.

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.

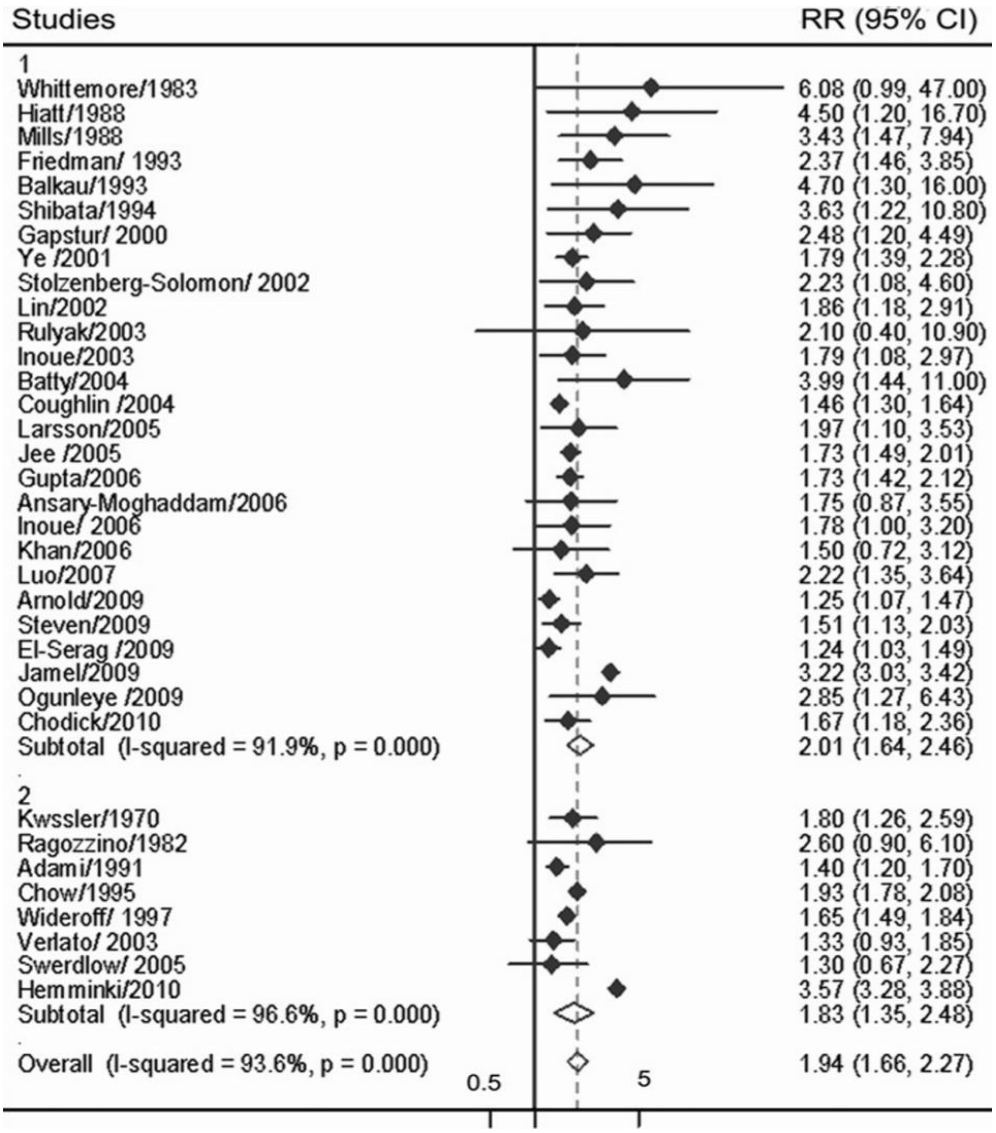

fig. 1 – Relative risks for the association between diabetes and risk of pancreatic cancer. Studies are sub-grouped according to design.study-specific relative risks or summary relative risks with 95% CIs is represented by demonds.; horizontal lines tells 95% confidence intervals (CIs). Test for heterogeneity among studies: $p < 0.001$, I 2 = 93.6%. 1, cohort studies (n = 27) use mortality rate as the measurements of relative risk. 2, cohort studies (n = 8) used.

Cohort and nested case – control studies of diabetes and pancreatic cancer

		Diabetes PC					among individuals with diabetes		
year	Cohort source	diagnosis	Duration	follow-up	Source	cases	adjustment	Risk	95% CI
Ragozzino, 1982	Rochester, US	MR	41	9800	MR, DC	3 M	Age, sex	2.70	0.60 – 9.50
						2 F		2.50	0.30 – 18.4
Whittemore, 1983	50 000 students, Harvard University, US	SR	46	NA	DC	3	Age	6.08	0.99 – 47.0
Rulyak, 2003	251 subjects, Washington, US	SR	NA	NA	MR, P, DC	NA	Age, smoking, sex, prior history of nonPC	2.10	0.40 – 10.9
Hiatt, 1988	122 894, San Francisco, US	SR	45	NA	MR, CR	5	Age, sex, race, smoking, alcohol, coffee	4.50	1.20 – 16.7
Balkau, 1993	6988 male civil servants, France	OGTT	42	NA	MR, P	NA	Age, smoking	3.60	1.00 – 13.0
Shibata, 1994	13 976 Southern California retirees, US	SR	¼o4	3057	MR	4	Age, sex, smoking	3.63	1.22 – 10.8
Inoue, 2003	200, Japan	SR	41	NA	MR, CR	NA	Age, sex, family history, alcohol, exercise, diet	2.07	1.14 – 3.74
								1.29	0.46 – 3.56
Batty, 2004	18 006 male civil servants, UK	OGTT	NA	NA	DC	4	Age, employment, smoking, SBP, physical activity, disease history	3.99	1.44 – 11.0
Jee, 2005	1 298 385, Korea	OGTT	41	NA	MR, CR	NA	Age, smoking, alcohol use	1.71	1.42 – 2.06
								1.71	1.25 – 2.34
Lund Nilsen 2000	31 000 M	SR	NA	6181	CR	4 M	Age, sex	1.10	0.40 – 3.00
	32 374 F, Norway			8059		3 F		0.80	0.30 – 2.70

Mills, 1988	34 000 Adventists, California	SR	41	9683	DC	8	Age, sex	3.43	1.47 – 7.94
Gapstur, 2000	20 473 M, 15 183 F, Chio	SR	NA	NA	DC	NA	Age	2.48	1.20 – 4.49
Stolzenberg-	29 084 M, Finland	SR	45	10 669	CR, MR	14	Age, smoking, occupational activity, asthma, blood pressure	2.23	1.08 – 4.60
Lino, 2002	110 792, Japan	SR	41	20 859 M, 15 389 F	DC	17	Age, sex, and smoking	2.10	1.20 – 3.60
						9		1.50	0.73 – 3.12
Friedman, 1993	175 000, San Francisco	SR	41	NA	MR, CR		Age, weight	2.37	1.46 – 3.85
Adami, 1994	1.2 million, Sweden	Hospitalised patients	41	143 618 M	CR	68 M	Age, sex	1.40	1.10 – 1.80
				119 643 F		88 F		1.50	1.20 – 1.80
Coughlin, 2004	467 922 M, 588 322 F, Columbia and Puerto Rico	SR	41	NA	DC	NA	Age, sex, race, education, family history, BMI, smoking, alcohol, diet history	1.48	1.27 – 1.73
								1.44	1.21 – 1.72
Chow, 1995	134 096 hospitalised for Hospitalised diabetes, Sweden patients		41	432 643 M	CR	303	Age, sex, year of follow-up	1.88	1.62 – 2.10
				468493 F		347		1.97	1.77 – 2.19
Wideroff, 1997	109 581 hospitalised for Hospitalised diabetes, Denmark patients		41	628 129	MR, CR	417	Age, sex, year of follow-up	1.70	1.50 – 2.50
								1.60	1.40 – 2.90

CONCLUSION:

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. The death rate from pancreatic cancer was double in diabetics (adjusted RR = 2.05, CI = 1.56-2.69).

REFERENCE:

1. Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath CW. Diabetes mellitus and pancreaticcancer mortality in a prospectivecohort of United States adults. Cancer Causes & Control. 1998 Aug 1;9(4):403-10.
2. Hezel AF, Kimmelman AC, Stanger BZ, Bardeesy N, Depinho RA. Genetics and biology of pancreatic ductal adenocarcinoma. Genes Dev 2006;20(10):1218–49.
3. WCRF. World Cancer Research Fund. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. 2nd ed.

Washington, DC: American Institute for Cancer Research; 2007 (p. 215–6)

4. . Lowenfels AB, Maisonneuve P. Risk factors for pancreatic cancer. J Cell Biochem 2005;95(4):649–56.
5. Heidemann C, Boeing H, Pischon T, et al. Association of a diabetes risk score with risk of myocardial infarction, stroke, specific types of cancer, and mortality: a prospective study in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort. Eur J Epidemiol 2009;24(6):281–8
6. Ben Q, Cai Q, Li Z, et al. The relationship between new-onset diabetes mellitus and pancreatic cancer risk: A case-control study. Eur J Cancer 2011;48:248–54
7. . El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4(3):369–80.
8. Ulanet DB, Ludwig DL, Kahn CR, Hanahan D. Insulin receptor functionally enhances multistage tumor progression and conveys intrinsic resistance to IGF-1R targeted therapy. Proc Natl Acad Sci USA 2010;107(24):10791–8.
9. Pannala R, Leirness JB, Bamlet WR, et al. Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. Gastroenterology 2008;134(4):981–7.
10. . Gapstur SM, Gann PH, Lowe W, et al. Abnormal glucose metabolism and pancreatic cancer mortality. Jama 2000;283(19):2552–8.
11. Coughlin SS, Calle EE, Patel AV, Thun MJ. Predictors of pancreatic cancer mortality among a large cohort of United States adults. Cancer Causes Control 2000;11(10):915–23. 22. Smith GD,
12. Egger M, Shipley MJ, Marmot MG. Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. Am J Epidemiol 1992;136(9):1110–4. 23.
13. Calle EE, Murphy TK, Rodriguez C, Thun MJ, Heath Jr CW. Diabetes mellitus and pancreatic cancer mortality in a prospective cohort of United States adults. Cancer Causes Control 1998;9(4):403–10.