

experimental pancreatic cancer. *Am J Surg.* 1988;155:159-164.

69.**Lindblad P, Chow WH, Chan J, et al.** The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologia.* 1999;42:107-112.

70.**Brinton LA, Berman ML, Mortel R, et al.** Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. *Am J Obstet Gynecol.* 1992;167:1317-1325.

71.**Zendehdel K, Nyren O, Ostenson CG, Adami HO, Ekblom A, Ye W.** Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Natl Cancer Inst.* 2003;95:1797-1800.

72.**Shu X, Ji J, Li X, Sundquist J, Sundquist K, Hemminki K.** Cancer risk among patients hospitalized for Type 1 diabetes mellitus: a population-based cohort study in Sweden. *Diabet Med.* 2010;27:791-797.

73.**Johnson JA, Gale EA.** Diabetes, insulin use, and cancer risk: are observational studies part of the solution-or part of the problem? *Diabetes.* 2010;59:1129-1131.

74.**Pocock SJ, Elbourne DR.** Randomized trials or observational tribulations? *N Engl J Med.* 2000;342:1907-1909.

75.**McFarland MS, Cripps R.** Diabetes mellitus and increased risk of cancer: focus on metformin and the insulin analogs. *Pharmacotherapy.* 2010;30:1159-1178.

76. **Grossmann M, Thomas MC, Panagiotopoulos S, et al.** Low testosterone levels are common and associated with insulin resistance in men with diabetes. *J Clin Endocrinol Metab.* 2008;93:1834-1840.

77. **Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P.** Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab.* 2004;89:5462-5468.

78. **Ding EL, Song Y, Malik VS, Liu S.** Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA.* 2006;295:1288-1299.

79. **Noto H, Osame K, Sasazuki T, Noda M.** Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. *J Diabetes Complications.* 2010;24:345-353.

80. **Richardson LC, Pollack LA.** Therapy insight: Influence of type 2 diabetes on the development, treatment and outcomes of cancer. *Nat Clin Pract Oncol.* 2005;2:48-53.

81. **Morss AS, Edelman ER.** Glucose modulates basement membrane fibroblast growth factor-2 via alterations in endothelial cell permeability. *J Biol Chem.* 2007;282:14635-14644.

82. **Currie CJ, Poole CD, Gale EA.** The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia.* 2009;52:1766-1777.

83. **Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM.** New users of

metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes.

Diabetes Care. 2009;32:1620-1625.

84.**Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L.** Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care.* 2000;23:465-471.

85.**Chan WB, Tong PC, Chow CC, et al.** The associations of body mass index, C-peptide and metabolic status in Chinese Type 2 diabetic patients. *Diabet Med.* 2004;21:349-353.

86.**Fukushima M, Usami M, Ikeda M, et al.** Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. *Metabolism.* 2004;53:831-835.

87.**Kadowaki T, Miyake Y, Hagura R, et al.** Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia.* 1984;26:44-49.

88.**Kuroe A, Fukushima M, Usami M, et al.** Impaired beta-cell function and insulin sensitivity in Japanese subjects with normal glucose tolerance. *Diabetes Res Clin Pract.* 2003;59:71-77.

89.**Karin M, Lawrence T, Nizet V.** Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell.* 2006;124:823-835.

90.**Chan JC, Malik V, Jia W, et al.** Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA.* 2009;301:2129-2140.

91. **McCall JL, Tuckey JA, Parry BR.** Serum tumour necrosis factor alpha and insulin resistance in gastrointestinal cancer. *Br J Surg.* 1992;79:1361-1363.
92. **Noguchi Y, Yoshikawa T, Marat D, et al.** Insulin resistance in cancer patients is associated with enhanced tumor necrosis factor-alpha expression in skeletal muscle. *Biochem Biophys Res Commun.* 1998;253:887-892.
93. **Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC.** Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol.* 2010;11:627-636.
94. **Giovannucci E, Harlan DM, Archer MC, et al.** Diabetes and cancer: a consensus report. *Diabetes Care.* 2010;33:1674-1685.

Figure legends

Fig. 1. Summary of the study selection.

Fig. 2. Adjusted risk ratios (RRs) for the all-cancer incidence among subjects with diabetes. Boxes, estimated RRs; bars, 95% confidence intervals (CIs). Diamonds, Mantel-Haenszel RRs; width of diamonds; pooled CIs. The size of the box is proportional to the weight of each study in the meta-analysis.

Fig. 3. Adjusted risk ratios (RRs) for the all-cancer mortality among subjects with diabetes. Boxes, estimated RRs; bars, 95% confidence intervals (CIs). Diamonds, Mantel-Haenszel RRs; width of diamonds; pooled CIs. The size of the box is proportional to the weight of each study in the meta-analysis.

Table legends

Table 1. Characteristics of the studies included in the systematic review and meta-analysis of the cancer incidence risk in subjects with diabetes.

The data for men and for women were combined. *: not included in the meta-analysis. NS: not specified.

Table 2. Characteristics of the studies included in the systematic review and meta-analysis of the cancer mortality risk in subjects with diabetes.

The data for men and for women were combined. *: not included in the meta-analysis. NS: not specified.

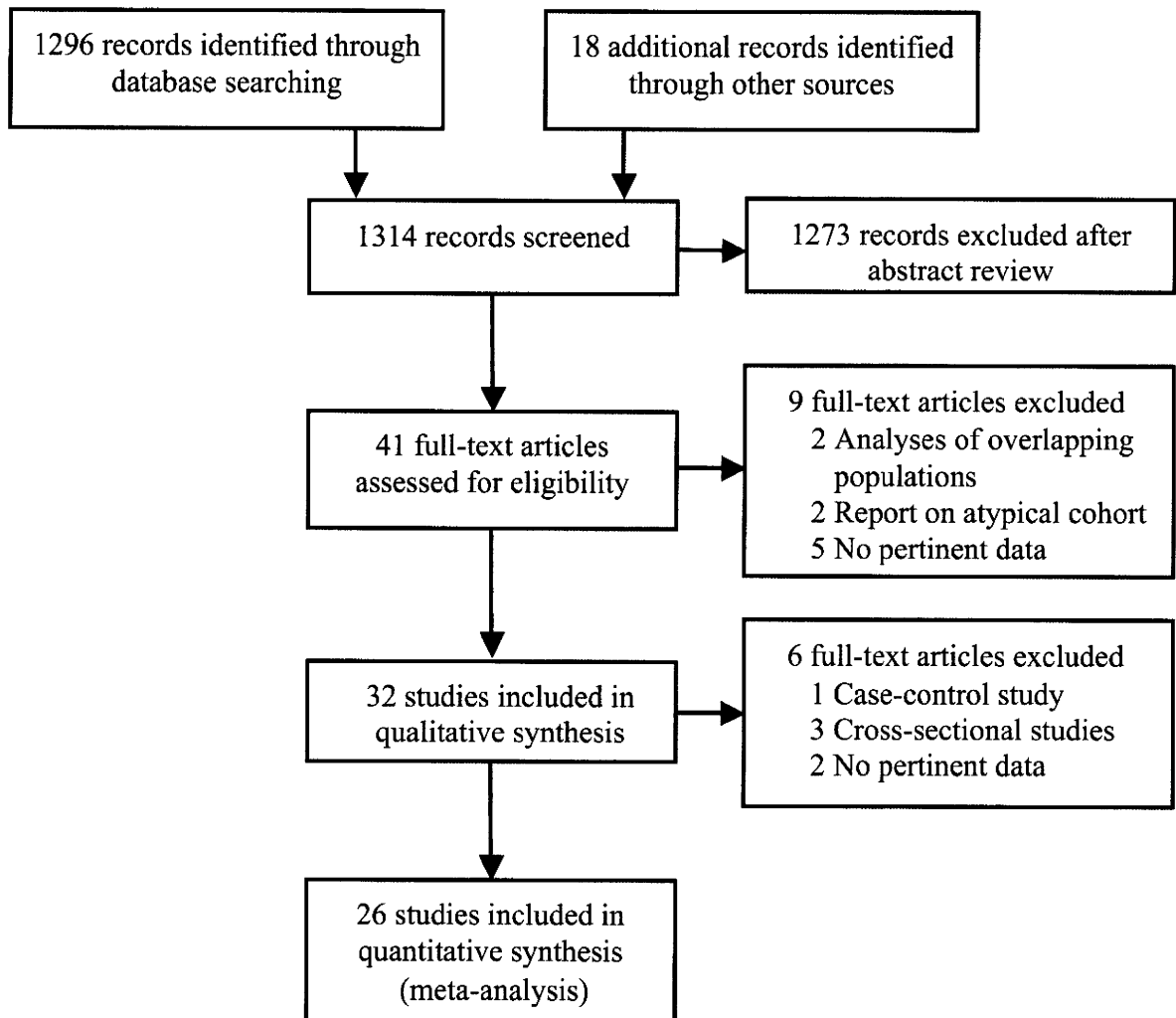
Table 3. Quality assessments of the included studies on cancer incidence.

The data for men and for women were combined. SIR: standardized incidence ratio. BMI: body mass index *: not included in the meta-analysis.

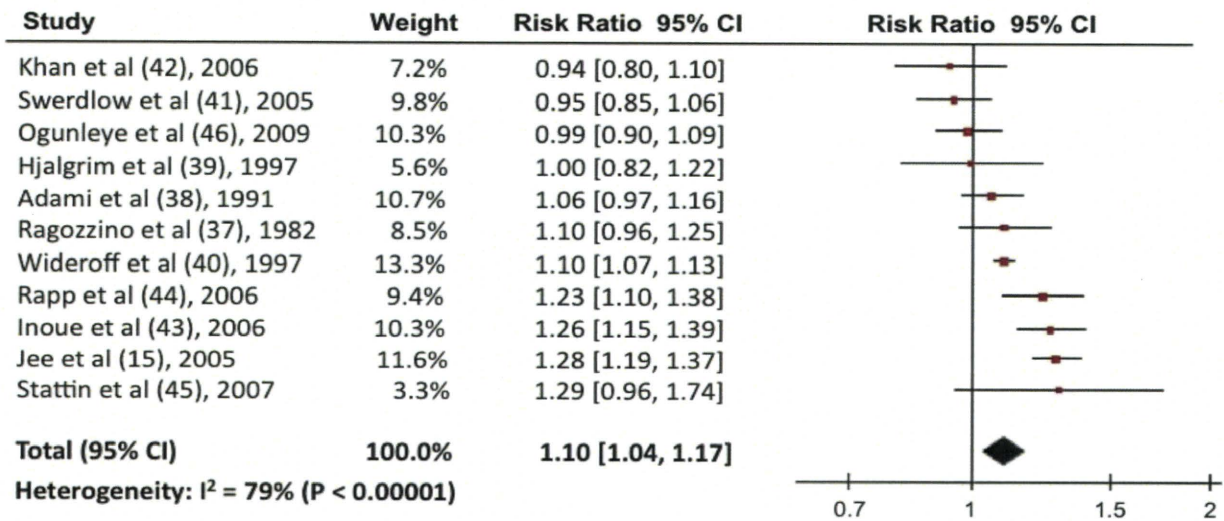
Table 4. Quality assessments of the included studies on cancer mortality.

The data for men and for women were combined. SMR: standardized mortality ratio. SBP: systolic blood pressure. BMI: body mass index. HTN: hypertension. CHD: coronary heart

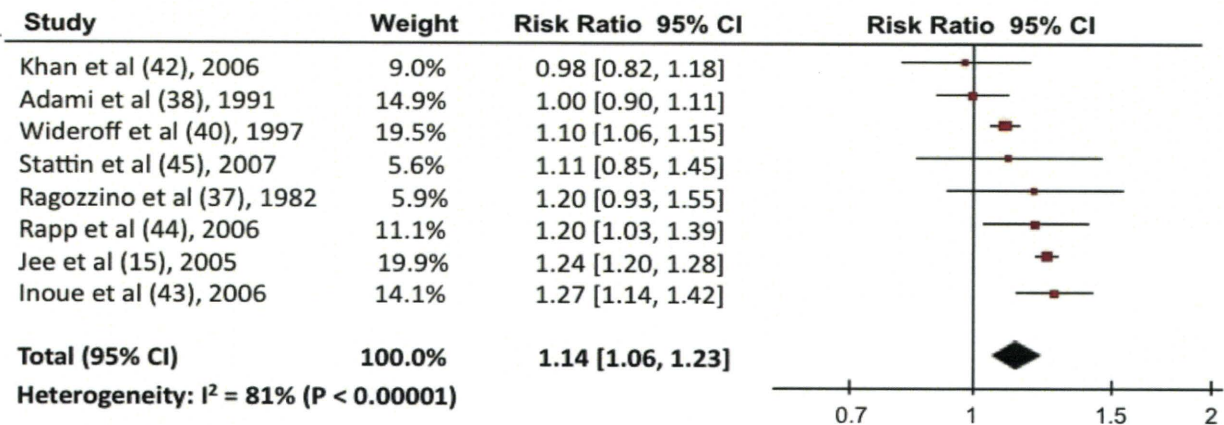
disease. *: not included in the meta-analysis.



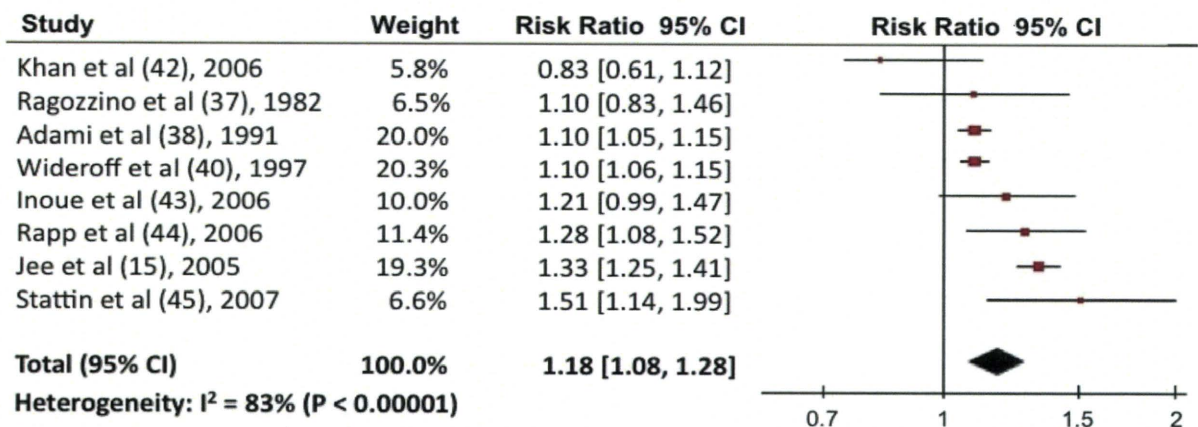
Overall



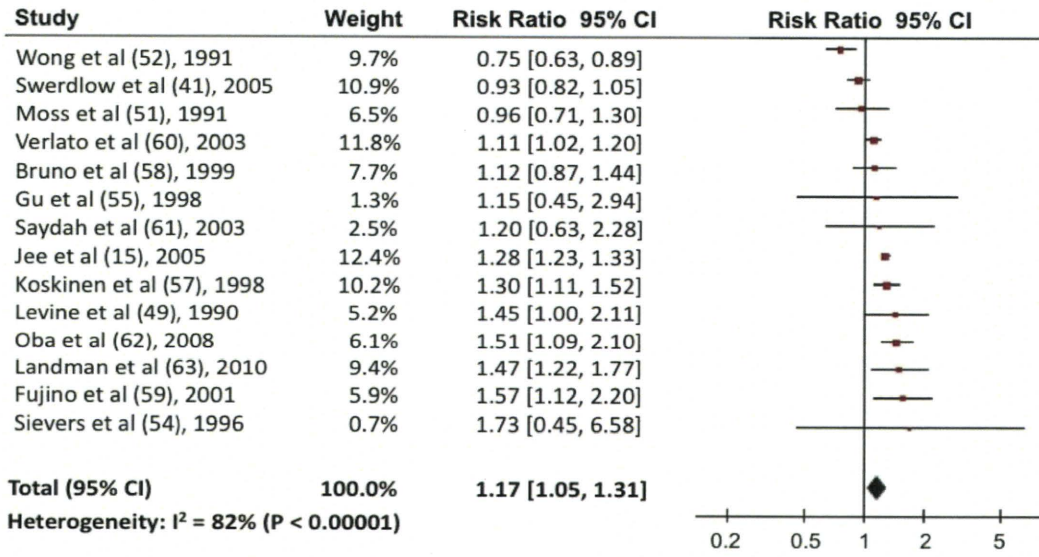
Men



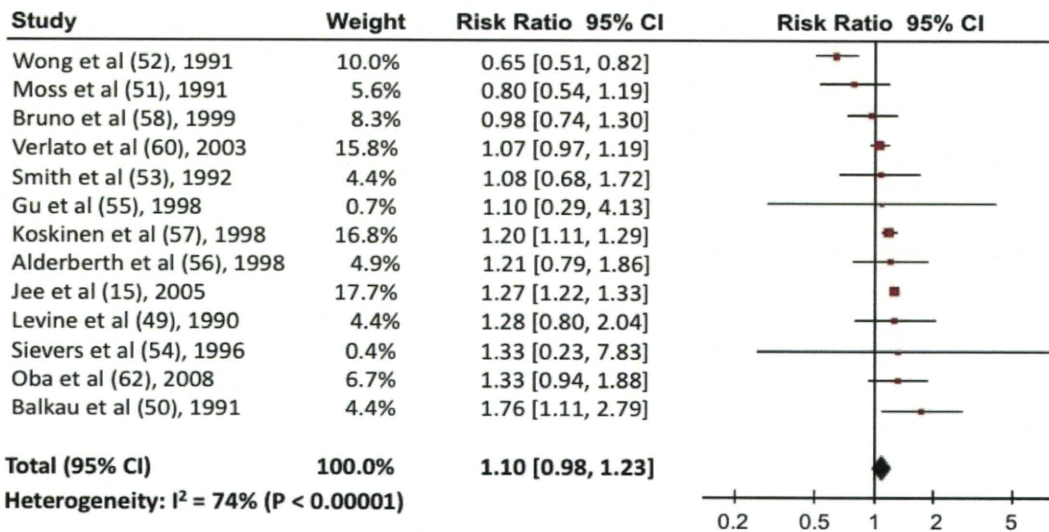
Women



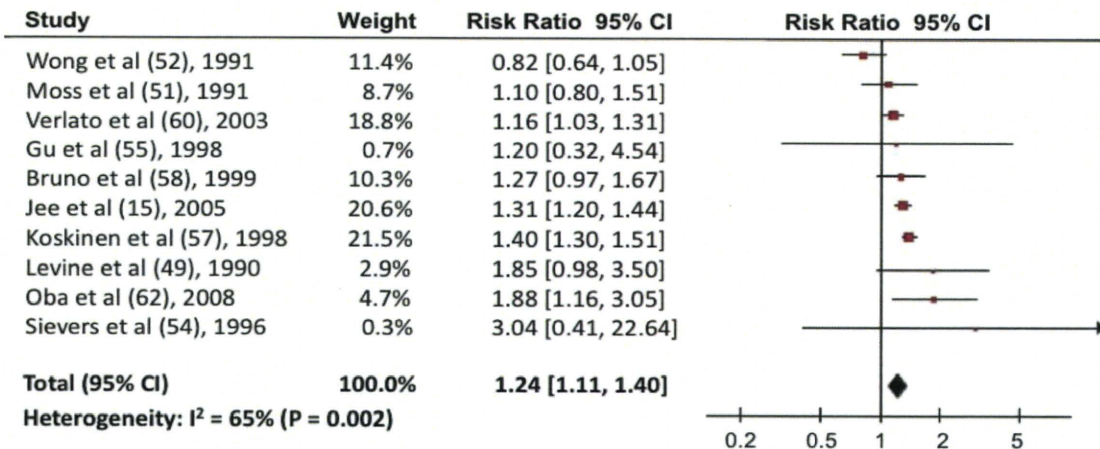
Overall



Men



Women



Source	Follow-up, y	DM		
		N (men, %)	Age, y	Cancer case, n
Cohort studies				
Jee et al (15), 2005	10	62924 (60)	Men: mean 45 Women: mean 50	NS
Kath et al (36), 2000*	Mean 4.3	2720 (NS)	NS	28
Ragozzino et al (37), 1982	25	1135 (NS)	NS	120
Adami et al (38), 1991	Range 1-19	51008 (45)	Mean 45	2417
Hjalgrim et al (39), 1997	Range 1-19	772 (48)	≥30	101
Wideroff et al (40), 1997	Range 1-16	109581 (50)	Men: median 64 Women: median 69	8831
Swerdlow et al (41), 2005	Mean 18.0	5066 (58)	Range 30-49	341
Khan et al (42), 2006	9	3307 (41)	Range 40-79	215
Inoue et al (43), 2006	Mean 10.7	4668 (48)	Men: mean 54 Women: mean 51	470
Rapp et al (44), 2006	Men: mean 8.2 Women: mean 8.6	4758 (44)	Men: mean 43 Women: mean 43	353
Stattin et al (45), 2007	Men: mean 8.3 Women: mean 8.2	1706 (52)	Men: mean 46 Women: mean 46	110
Ogunleye et al (46), 2009	Mean 3.9	9577 (53)	Mean 62	661
Case-control study				
Kuriki et al (47), 2007*		2191 (33)	Mean 59	766

Source	Follow-up, y	DM		
		N (men, %)	Age, y	Cancer death, n
Cohort studies				
Jee et al (15), 2005	10	62924 (60)	Men: mean 45 Women: mean 50	NS
Green et al (35), 1984*	7	1499 (52)	NS	39
Swerdlow et al (41), 2005	Mean 18.0	5066 (58)	Range 30-49	255
Fuller et al (48), 1983*	Range 11-14	5971 (50)	NS	247
Levine et al (49), 1990	12	643 (58)	Range 35-64	29
Balkau et al (50), 1991	15	298 (100)	Range 44-55	22
Moss et al (51), 1991	8.5	1772 (45)	Mean 67	85
Wong et al (52), 1991	5	4186 (51)	≥15	131
Smith et al (53), 1992	Range 18-20	224 (100)	Range 40-64	18
Sievers et al (54), 1996	7.5	1562 (48)	≥15	27
Gu et al (55), 1998	22	710 (41)	Range 25-75	61
Alderberth et al (56), 1998	16	249 (100)	Mean 56	22
Koskinen et al (57), 1998	5	58000 (41)	Range 30-74	1421
Bruno et al (58), 1999	7	1967 (68)	Men: mean 64 Women: mean 68	NS
Fujino et al (59), 2001	10	364 (49)	Mean 59	38
Verlato et al (60), 2003	10	3659 (47)	Men: mean 63 Women: mean 69	409
Saydah et al (61), 2003	16	427 (39)	Mean 58	26
Oba et al (62), 2008	7	1217 (46)	Men: mean 59 Women: mean 63	55
Landman et al (63), 2010	Median 9.6	1353 (42)	Mean 68	122
Cross-sectional studies				
Fuller et al (48), 1983*		43336 (42)	NS	3135
Sasaki et al (64), 1985*		6600 (NS)	Mean 67.1	513
Tierney et al (65), 2001*		4287 (NS)	≥18	9.7/y

Source	Country	Subject source	Comorbidity	Diagnosis of diabetes	Cancer ascertainment	Adjustment factors
Cohort studies						
Jee et al (15), 2005	Korea	Insurance registry-based		Self-report or Blood test	Medical records, Population registries, Death certificates	SIR
Kath et al (36), 2000*	Germany	Hospital-based	Insulin treated Type 1/Type 2 mixed	Blood test	Medical records	None
Ragozzino et al (37), 1982	United States	Population-based		Blood test	Medical records, Death certificates, Autopsy reports	SIR
Adami et al (38), 1991	Sweden	Population-based		Hospital record	Population registries	SIR
Hjalgrim et al (39), 1997	Denmark	Population-based	Insulin treated	Prescription database	Population registries	SIR
Wideroff et al (40), 1997	Denmark	Hospital-based	Type 1/Type 2 mixed	Hospital record	Population registries	SIR
Swerdlow et al (41), 2005	United Kingdom	Population-based	Insulin treated	Prescription database	Population registries	SIR
Khan et al (42), 2006	Japan	Population-based		Self-report	Population registries	Age, BMI, smoking, alcohol
Inoue et al (43), 2006	Japan	Population-based		Self-report	Population registries	Age, cardiovascular disease, smoking, alcohol, BMI, physical activity, vegetable, coffee
Rapp et al (44), 2006	Austria	Population-based		Blood test	Population registries	Age, BMI, occupation, smoking
Stattin et al (45), 2007	Sweden	Population-based		Blood test	Population registries	None
Ogunleye et al (46), 2009	Scotland	Hospital-based		Physician-report	Population registries	Deprivation

Case-control study

Kuriki et al (47), Japan
2007*

Hospital-based

Self-report

Outpatient
registries

Age, BMI,
alcohol,
physical
activity, bowel
movement,
family history,
diet

Source	Country	Subject source	Comorbidity	Diagnosis of diabetes	of Cancer ascertainment	Adjustment factors
Cohort studies						
Jee et al (15), 2005	Korea	Insurance registry-based		Self-report or blood test	Medical records, Population registries, Death certificates	SMR
Green et al (35), 1984*	Denmark	Population-based	Insulin treated	Prescription database	Population registries	SMR
Swerdlow et al (41), 2005	United Kingdom	Population-based	Insulin treated	Prescription database	Population registries	SMR
Fuller et al (48), 1983*	United Kingdom	Population-based		Self-report	Population registries	SMR
Levine et al (49), 1990	United States	Employment registry-based		Self-report or Medical records	Death certificates	Age, BMI, smoking, SBP, cholesterol, education, HTN treatment
Balkau et al (50), 1991	France	Employment registry -based		Blood test	Family-report, Medical records	SMR
Moss et al (51), 1991	United States	Population-based		Blood test	Death certificates	SMR
Wong et al (52), 1991	United Kingdom	Clinic-based	Type 1/Type 2 mixed	Medical Records	Medical Records	SMR
Smith et al (53), 1992	United Kingdom	Population-based		Self-report or blood test	Death certificates	Age
Sievers et al (54), 1996	United States (Pima Indians)	Population-based		Blood test	Death certificates	Age, sex
Gu et al (55), 1998	United States	Population-based		Self-report	Death certificates	Age
Alderberth et al (56), 1998	Sweden	Population-based		Self-report	Population registries	Age, cholesterol, SBP, smoking, BMI, CHD

Koskinen et al (57), 1998	Finland	Population-based	Prescription database	Death certificates	None
Bruno et al (58), 1999	Italy	Population-based	Medical records, Prescription database	Population registries	Population-based
Fujino et al (59), 2001	Japan	Population-based	Self-report	Death certificates	Age, sex, smoking, alcohol
Verlato et al (60), 2003	Italy	Population-based	Medical records	Death certificates	SMR
Saydah et al (61), 2003	United States	Population-based	Self-report, Blood test	Death certificates	Age, sex, race, education, smoking, alcohol intake, physical activity, HDL, SBP, BMI
Oba et al (62), 2008	Japan	Population-based	Self-report	Death certificates	Age, smoking, BMI, physical activity, education, hypertension, diet, alcohol
Landman et al (63), 2010	Netherland	Clinic-based	Physician-report	Medical records	SMR
Cross-sectional studies					
Fuller et al (48), 1983*	United Kingdom	Death certificates	Death certificates	Death certificates	SMR
Sasaki et al (64), 1985*	Japan	Population-based	Death certificates	Death certificates	SMR (age)
Tierney et al (65), 2001*	United States	Population-based	Death certificates	Death certificates	Age

