Thus, the true prevalence of diabetes and its effect on cancer risk may have been underestimated. Lastly, possible modification of carcinogenesis by diabetes medication cannot be completely excluded in descriptive studies, although relevant data are currently limited and further investigation is needed (93,94).

CONCLUSION

Our review and analysis strongly suggest that diabetes is associated with an increased risk of all-cancer incidence and mortality worldwide. In light of the exploding global epidemic of diabetes, a modest increase in the risk of cancer will translate into a substantial socioeconomic burden. Our current findings underscore the need for diabetes prevention, particularly by weight management, and for exploration of effective cancer prevention, screening policies, and implementation of diabetes treatment with potentially protective effects against cancer. Finally, integrated clinical attention and better-designed studies of the complex interactions between diabetes and cancer are urgently needed.

AUTHOR CONTRIBUTIONS

Dr. Hiroshi Noto researched the data, contributed to the discussion, and wrote the manuscript. Dr. Tetsuro Tsujimoto researched the data, contributed to the discussion, and reviewed and edited the manuscript. Dr. Takehiko Sasazuki contributed to the discussion. Dr. Mitsuhiko Noda contributed to the discussion and reviewed and edited the manuscript.

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DISCLOSURE

The authors have no multiplicities of interest to disclose.

REFERENCES

1. **White MF.** The insulin signalling system and the IRS proteins. *Diabetologia.* 1997;40(suppl 2):S2-S17.
2. **Kim YI.** Diet, lifestyle, and colorectal cancer: is hyperinsulinemia the missing link? *Nutr Rev.* 1998;56:275-279.
3. **Kaaks R.** Nutrition, hormones, and breast cancer: is insulin the missing link? *Cancer Causes Control.* 1996;7:605-625.
4. **Giovannucci E.** Insulin and colon cancer. *Cancer Causes Control.* 1995;6:164-179.
5. **Yu H, Berkel H.** Insulin-like growth factors and cancer. *J La State Med Soc.* 1999;151:218-223.
6. **Zhang W, Thornton WH, MacDonald RS.** Insulin-like growth factor-I and II receptor expression in rat colon mucosa are affected by dietary lipid intake. *J Nutr.* 1998;128:158-165.
7. **Bruning PF, Bonfrèr JM, van Noord PA, Hart AA, de Jong-Bakker M, Nooijen WJ.** Insulin resistance and breast-cancer risk. *Int J Cancer.* 1992;52:511-516.
8. **Hu FB, Manson JE, Liu S, et al.** Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. *J Natl Cancer Inst.* 1999;91:542-547.
9. **Silverman DT, Schiffman M, Everhart J, et al.** Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer.* 1999;80:1830-1837.
10. **Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B.** Diabetes mellitus and breast cancer. *Lancet Oncol.* 2005;6:103-111.
11. **Le Roith D.** Seminars in medicine of the Beth Israel Deaconess Medical Center: insulin-like growth factors. *N Engl J Med.* 1997;336:633-640.
12. **Barclay AW, Petocz P, McMillan-Price J, et al.** Glycemic index, glycemic load, and chronic disease risk—a meta-analysis of observational studies. *Am J Clin Nutr.* 2008;87:627-637.
13. **Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A.** Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA.* 2000;283:2552-2558.
14. **Seow A, Yuan JM, Koh WP, Lee HP, Yu MC.** Diabetes mellitus and risk of colorectal cancer in the Singapore Chinese Health Study. *J Natl Cancer Inst.* 2006;98:135-138.
15. **Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM.** Fasting serum glucose level and cancer risk in Korean men and women. *JAMA.* 2005;293:194-202.
16. **Stocks T, Rapp K, Bjørge T, et al.** Blood glucose and risk of incident and fatal cancer in the Metabolic Syndrome and Cancer Project (Me-Can): analysis of six prospective cohorts. *PLoS Med.* 2009;6:e1000201. Epub 2009 Dec 22.
17. **Abe R, Yamagishi S.** AGE-RAGE system and carcinogenesis. *Curr Pharm Des.* 2008;14:940-945.
18. **Inoue M, Kurahashi N, Iwasaki M, et al (Japan Public-Health Center-Based Prospective Study Group).** Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II). *Cancer Causes Control.* 2009;20:741-750.
19. **Larsson SC, Mantzoros CS, Wolk A.** Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer.* 2007;121:856-862.
20. **Friberg E, Orsini N, Mantzoros CS, Wolk A.** Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia.* 2007;50:1365-1374.
21. **Larsson SC, Orsini N, Brismar K, Wolk A.** Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia.* 2006;49:2819-2823.
22. **El-Serag HB, Hampel H, Javadi F.** The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol.* 2006;4:369-380.

23. **Larsson SC, Orsini N, Wolk A.** Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst.* 2005;97:1679-1687.
24. **Huxley R, Ansary-Moghaddam A, Berrington de Gonzaléz A, Barzi F, Woodward M.** Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer.* 2005;92:2076-2083.
25. **Everhart J, Wright D.** Diabetes mellitus as a risk factor for pancreatic cancer: a meta-analysis. *JAMA.* 1995;273: 1605-1609.
26. **Bonovas S, Filioussi K, Tsantes A.** Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia.* 2004;47:1071-1078.
27. **Kasper JS, Giovannucci E.** A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2006;15:2056-2062.
28. **Barone BB, Yeh HC, Snyder CF, et al.** Postoperative mortality in cancer patients with preexisting diabetes: systematic review and meta-analysis. *Diabetes Care.* 2010; 33:931-939.
29. **Barone BB, Yeh HC, Snyder CF, et al.** Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA.* 2008;300:2754-2764.
30. **von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (STROBE initiative).** The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol.* 2008;61: 344-349.
31. **de Marco R, Locatelli F, Zoppini G, Verlato G, Bonora E, Muggeo M.** Cause-specific mortality in type 2 diabetes: the Verona Diabetes Study. *Diabetes Care.* 1999;22:756-761.
32. **Nerlich AG, Hagedorn HG, Böheim M, Schleicher ED.** Patients with diabetes-induced microangiopathy show a reduced frequency of carcinomas. *In Vivo.* 1998;12:667-670.
33. **Stroup DF, Berlin JA, Morton SC, et al (Meta-analysis of Observational Studies in Epidemiology [MOOSE] Group).** Meta-analysis of Observational Studies in Epidemiology: a proposal for reporting. *JAMA.* 2000;283:2008-2012.
34. **Liberati A, Altman DG, Tetzlaff J, et al.** The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151: W65-W94.
35. **Green A, Hougaard P.** Epidemiological studies of diabetes mellitus in Denmark. 5. Mortality and causes of death among insulin-treated diabetic patients. *Diabetologia.* 1984;26:190-194.
36. **Kath R, Schiel R, Müller UA, Höffken K.** Malignancies in patients with insulin-treated diabetes mellitus. *J Cancer Res Clin Oncol.* 2000;126:412-417.
37. **Ragozzino M, Melton LJ III, Chu CP, Palumbo PJ.** Subsequent cancer risk in the incidence cohort of Rochester, Minnesota, residents with diabetes mellitus. *J Chronic Dis.* 1982;35:13-19.
38. **Adami HO, McLaughlin J, Ekbom A, et al.** Cancer risk in patients with diabetes mellitus. *Cancer Causes Control.* 1991;2:307-314.
39. **Hjalgrim H, Frisch M, Ekbom A, Kyvik KO, Melbye M, Green A.** Cancer and diabetes—a follow-up study of two population-based cohorts of diabetic patients. *J Intern Med.* 1997;241:471-475.
40. **Wideroff L, Gridley G, Mellemkjaer L, et al.** Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst.* 1997;89:1360-1365.
41. **Swerdlow AJ, Laing SP, Qiao Z, et al.** Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study. *Br J Cancer.* 2005;92:2070-2075.
42. **Khan M, Mori M, Fujino Y, et al (Japan Collaborative Cohort Study Group).** Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev.* 2006;7:253-259.
43. **Inoue M, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S.** Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med.* 2006;166:1871-1877.
44. **Rapp K, Schroeder J, Klenk J, et al.** Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia.* 2006;49:945-952.
45. **Stattin P, Björ O, Ferrari P, et al.** Prospective study of hyperglycemia and cancer risk. *Diabetes Care.* 2007;30:561-567.
46. **Ogunleye AA, Ogston SA, Morris AD, Evans JM.** A cohort study of the risk of cancer associated with type 2 diabetes. *Br J Cancer.* 2009;101:1199-1201.
47. **Kuriki K, Hirose K, Tajima K.** Diabetes and cancer risk for all and specific sites among Japanese men and women. *Eur J Cancer Prev.* 2007;16:83-89.
48. **Fuller JH, Elford J, Goldblatt P, Adelstein AM.** Diabetes mortality: new light on an underestimated public health problem. *Diabetologia.* 1983;24:336-341.
49. **Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J.** Post-load plasma glucose and cancer mortality in middle-aged men and women: 12-year follow-up findings of the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol.* 1990;131:254-262.
50. **Balkau B, Eschwège E, Ducimetière P, Richard JL, Warnet JM.** The high risk of death by alcohol related diseases in subjects diagnosed as diabetic and impaired glucose tolerant: the Paris Prospective Study after 15 years of follow-up. *J Clin Epidemiol.* 1991;44:465-474.
51. **Moss SE, Klein R, Klein BE.** Cause-specific mortality in a population-based study of diabetes. *Am J Public Health.* 1991;81:1158-1162.
52. **Wong JS, Pearson DW, Murchison LE, Williams MJ, Narayan V.** Mortality in diabetes mellitus: experience of a geographically defined population. *Diabet Med.* 1991;8:135-139.
53. **Smith GD, Egger M, Shipley MJ, Marmot MG.** Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. *Am J Epidemiol.* 1992;136:1110-1114.
54. **Sievers ML, Nelson RG, Bennett PH.** Sequential trends in overall and cause-specific mortality in diabetic and non-diabetic Pima Indians. *Diabetes Care.* 1996;19:107-111.
55. **Gu K, Cowie CC, Harris MI.** Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. *Diabetes Care.* 1998;21:1138-1145.
56. **Adlerberth AM, Rosengren A, Wilhelmsen L.** Diabetes and long-term risk of mortality from coronary and other causes in middle-aged Swedish men: a general population study. *Diabetes Care.* 1998;21:539-545.
57. **Koskinen SV, Reunanen AR, Martelin TP, Valkonen T.** Mortality in a large population-based cohort of patients with drug-treated diabetes mellitus. *Am J Public Health.* 1998;88:765-770.

58. **Bruno G, Merletti F, Boffetta P, et al.** Impact of glycaemic control, hypertension and insulin treatment on general and cause-specific mortality: an Italian population-based cohort of type II (non-insulin-dependent) diabetes mellitus. *Diabetologia.* 1999;42:297-301.
59. **Fujino Y, Mizoue T, Tokui N, Yoshimura T.** Prospective study of diabetes mellitus and liver cancer in Japan. *Diabetes Metab Res Rev.* 2001;17:374-379.
60. **Verlato G, Zoppini G, Bonora E, Muggeo M.** Mortality from site-specific malignancies in type 2 diabetic patients from Verona. *Diabetes Care.* 2003;26:1047-1051.
61. **Saydah SH, Loria CM, Eberhardt MS, Brancati FL.** Abnormal glucose tolerance and the risk of cancer death in the United States. *Am J Epidemiol.* 2003;157:1092-1100.
62. **Oba S, Nagata C, Nakamura K, Takatsuka N, Shimizu H.** Self-reported diabetes mellitus and risk of mortality from all causes, cardiovascular disease, and cancer in Takayama: a population-based prospective cohort study in Japan. *J Epidemiol.* 2008;18:197-203.
63. **Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, Bilo HJ.** Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care.* 2010;33:322-326.
64. **Sasaki A, Horiuchi N, Hasegawa K, Uehara M.** Causes of death in Japanese diabetics: a 20-year study of death certificates. *J Chronic Dis.* 1985;38:655-661.
65. **Tierney EF, Geiss LS, Engelgau MM, et al.** Population-based estimates of mortality associated with diabetes: use of a death certificate check box in North Dakota. *Am J Public Health.* 2001;91:84-92.
66. **Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ.** Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet.* 2006;367:1747-1757.
67. **Fisher WE, Boros LG, O'Dorisio TM, O'Dorisio MS, Schirmer WJ.** GI hormonal changes in diabetes influence pancreatic cancer growth. *J Surg Res.* 1995;58:754-758.
68. **Bell RH Jr, McCullough PJ, Pour PM.** Influence of diabetes on susceptibility to 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, Nyrén O, Ostenson CG, Adami HO, Ekbom 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.

発表論文

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Significantly increased risk of cancer in diabetes mellitus patients: A meta-analysis of epidemiologic evidence in Asians and non-Asians.
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REVIEW ARTICLE

Significantly increased risk of cancer in diabetes mellitus patients: A meta-analysis of epidemiological evidence in Asians and non-Asians

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ABSTRACT

Aims/Introduction: Emerging evidence from observational studies suggests that diabetes mellitus affects the cancer risk. However, whether there are differences in the magnitude of the influence of diabetes among ethnic groups is unknown.

Materials and Methods: We searched MEDLINE and the Cochrane Library for pertinent articles that had been published as of 4 April 2011, and included them in a meta-analysis of the risk of all-cancer mortality and incidence in diabetic subjects.

Results: A total of 33 studies were included in the meta-analysis, and they provided 156,132 diabetic subjects for the mortality analysis and 993,884 for the incidence analysis. Cancer mortality was approximately 3%, and cancer incidence was approximately 8%. The pooled adjusted risk ratio (RR) of all-cancer mortality was significantly higher than for non-diabetic people (RR 1.32 [CI 1.20–1.45] for Asians; RR 1.16 [CI 1.01–1.34] for non-Asians). Diabetes was also associated with an increased RR of incidence across all cancer types (RR 1.23 [CI 1.09–1.39] for Asians; RR 1.15 [CI 0.94–1.43] for non-Asians). The RR of incident cancer for Asian men was significantly higher than for non-Asian men ($P = 0.021$).

Conclusions: Diabetes is associated with a higher risk for incident cancer in Asian men than in non-Asian men. In light of the exploding global epidemic of diabetes, particularly in Asia, a modest increase in the cancer risk will translate into a substantial socioeconomic burden. Our current findings underscore the need for clinical attention and better-designed studies of the complex interactions between diabetes and cancer. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00183.x, 2012)

KEY WORDS: Cancer, Diabetes, Meta-analysis

INTRODUCTION

Emerging evidence from observational data and meta-analyses of the data suggest that diabetes mellitus is associated with an increased risk of cancer. The mechanisms responsible for the increase in risk have yet to be investigated, but as insulin might have a mitogenic effect through binding the insulin-like growth factor-1 receptor[1–11], insulin resistance and secondary hyperinsulinemia is the most frequently proposed hypothesis and hyperglycemia itself might promote carcinogenesis[12–18]. However, the possibility of methodological issues, bias and occult malignant tumors cannot be completely excluded. Meta-analyses have shown that diabetes increases the risks of total cancer[19,20] and of site-specific cancers of the breast[21], endometrium[22], bladder[23], liver[24], colorectum[25] and pancreas[26,27], and that it decreases the risk of prostate cancer[28,29].

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The same as in Western countries, the prevalence of diabetes is markedly increasing in Asia. This trend is presumably attributable to the rapid Westernization of people's lifestyle, a trend that is likely shared by the majority of Asian populations[30]. Although cardiovascular disease is the main cause of mortality in Western countries and patients with diabetes have a high risk of such disease, cancer is the leading cause of death in Asian countries, including Japan[31,32]. As the current diabetes epidemic and the higher mortality in cancer patients with diabetes[33], particularly in Asia, will translate into crucial clinical and public health consequences on a global scale, attention should be directed to elucidating the association between these diseases in populations with increased risks to make timely, rational and informed decisions, not only in the public health area and socioeconomic area, but also for the prevention and targeted management of diabetes in routine clinical practice both domestically and globally.

The aforementioned circumstances prompted us to more precisely investigate the effect of diabetes on all-cancer mortality and incidence among Asians and non-Asians by carefully reviewing pertinent original reports and combining their data in

an attempt to obtain meaningful clues to the prevention and management of cancer in diabetes.

MATERIALS AND METHODS

Data Sources and Searches

Searches of MEDLINE and the Cochrane Library from their inception until 4 April 2011 were carried out, and articles that reported investigations of cancer mortality and incidence in diabetic patients and non-diabetic subjects were extracted. Relevant reports were identified by using a combination of the following medical subject headings as search terms: 'diabetes', 'cancer' or 'neoplasms', and 'risk' or 'risk factors'. The literature reference lists of the pertinent articles were also examined.

Relevant reports included those of observational studies that evaluated type 2 diabetes, but not reports of studies that focused on impaired glucose tolerance/impaired fasting glucose, or solely type 1 diabetes. Cohort, case–control and cross-sectional studies carried out to evaluate the risk of cancer based on original data analyses were assessed to determine their eligibility for inclusion in a qualitative analysis, and those of them that reported risk ratios (RR), that is, hazard ratios (HR), relative risks or odds ratios (OR) adjusted for possible confounders with confidence intervals (CI), were eligible for inclusion in the meta-analysis.

Data Extraction and Quality Assessment

We reviewed each full-text report to determine its eligibility, and extracted and tabulated all of the relevant data independently. The majority of the studies that were included had been systematically reviewed elsewhere[19,20], and the additional studies[34–40] used for inclusion in the present analysis were evaluated in the same manner: the data extracted included the subjects' characteristics (including age, sex and comorbidities), study design, study years, follow-up period, and the methods used to ascertain the presence or absence of diabetes and cancer. Any disagreement was resolved by consensus among the investigators. To ascertain the validity of the eligible studies, the quality of each report was appraised in reference to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement[41].

Data Synthesis and Statistical Analysis

If more than one study was published in regard to the same cohort, the report with information on the most comprehensive population was included to avoid overlapping populations. This process resulted in the exclusion of two articles from the meta-analysis[16,42]. Another investigation, carried out on diabetic patients with autopsy-proven nephropathy[43], was also excluded, because cohorts with this condition are rare, and the generalizability of the findings was deemed to be poor.

The reports were summarized quantitatively into a meta-analysis. The individual RR were combined, and the pooled RR adjusted for possible confounders with 95% CI was calculated by using the random-effects model with inverse-variance weighting. If not provided in the original study, the RR for the men and women combined was estimated before pooling. The equality of RR between Asian and non-Asian studies were assessed by using z-statistic tests. Heterogeneity among studies was evaluated using I^2 statistics. The possibility of a publication bias, which can result from non-publication of small studies with negative findings, was assessed visually by using a funnel plot for asymmetry. Subgroup analyses for each sex were carried out to further elucidate the impact of the risk of all-cancer mortality and incidence in diabetic patients. The RevMan software program (version 5.1, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used to make all of the calculations. All of the procedures were in accordance with the guidelines for the meta-analysis of observational studies in epidemiology[44] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[45].

RESULTS

Search Results

A total of 1514 citations were identified during our search, and 45 of them were evaluated as eligible for inclusion in our meta-analysis aimed at determining the influence of diabetes on all-cancer mortality and all-cancer incidence among Asians and non-Asians (Figure 1). The 33 (31 cohort studies, one cross-sectional study and one case–control study) of these 45 articles that provided sufficient information were included in the meta-analysis. The 33 articles[15,34–39,46–71] that were selected for inclusion in the meta-analysis were moderately heterogeneous in terms of the population demographics and assessment of confounding factors, and the methodological quality of the majority of the studies included was fair[20] (data not shown for the additional data[34–40]). The sizes of the diabetic patient samples in the studies ranged from 224 to 594,815. Cancer mortality and cancer incidence were approximately 3 and 8%, respectively.

Quantitative Summary (Meta-analysis)

As shown in Figures 2 and 3, the diabetic patients worldwide had a significantly increased risk of all-cancer mortality in com-

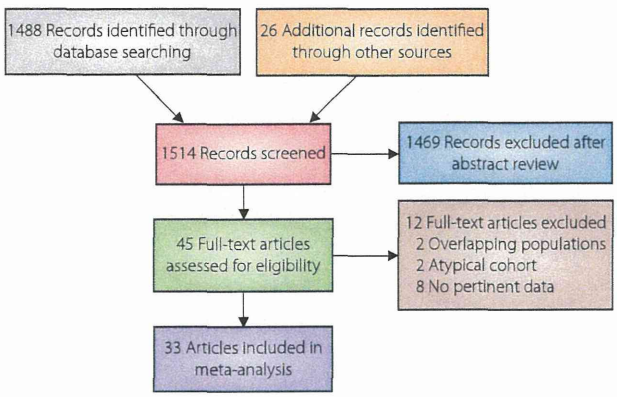

Figure 1 | Summary of the procedure used to select studies for inclusion in the meta-analysis.

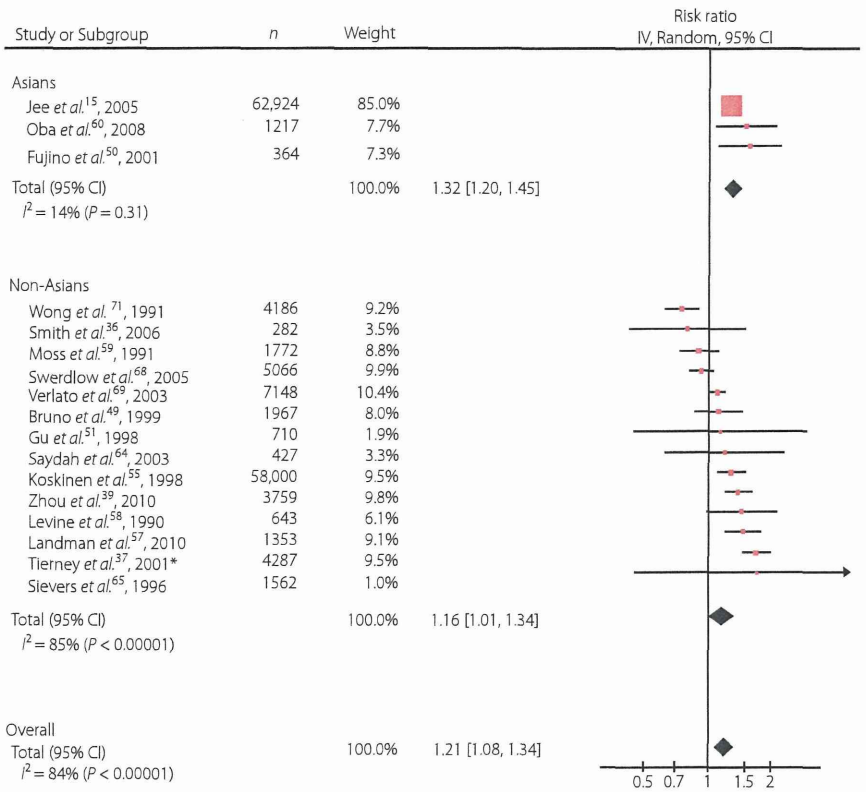

Figure 2 | Adjusted risk ratios (RR) for all-cancer mortality among the subjects with diabetes. *Cross-sectional study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI.

parison with the non-diabetic subjects. The adjusted RR for both men and women were also significantly higher, and the RR were consistently higher for Asians than for non-Asians across the analyses, although they did not reach statistical significance ($P = 0.130$ for men and women; 0.086 for men; 0.536 for women). As shown in Figures 4 and 5, diabetes was also associated with an increased RR of incidence across all cancer types worldwide, and the RR was significantly higher for Asian men than for non-Asian men ($P = 0.585$ for men and women; 0.021 for men; 0.467 for women). Significant heterogeneity was observed across these studies. No clear publication bias was detected by a funnel plot assessment (data not shown).

DISCUSSION

We recently showed a worldwide increased risk of all-cancer mortality and incidence among diabetic patients in a meta-analysis of population-based observational reports of epidemiological data[20]. In the present study we found associations between diabetes and a moderately increased risk of all-cancer mortality and all-cancer incidence among both Asians and non-Asians, and confirmed the worldwide trend[20] with the updated data. Few reports have addressed the risk of total cancer in diabetes, and, to the best of our knowledge, ours is the first meta-analysis to compare the magnitude of risk in different races. Our findings are of considerable clinical and socioeconomic importance, because the cancer risk proved to be significantly increased in the rapidly growing Asian diabetic population as well, and the risk increment in incidence was found to be larger for Asian men than for the diabetic men in the other areas.

The strength of the present study lies in the fact that the analysis regarding overall cancer was mainly based on large population-based cohorts from several different countries and ethnic groups, and was carried out with high levels of precision and generalizability. Although the pooled RR were robust, the results of the component studies were statistically heterogeneous. The large I^2 values showed that the range of plausible risk estimates is wide, but there was very little evidence in our analysis to support a protective effect of diabetes on all-cancer incidence and mortality. These findings might reflect the different mechanisms of development of cancer at different sites and/or different epidemiological characteristics among the diverse populations.

Type 2 diabetes is characterized by insulin resistance and compensatory hyperinsulinemia, and people with type 2 diabetes are typically obese and lead sedentary lives, both of which also contribute to their hyperinsulinemia. It has been postulated that insulin has a mitogenic effect by multiple and complex mechanisms. First, insulin might bind and activate its related insulin-like growth factor-1 receptor, which is the most fre-

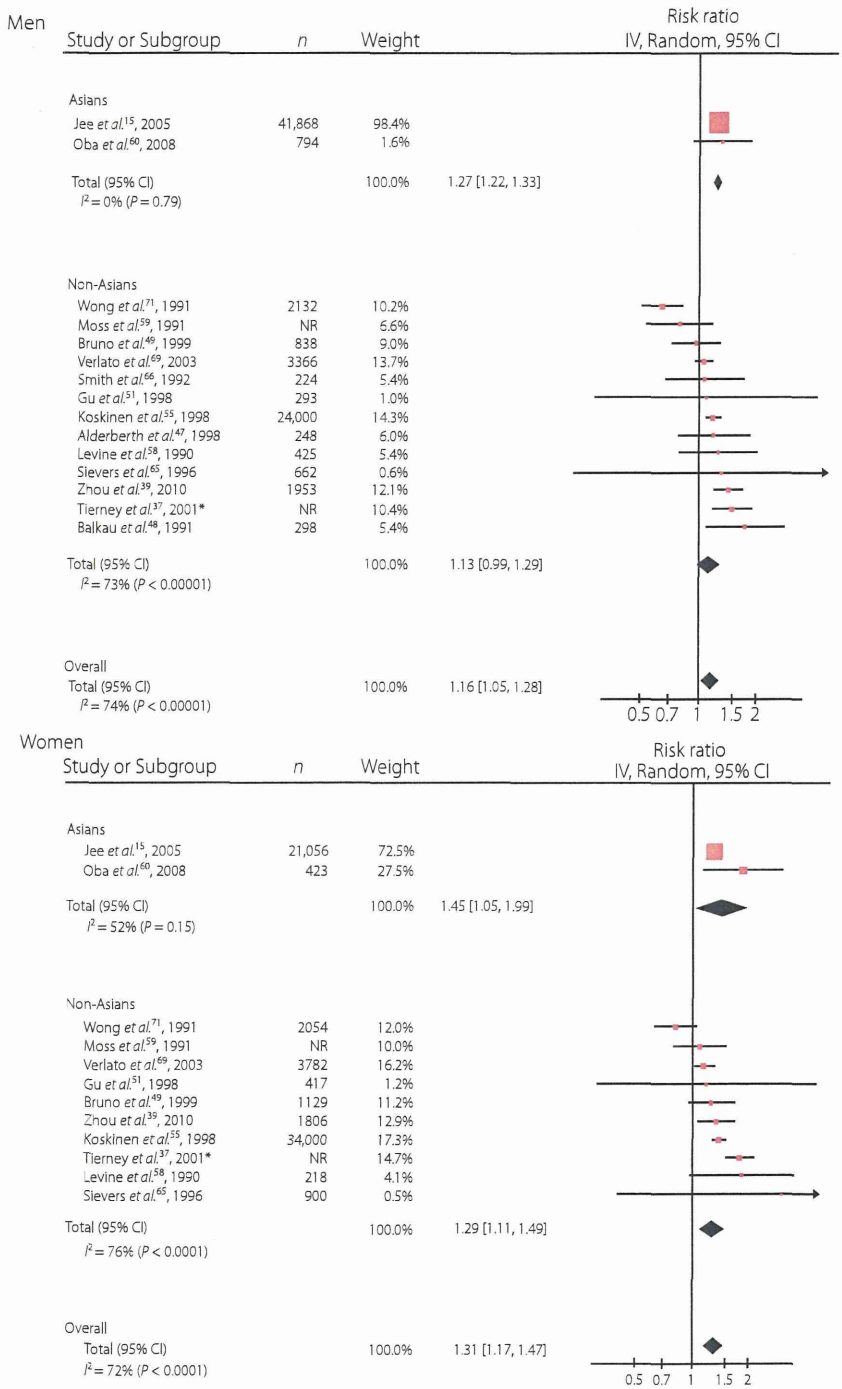

Figure 3 | Adjusted risk ratios (RR) for all-cancer mortality among men and women with diabetes. *Cross-sectional study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI. NR, not reported.

quently proposed mechanism to explain the clearly increased risk of cancer in diabetic patients[1–11]. Second, hyperinsulinemia might increase the risk of certain cancers by increased insulin receptor signaling, leading to proliferative and anti-apoptotic effects[72]. Finally, the mitogenic activity of insulin might be enhanced at the cellular level by post-receptor molecular mechanisms, including insulin residence time on the receptor and the intracellular upregulation of the insulin mitogenic pathway[73].

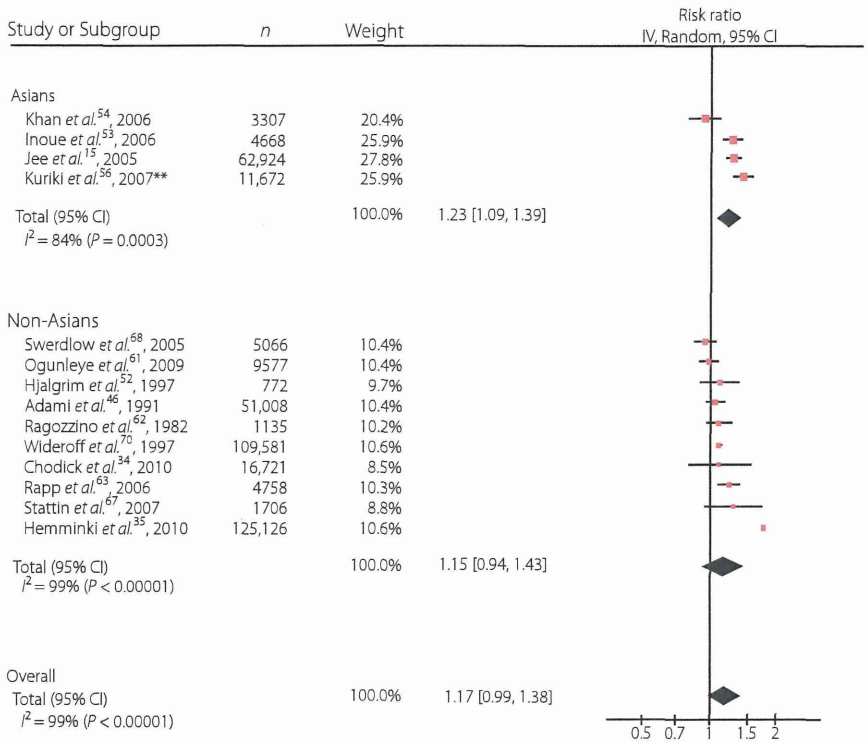

Figure 4 | Adjusted risk ratios (RR) for all-cancer incidence among the subjects with diabetes. **Case–control study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI.

It has been reported that this mitogenic pathway, unlike the metabolic pathway, might not be blunted in the condition of insulin resistance. The activated protein kinase (AMPK), mammalian target of rapamycin and insulin-signaling pathway represent three interrelated components of a complex mechanism controlling cell responses to nutrient availability. It is suggested that metformin might have an anti-cancer effect by activating AMPK, followed by modulation of downstream tumor gene regulators.

Several findings would seem to support this insulin supply hypothesis. Pancreatic cancer has been reported to be induced more effectively with a carcinogen or by implantation of cancer cells when experimental insulin-deficient animals are given supplemental insulin[74,75]. Humans with type 1 diabetes have a lower risk of cancer than humans with type 2 diabetes[76,77], although the evidence for a higher risk than in the general population is inconclusive[78,79]. However, they are derived from retrospective observational studies, and because of the possible existence of confounders and biases in those studies, they do not necessarily indicate causality[80,81]. In fact, the data from insulin-treated patients are inconclusive[82].

Interestingly, diabetes has been reported to protect against the development of prostate cancer[28,29], which is testosterone-dependent. Testosterone deficiency is common in men with diabetes, because they have low levels of sex-hormone-binding globulin, and testosterone levels have been shown to be partly influenced by insulin resistance[83–85]. The magnitude of the decrease in cancer risk as a result of testosterone deficiency is likely to be higher than the magnitude of the increase in cancer risk as a result of insulin resistance, and thus this favorable effect of diabetes on prostate cancer might have contributed to the attenuation of the increase in cancer risk in men found in the current study and in our preceding report[19]. However, those meta-analyses[28,29] were mainly based on data for Caucasian men and the reported risks for Asian men have been either significantly elevated in Taiwan[86,87] or non-significant in Japan[53,54,56,88,89] and Korea[15], which points to the possibility that the effect of diabetes on prostate cancer might not be universal, probably because of genetic/cultural/socioeconomic factors. In fact, the current study showed that the RR for prostate cancer for Asian men were non-significant (data not shown) and that the RR for total cancer incidence was significantly higher for Asian men than for non-Asian men.

Hyperglycemia has also been reported to promote tumor cell proliferation and cancer metastasis in type 2 diabetes[90,91]. Indeed, this forms the basis for ^{18}F-fluorodeoxyglucose-positron emission tomography of cancers, which detects tissues with high rates of glucose uptake. In addition, hyperglycemia itself might promote carcinogenesis by generating oxidative stress[12–18], which is frequently observed to be increased in diabetes, in a

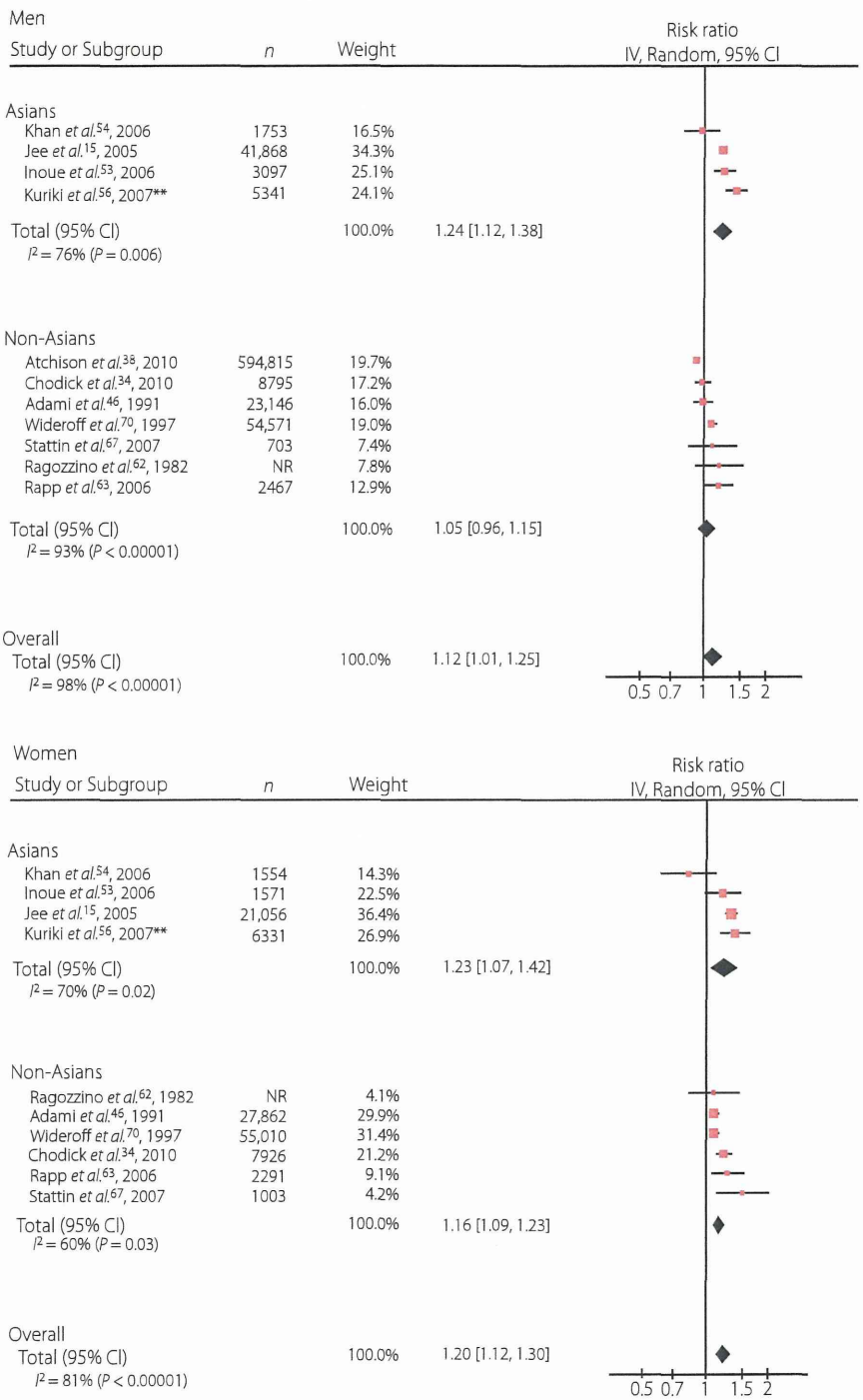

Figure 5 | Adjusted risk ratios (RR) for all-cancer incidence among men and women with diabetes. **Case–control study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI. NR, not reported.

variety of cells. The increase in oxidative stress would cause DNA damage, the initial step in carcinogenesis[17]. Community-based prospective surveys have documented associations between plasma glucose levels and the risk of cancer[12–15,92]. The results of the present study support this hypothesis, because the results showed that the risk of both cancer incidence and mortality is also generally higher among Japanese[19,50,53,56,60] and Korean[15] patients with diabetes, who have been reported

to be insulinopenic[30,93–97]. However, a meta-analysis of large randomized-controlled trials of intensified glycemic control did not support the hypothesis that hyperglycemia is causally linked to increased cancer risk[98,99].

Potential risk factors common to both cancer and diabetes need to be addressed, because it remains to be clarified whether the association between diabetes and the risk of cancer is mainly a result of shared risk factors or whether diabetes itself increases the risk of some types of cancer. Those risk factors include age, sex, race/ethnicity, obesity, physical activity, diet, alcohol and smoking[100]. Clearly, lower levels of adiposity, a healthy diet and regular physical activity are associated with a decreased risk of diabetes and several types of cancer; these factors are generally interrelated and thus it is difficult to assess the contribution of each factor.

It is particularly noteworthy that our meta-analysis showed that the RR was higher for Asian men than for non-Asian men. This finding suggests the presence of other factors that promote carcinogenesis, such as susceptibility to insulin/glucose and genetic/environmental factors. The current findings underscore the crucial need to understand the role of glucose metabolism and insulin resistance in carcinogenesis[30,101].

Alternative explanations for the increased risk of cancer in diabetic patients should be taken into consideration, because the relationship between the aforementioned factors and increased risk might not be causal. First, several comorbidity confounders exist. For example, coexisting obesity and a sedentary lifestyle, which induce hyperinsulinemia, might be the true causes, and diabetes might merely be an innocent bystander. The other possible confounders include age, sex, diet, consumption of alcoholic beverages, smoking, liver cirrhosis and the indication of insulin usage, which were not fully adjusted for in the present study. The second alternative explanation is that diabetic patients might receive medical care more frequently and thus have more opportunities for cancer detection than non-diabetic subjects. The third is that diabetes might develop as a consequence of cancer, as cancers generally cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis-α[102,103]. The fourth is that the studies that were included in the meta-analysis might have left room for confounding by treatment indication: differences between the treatment of cancer according to whether or not they had diabetes might have contributed to the increased mortality of the subjects. Diabetic patients often have other diabetes-related comorbidities that might influence the treatment decisions and prognosis. For example, diabetes might be accompanied by a higher risk of infection and the diagnosis of cancer might result in inappropriate glucose management, and Caucasians have higher cardiovascular mortality, which might lead to an underestimation of the absolute increment in cancer mortality risk among non-Asian diabetic people.

Several limitations of our meta-analysis should be noted. As with any overview, the possibility that relevant research papers were missed and the inability to adjust fully for confounders based on population-based databases must be recognized. It is also important to realize that the populations in the studies were heterogeneous, most likely because of ethnic diversity or study design variation, and that the risks of site-specific cancers might have varied. Therefore, an analysis of cancer at any sites might be overly simplistic and dilute the true associations. The small number of articles that reported studies carried out on Asian subjects that were included might have further restricted the generalizability of the results. Despite these limitations, the results of our meta-analysis should stir health-care providers, policy makers and patients into devising measures to prevent and manage cancer in diabetic patients. Another limitation is that the methods used to ascertain the presence of diabetes in the studies extracted included self-reports, which might have led to diagnostic inaccuracies. In addition, the baseline surveillance in most of the studies was carried out when the diagnostic cut-off value for fasting glucose was higher than the currently accepted value, and the prevalence of diabetes in the control groups most likely increased exponentially during the long follow-up period. Thus, the true prevalence of diabetes and its impact on cancer risk might have been underestimated. Last, the possibility of modification of cancer risk by diabetes medication cannot be completely excluded in descriptive studies, although relevant data are limited at present, and further investigation is required.

In conclusion, the results of our meta-analysis strongly suggest that diabetes is associated with an increased risk of all-cancer incidence and all-cancer mortality worldwide, and that the RR are higher for Asians. In light of the exploding global epidemic of diabetes, particularly in Asia, a modest increase in the risk of cancer will translate into a substantial socioeconomic burden. Our current findings underscore the need for clinical attention and better-designed studies of the complex interactions between diabetes and cancer.

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REFERENCES

1. White MF. The insulin signalling system and the IRS proteins. *Diabetologia* 1997; 40(Suppl 2): S2–S17.
2. Kim YI. Diet, lifestyle, and colorectal cancer: is hyperinsulinemia the missing link? *Nutr Rev* 1998; 56: 275–279.
3. Kaaks R. Nutrition, hormones, and breast cancer: is insulin the missing link? *Cancer Causes Control* 1996; 7: 605–625.
4. Giovannucci E. Insulin and colon cancer. *Cancer Causes Control* 1995; 6: 164–179.
5. Yu H, Berkel H. Insulin-like growth factors and cancer. *J La State Med Soc* 1999; 151: 218–223.

6. Zhang W, Thornton WH, MacDonald RS. Insulin-like growth factor-I and II receptor expression in rat colon mucosa are affected by dietary lipid intake. *J Nutr* 1998; 128: 158–165.
7. Bruning PF, Bonfrer JM, van Noord PA, *et al.* Insulin resistance and breast-cancer risk. *Int J Cancer* 1992; 52: 511–516.
8. Hu FB, Manson JE, Liu S, *et al.* Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. *J Natl Cancer Inst* 1999; 91: 542–547.
9. Silverman DT, Schiffman M, Everhart J, *et al.* Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer* 1999; 80: 1830–1837.
10. Wolf I, Sadetzki S, Catane R, *et al.* Diabetes mellitus and breast cancer. *Lancet Oncol* 2005; 6: 103–111.
11. Le Roith D. Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. *N Engl J Med* 1997; 336: 633–640.
12. Barclay AW, Petocz P, McMillan-Price J, *et al.* Glycemic index, glycemic load, and chronic disease risk – a meta-analysis of observational studies. *Am J Clin Nutr* 2008; 87: 627–637.
13. Gapstur SM, Gann PH, Lowe W, *et al.* Abnormal glucose metabolism and pancreatic cancer mortality. *JAMA* 2000; 283: 2552–2558.
14. Seow A, Yuan JM, Koh WP, *et al.* Diabetes mellitus and risk of colorectal cancer in the Singapore Chinese Health Study. *J Natl Cancer Inst* 2006; 98: 135–138.
15. Jee SH, Ohrr H, Sull JW, *et al.* Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005; 293: 194–202.
16. Stocks T, Rapp K, Bjorge T, *et al.* Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. *PLoS Med* 2009; 6: e1000201.
17. Abe R, Yamagishi S. AGE-RAGE system and carcinogenesis. *Curr Pharm Des* 2008; 14: 940–945.
18. Inoue M, Kurahashi N, Iwasaki M, *et al.* Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II). *Cancer Causes Control* 2009; 20: 741–750.
19. Noto H, Osame K, Sasazuki T, *et al.* 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.
20. Noto H, Tsujimoto T, Sasazuki T, *et al.* Significantly increased risk of cancer in patients with diabetes mellitus. *Endocr Pract* 2011; 17: 616–628.
21. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. *Int J Cancer* 2007; 121: 856–862.
22. Friberg E, Orsini N, Mantzoros CS, *et al.* Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 2007; 50: 1365–1374.
23. Larsson SC, Orsini N, Brismar K, *et al.* Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* 2006; 49: 2819–2823.
24. 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: 369–380.
25. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* 2005; 97: 1679–1687.
26. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, *et al.* Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 2005; 92: 2076–2083.
27. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA* 1995; 273: 1605–1609.
28. Bonovas S, Filioussi K, Tsantes A. Diabetes mellitus and risk of prostate cancer: a meta-analysis. *Diabetologia* 2004; 47: 1071–1078.
29. Kasper JS, Giovannucci E. A meta-analysis of diabetes mellitus and the risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2056–2062.
30. Chan JC, Malik V, Jia W, *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
31. Hotta N, Nakamura J, Iwamoto Y, *et al.* Causes of death in Japanese diabetics based on the results of a survey of 18,385 diabetics during 1991–2000. Report of Committee on Cause of Death in Diabetes Mellitus. *J Jpn Diabetes Soc* 2007; 50: 47–61.
32. Ministry of Health LaWoJ. Patient Survey, 2005.
33. Barone BB, Yeh HC, Snyder CF, *et al.* Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008; 300: 2754–2764.
34. Chodick G, Heymann AD, Rosenmann L, *et al.* Diabetes and risk of incident cancer: a large population-based cohort study in Israel. *Cancer Causes Control* 2010; 21: 879–887.
35. Hemminki K, Li X, Sundquist J, *et al.* Risk of cancer following hospitalization for type 2 diabetes. *Oncologist* 2010; 15: 548–555.
36. Smith NL, Barzilay JI, Kronmal R, *et al.* New-onset diabetes and risk of all-cause and cardiovascular mortality: the Cardiovascular Health Study. *Diabetes Care* 2006; 29: 2012–2017.
37. Tierney EF, Geiss LS, Engelgau MM, *et al.* Population-based estimates of mortality associated with diabetes: use of a death certificate check box in North Dakota. *Am J Public Health* 2001; 91: 84–92.
38. Atchison EA, Gridley G, Carreon JD, *et al.* Risk of cancer in a large cohort of U.S. veterans with diabetes. *Int J Cancer* 2011; 128: 635–643.

39. Zhou XH, Qiao Q, Zethelius B, *et al.* Diabetes, prediabetes and cancer mortality. *Diabetologia* 2010; 53: 1867–1876.
40. Driver JA, Yung R, Gaziano JM, *et al.* Chronic disease in men with newly diagnosed cancer: a nested case–control study. *Am J Epidemiol* 2010; 172: 299–308.
41. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61: 344–349.
42. de Marco R, Locatelli F, Zoppini G, *et al.* Cause-specific mortality in type 2 diabetes. The Verona Diabetes Study. *Diabetes Care* 1999; 22: 756–761.
43. Nerlich AG, Hagedorn HG, Boheim M, *et al.* Patients with diabetes-induced microangiopathy show a reduced frequency of carcinomas. *In Vivo* 1998; 12: 667–670.
44. Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–2012.
45. Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009; 151: W65–W94.
46. Adami HO, McLaughlin J, Ekbom A, *et al.* Cancer risk in patients with diabetes mellitus. *Cancer Causes Control* 1991; 2: 307–314.
47. Adlerberth AM, Rosengren A, Wilhelmsen L. Diabetes and long-term risk of mortality from coronary and other causes in middle-aged Swedish men. A general population study. *Diabetes Care* 1998; 21: 539–545.
48. Balkau B, Eschwege E, Ducimetiere P, *et al.* The high risk of death by alcohol related diseases in subjects diagnosed as diabetic and impaired glucose tolerant: the Paris Prospective Study after 15 years of follow-up. *J Clin Epidemiol* 1991; 44: 465–474.
49. Bruno G, Merletti F, Boffetta P, *et al.* Impact of glycaemic control, hypertension and insulin treatment on general and cause-specific mortality: an Italian population-based cohort of type II (non-insulin-dependent) diabetes mellitus. *Diabetologia* 1999; 42: 297–301.
50. Fujino Y, Mizoue T, Tokui N, *et al.* Prospective study of diabetes mellitus and liver cancer in Japan. *Diabetes Metab Res Rev* 2001; 17: 374–379.
51. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971–1993. *Diabetes Care* 1998; 21: 1138–1145.
52. Hjalgrim H, Frisch M, Ekbom A, *et al.* Cancer and diabetes – a follow-up study of two population-based cohorts of diabetic patients. *J Intern Med* 1997; 241: 471–475.
53. Inoue M, Iwasaki M, Otani T, *et al.* Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med* 2006; 166: 1871–1877.
54. Khan M, Mori M, Fujino Y, *et al.* Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev* 2006; 7: 253–259.
55. Koskinen SV, Reunanen AR, Martelin TP, *et al.* Mortality in a large population-based cohort of patients with drug-treated diabetes mellitus. *Am J Public Health* 1998; 88: 765–770.
56. Kuriki K, Hirose K, Tajima K. Diabetes and cancer risk for all and specific sites among Japanese men and women. *Eur J Cancer Prev* 2007; 16: 83–89.
57. Landman GW, Kleefstra N, van Hateren KJ, *et al.* Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. *Diabetes Care* 2010; 33: 322–326.
58. Levine W, Dyer AR, Shekelle RB, *et al.* Post-load plasma glucose and cancer mortality in middle-aged men and women. 12-year follow-up findings of the Chicago Heart Association Detection Project in Industry. *Am J Epidemiol* 1990; 131: 254–262.
59. Moss SE, Klein R, Klein BE. Cause-specific mortality in a population-based study of diabetes. *Am J Public Health* 1991; 81: 1158–1162.
60. Oba S, Nagata C, Nakamura K, *et al.* Self-reported diabetes mellitus and risk of mortality from all causes, cardiovascular disease, and cancer in Takayama: a population-based prospective cohort study in Japan. *J Epidemiol* 2008; 18: 197–203.
61. Ogunleye AA, Ogston SA, Morris AD, *et al.* A cohort study of the risk of cancer associated with type 2 diabetes. *Br J Cancer* 2009; 101: 1199–1201.
62. Ragozzino M, Melton LJ 3rd, Chu CP, *et al.* Subsequent cancer risk in the incidence cohort of Rochester, Minnesota, residents with diabetes mellitus. *J Chronic Dis* 1982; 35: 13–19.
63. Rapp K, Schroeder J, Klenk J, *et al.* Fasting blood glucose and cancer risk in a cohort of more than 140,000 adults in Austria. *Diabetologia* 2006; 49: 945–952.
64. Saydah SH, Loria CM, Eberhardt MS, *et al.* Abnormal glucose tolerance and the risk of cancer death in the United States. *Am J Epidemiol* 2003; 157: 1092–1100.
65. Sievers ML, Nelson RG, Bennett PH. Sequential trends in overall and cause-specific mortality in diabetic and non-diabetic Pima Indians. *Diabetes Care* 1996; 19: 107–111.
66. Smith GD, Egger M, Shipley MJ, *et al.* Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. *Am J Epidemiol* 1992; 136: 1110–1114.
67. Stattin P, Bjor O, Ferrari P, *et al.* Prospective study of hyperglycemia and cancer risk. *Diabetes Care* 2007; 30: 561–567.
68. Swerdlow AJ, Laing SP, Qiao Z, *et al.* Cancer incidence and mortality in patients with insulin-treated diabetes: a UK cohort study. *Br J Cancer* 2005; 92: 2070–2075.
69. Verlato G, Zoppini G, Bonora E, *et al.* Mortality from site-specific malignancies in type 2 diabetic patients from Verona. *Diabetes Care* 2003; 26: 1047–1051.

70. Wideroff L, Gridley G, Mellemkjaer L, *et al.* Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst* 1997; 89: 1360–1365.
71. Wong JS, Pearson DW, Murchison LE, *et al.* Mortality in diabetes mellitus: experience of a geographically defined population. *Diabet Med* 1991; 8: 135–139.
72. Gallagher EJ, Leroith D. Minireview: IGF, insulin, and cancer. *Endocrinology* 2011; 152: 2546–2551.
73. Vigneri P, Frasca F, Sciacca L, *et al.* Diabetes and cancer. *Endocr Relat Cancer* 2009; 16: 1103–1123.
74. Fisher WE, Boros LG, O'Dorisio TM, *et al.* GI hormonal changes in diabetes influence pancreatic cancer growth. *J Surg Res* 1995; 58: 754–758.
75. Bell RH Jr, McCullough PJ, Pour PM. Influence of diabetes on susceptibility to experimental pancreatic cancer. *Am J Surg* 1988; 155: 159–164.
76. 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.
77. 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.
78. Zendehdel K, Nyren O, Ostenson CG, *et al.* Cancer incidence in patients with type 1 diabetes mellitus: a population-based cohort study in Sweden. *J Natl Cancer Inst* 2003; 95: 1797–1800.
79. Shu X, Ji J, Li X, *et al.* Cancer risk among patients hospitalized for Type 1 diabetes mellitus: a population-based cohort study in Sweden. *Diabet Med* 2010; 27: 791–797.
80. 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.
81. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Engl J Med* 2000; 342: 1907–1909.
82. McFarland MS, Cripps R. Diabetes mellitus and increased risk of cancer: focus on metformin and the insulin analogs. *Pharmacotherapy* 2010; 30: 1159–1178.
83. 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.
84. Dhindsa S, Prabhakar S, Sethi M, *et al.* Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab* 2004; 89: 5462–5468.
85. Ding EL, Song Y, Malik VS, *et al.* Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2006; 295: 1288–1299.
86. Tseng CH. Prostate cancer mortality in Taiwanese men: increasing age-standardized trend in general population and increased risk in diabetic men. *Ann Med* 2011; 43: 142–150.
87. Tseng CH. Diabetes and risk of prostate cancer: a study using the National Health Insurance. *Diabetes Care* 2011; 34: 616–621.
88. Mishina T, Watanabe H, Araki H, *et al.* Epidemiological study of prostatic cancer by matched-pair analysis. *Prostate* 1985; 6: 423–436.
89. Li Q, Kuriyama S, Kakizaki M, *et al.* History of diabetes mellitus and the risk of prostate cancer: the Ohsaki Cohort Study. *Cancer Causes Control* 2010; 21: 1025–1032.
90. 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.
91. 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.
92. Seshasai SR, Kaptoge S, Thompson A, *et al.* Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011; 364: 829–841.
93. 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.
94. 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.
95. 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.
96. Boyko EJ, Fujimoto WY, Leonetti DL, *et al.* Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care* 2000; 23: 465–471.
97. 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.
98. Stefansdottir G, Zoungas S, Chalmers J, *et al.* Intensive glucose control and risk of cancer in patients with type 2 diabetes. *Diabetologia* 2011; 54: 1608–1614.
99. Johnson JA, Bowker SL. Intensive glycaemic control and cancer risk in type 2 diabetes: a meta-analysis of major trials. *Diabetologia* 2011; 54: 25–31.
100. Giovannucci E, Harlan DM, Archer MC, *et al.* Diabetes and cancer: a consensus report. *Diabetes Care* 2010; 33: 1674–1685.
101. Karin M, Lawrence T, Nizet V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. *Cell* 2006; 124: 823–835.
102. McCall JL, Tuckey JA, Parry BR. Serum tumour necrosis factor alpha and insulin resistance in gastrointestinal cancer. *Br J Surg* 1992; 79: 1361–1363.
103. 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.

発表論文

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Cancer Risk in Diabetic Patients Treated with Metformin: A Systematic Review and Meta-analysis

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Abstract

Background: A growing body of evidence has suggested that metformin potentially reduces the risk of cancer. Our objective was to enhance the precision of estimates of the effect of metformin on the risk of any-site and site-specific cancers in patients with diabetes.

Methods/Principal Findings: We performed a search of MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and ClinicalTrials.gov for pertinent articles published as of October 12, 2011, and included them in a systematic review and meta-analysis. We calculated pooled risk ratios (RRs) for overall cancer mortality and cancer incidence. Of the 21,195 diabetic patients reported in 6 studies (4 cohort studies, 2 RCTs), 991 (4.5%) cases of death from cancer were reported. A total of 11,117 (5.3%) cases of incident cancer at any site were reported among 210,892 patients in 10 studies (2 RCTs, 6 cohort studies, 2 case-control studies). The risks of cancer among metformin users were significantly lower than those among non-metformin users: the pooled RRs (95% confidence interval) were 0.66 (0.49–0.88) for cancer mortality, 0.67 (0.53–0.85) for all-cancer incidence, 0.68 (0.53–0.88) for colorectal cancer (n = 6), 0.20 (0.07–0.59) for hepatocellular cancer (n = 4), 0.67 (0.45–0.99) for lung cancer (n = 3).

Conclusion/Significance: The use of metformin in diabetic patients was associated with significantly lower risks of cancer mortality and incidence. However, this analysis is mainly based on observational studies and our findings underscore the more need for long-term RCTs to confirm this potential benefit for individuals with diabetes.

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Introduction

Hyperinsulinemia and hyperglycemia are thought to promote carcinogenesis in patients with diabetes mellitus. Several meta-analyses have demonstrated that diabetes is associated with increased risks of site-specific cancers of the breast (1.2) [1], endometrium (2.1) [2], bladder (1.2) [3], liver (2.5) [4], colorectum (1.3) [5], and pancreas (1.8–2.1) [6,7], and also a decreased risk of prostate cancer (0.8–0.9) [8,9]. The evidence for non-Hodgkin's lymphoma remains inconclusive [10,11]. Our previous meta-analyses showed that patients with diabetes have an inscreased risk of total cancer (relative risk, 1.1–1.7) [12–14], whereas more recent studies did not [15,16]. Metformin is an insulin sensitizer that is the drug of first choice in the management of type 2 diabetes [17], given its safety profile and lower cost. Metformin reportedly has a potential anti-cancer effect by activating adenosine 5′-mono-phosphate-activated protein kinase (AMPK) in addition to alleviating hyperinsulinemia and hyperglycemia. Although other mechanisms for this risk reduction have been hypothesized, none have been elucidated entirely. Previous meta-analyses have suggested that metformin is associated with a reduced risk of cancer in diabetic subjects [18,19]. However, those analyses were based solely on a few observational studies and additional reports have been published recently.

In light of the worldwide diabetes epidemic and the higher mortalities in cancer patients with diabetes [20,21], explorations of effective cancer prevention are of clinical importance for the targeted management of diabetes in daily practice. Moreover, they are crucial in the areas of public health, since a modest increase in the risk of cancer translates into a substantial social burden. These circumstances prompted us to investigate, with greater precision, the preventive effect of metformin on cancer mortality and incidence by scrutinizing pertinent original reports including randomized controlled trials (RCTs), and combining their data in an attempt to obtain meaningful clues for the prevention of cancer in patients with diabetes [13].

Methods

Search

Searches of MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and ClinicalTrials.gov from their inception until October 12, 2011, were performed. Studies evaluating the risks of cancer mortality or incidence among diabetic patients

taking metformin, compared with those not taking metformin, were identified using a combination of the following medical subject heading terms: 'diabetes', 'metformin', 'cancer' or 'neoplasms', and 'risk' or 'risk factors'. The reference lists of the pertinent articles were also inspected.

Selection/Study Characteristics

We assessed all the identified RCTs, cohort studies, case-control studies, and cross-sectional studies on the risk of cancer based on original data analyses to determine their eligibility for inclusion in a qualitative analysis. The inclusion criteria in the meta-analysis are as follows: published full-text report in English-language, RCTs with parallel-design of metformin as a treatment of type 2 diabetes at least one year's follow-up period, observational studies of any duration in patients with type 2 diabetes, reporting relative risks, i.e. hazard ratios (HRs), RRs, or odds ratios, adjusted for possible confounders with confidence intervals (CIs). The comparators were defined as any treatment not including metformin.

Validity assessment

To ascertain the validity of the eligible studies, the quality of each report was appraised in reference to the CONSORT statement [22] and the STROBE statement [23].

Data abstraction

We reviewed each full-text report to determine its eligibility and extracted and tabulated all the relevant data independently. The extracted data included the characteristics of the subjects (including age, sex, and other treatment), study design, published year, follow-up period, and the methods used for ascertaining the diagnosis of cancer. Study authors were contacted as needed to obtain detailed data. Any disagreement was resolved by a consensus among the investigators.

Quantitative data synthesis

If more than one study was published for the same cohort, the report containing the most comprehensive information on the population was included to avoid overlapping populations. The reports were summarized both qualitatively and quantitatively. Three articles that did not specify the case numbers were not included in the calculation of the mortality and incidence. If the metformin comparator included more than one treatment, the oral monotherapy groups were included in the analysis because these groups were deemed to be at an equivalent stage of diabetes. If an article provided the relative risks for all cancer and site-specific cancers, the all cancer data were included in the primary qualitative and quantitative analyses and the site-specific data were used in the secondary analyses performed according to cancer site. The risks for site-specific cancers were appraised if three or more qualified reports were identified for a given cancer site. Response to metformin exposure was evaluated by using linear-regression analysis.

In the meta-analysis, each adjusted relative risk was combined and the pooled RRs with the 95% CI was calculated using the random-effects model with inverse-variance weighting. Heterogeneity among the studies was evaluated using I^2 statistics. The possibility of a publication bias, which can result from the non-publication of small studies with negative findings, was assessed visually using a funnel plot for asymmetry. RevMan (version 5.1) was used for these calculations. A sensitivity analysis was performed by separating the RCTs and the observational cohort / case-control studies and the equality of RRs between RCTs and observational studies were assessed by using z-statistic tests. All the procedures were in accordance with the guidelines for the Quality of Reporting of Meta-analyses [24], the meta-analysis of observational studies in epidemiology [25] and the PRISMA statement [26].

Results

Search Results

A total of 412 articles were identified during our search; of these, 32 were assessed with respect to their eligibility for inclusion in our review, which was aimed at determining the influence of metformin on cancer mortality and incidence in patients with diabetes (**Fig. 1**). Four articles [27–30] were excluded from the systematic review because of population overlapping and four other reports were excluded because they investigated the overall survival rate [31,32], cancer incidence exclusively in patients with hepatitis C [33], and biochemical recurrence [34]. Out of these 32 articles, a total of 24 (11 observational cohort studies [35–45], 3 randomized controlled trials [46–49], and 10 case-control studies [29,50–58]) were included in the systematic review and meta-analysis. The UK Prospective Diabetes Study (UKPDS) 34 [49] involved two independent investigational trials (metformin vs. conventional therapy and sulfonylurea vs. sulfonylurea plus metformin), and these trials were included in the meta-analysis as two separate data.

Table S1 shows the characteristics of each included study according to the study design. The 24 selected articles included in the systematic review were moderately heterogeneous in terms of population demographics, study design, and the assessment of confounding factors. The diabetes sample size in these studies ranged from 361 to 998,947 patients. Of the 21,195 diabetic patients in 6 studies, 991 (4.5%) cases of cancer death were reported. A total of 11,117 (5.3%) cases of incident cancer at any site were reported among 210,892 patients in 10 studies. Major confounding factors such as cigarette smoking, alcohol intake, and hyperglycemia were not reported in several studies.

The risk of bias and the adjustment factors among the studies are summarized in **Table S2**. Diabetes was diagnosed using blood tests (n = 8), prescription databases (n = 6), medical records (n = 4), self-reports (n = 3), and health insurance database (n = 4). All the diagnoses of cancer were confirmed using valid records or registries. All the studies, except for the RCTs, adjusted the estimates for potential confounding factors. The analysis of dose-response was performed in 3 studies [38–40]. Some studies excluded the data for metformin exposure less than 1 year [50,52] or 2 years [58] to minimize bias. The effect on the total cancer risk over the follow-up period was inspected in 3 studies [40,55,58]. Direct comparison of the effect between metformin and other specific medications were reported in 2 RCTs [46–48].

Qualitative Summary

The majority of the studies included were methodologically fair in quality. Among 10 case-control studies, six were nested ones [50–52,55,56,58]. All the four cohort studies [35,38,40,41] on cancer mortality revealed a significant decrease (range, 23%–75%), and the two RCTs showed no significant effect of metformin [49]. There was no study that directly compared the risk associated with metformin vs other medications or analyzed the correlation between the follow-up length and the effect of metformin on cancer mortality. The overall correlation of the follow-up period with the mortality was nonsignificant ($r = -0.04$, $p = 0.9$). One study revealed that the HR (95% CI) for cancer mortality with every increase of 1 g metformin was 0.58 (0.36–0.93) [38].

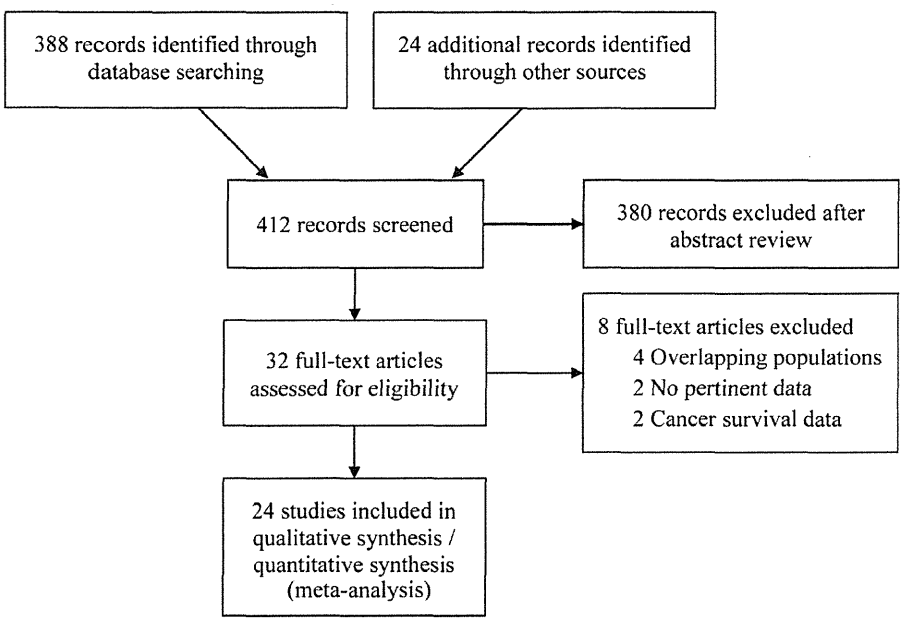

Figure 1. Flow diagram of study selection.
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Five studies (3 cohort studies [36,39,40] and 2 case-control studies [55,56]) reported a significant decrease (range, 26%–88%), the two RCTs showed no significant effect of association [46–48] and none demonstrated a statistically significant increase in the risk of all-cancer incidence among metformin users. The cancer risk for metformin users was not significantly different from that for rosiglitazone or sulfonylurea users in RCTs [46–48]. One cohort study showed a trend for metformin users to have a higher risk of cancer in the first 2 years of follow-up. The beneficial effect of metformin on the risk of total cancer incidence was exposure-dependent in 2 case-control studies [55,56]. The overall correlation of the follow-up period with the incidence was nonsignificant ($r = -0.32$, $p = 0.4$). One study reported that its effect on cancer incidence was dose-dependent (p for trend <0.05) [39] suggesting that the minimal effective dose can be 500 mg /day, while the other showed no significant differences among doses [40].

Among the studies evaluating the risks of site-specific incident cancers in patients with diabetes who were taking metformin, more than two studies (including subgroup analyses) recognized significantly reduced risks for cancers of the pancreas [36,39,54], colorectum [36,39,40], and liver [29,39,53], and none showed a significantly increased risk of a site-specific cancer. All these risk decrements were moderate (RR range, 0.06–0.60). Of note, no significant increases or decreases in the risk of cancers of the breast, prostate or stomach were reported, except for a significant decrease in the risk of prostate cancer in one report [42] and breast cancer in another [52]. The number of studies examining other cancer sites was two or fewer, and these studies were not reviewed in the present analysis.

Quantitative Summary (Meta-analysis)

Based on the quality appraisal in our systematic review, a total of 24 articles that provided sufficient information were included in the meta-analysis (**Fig. 1**). **Fig. 2** illustrates the significantly decreased risks of all-cancer mortality and incidence in metformin-users, compared with non-metformin users. In a sensitivity analysis, the pooled estimate (95% CI) for all-cancer mortality among the observational cohort studies was 0.62 (0.46–0.82), $I^2 = 56\%$, $p = 0.08$ and the estimate among the RCTs was 1.22 (0.36–4.11), $I^2 = 60\%$, $p = 0.12$. The difference in the RRs between the observational studies and the RCTs was not statistically significant ($p = 0.35$). The pooled RR (95% CI) for all-cancer incidence among the observational cohort studies was 0.66 (0.49–0.88), $I^2 = 96\%$, $p<0.00001$, the pooled RR among the case-control studies was 0.38 (0.23–0.61), $I^2 = 3\%$, $p = 0.31$ and the estimate among the RCTs was 1.03 (0.82–1.31), $I^2 = 30\%$, $p = 0.23$. The difference in the RRs between the observational studies and the RCTs was statistically significant ($p = 0.019$). As summarized in **Fig. 3 and Fig. 4**, the incident cancer risks were also significantly decreased for cancers of the colorectum, liver and lung. The RRs of prostate cancer, breast cancer, pancreatic cancer and gastric cancer were not statistically significant. Significant heterogeneity was observed in the majority of these analyses. No apparent publication bias was apparent, as assessed using a funnel plot (**Fig. S1**).

Discussion

Our systematic review and meta-analyses of worldwide reports demonstrated that metformin is associated with a substantially lower risk of all-cancer mortality and incidence, compared with other treatments for diabetes. They also showed that metformin significantly reduced the risks of cancers of the colorectum, liver and lung. These findings support the hypothesis that metformin potentially has an anti-cancer effect. In light of the fact that cancer is the second and diabetes the twelfth leading cause of death worldwide [59] and that the number of people with diabetes is rapidly increasing, our findings have substantial clinical and public implications on a global scale and point to the need for the further investigation of the anti-cancer mechanism of metformin and for long-term RCTs to confirm this clinical benefit.

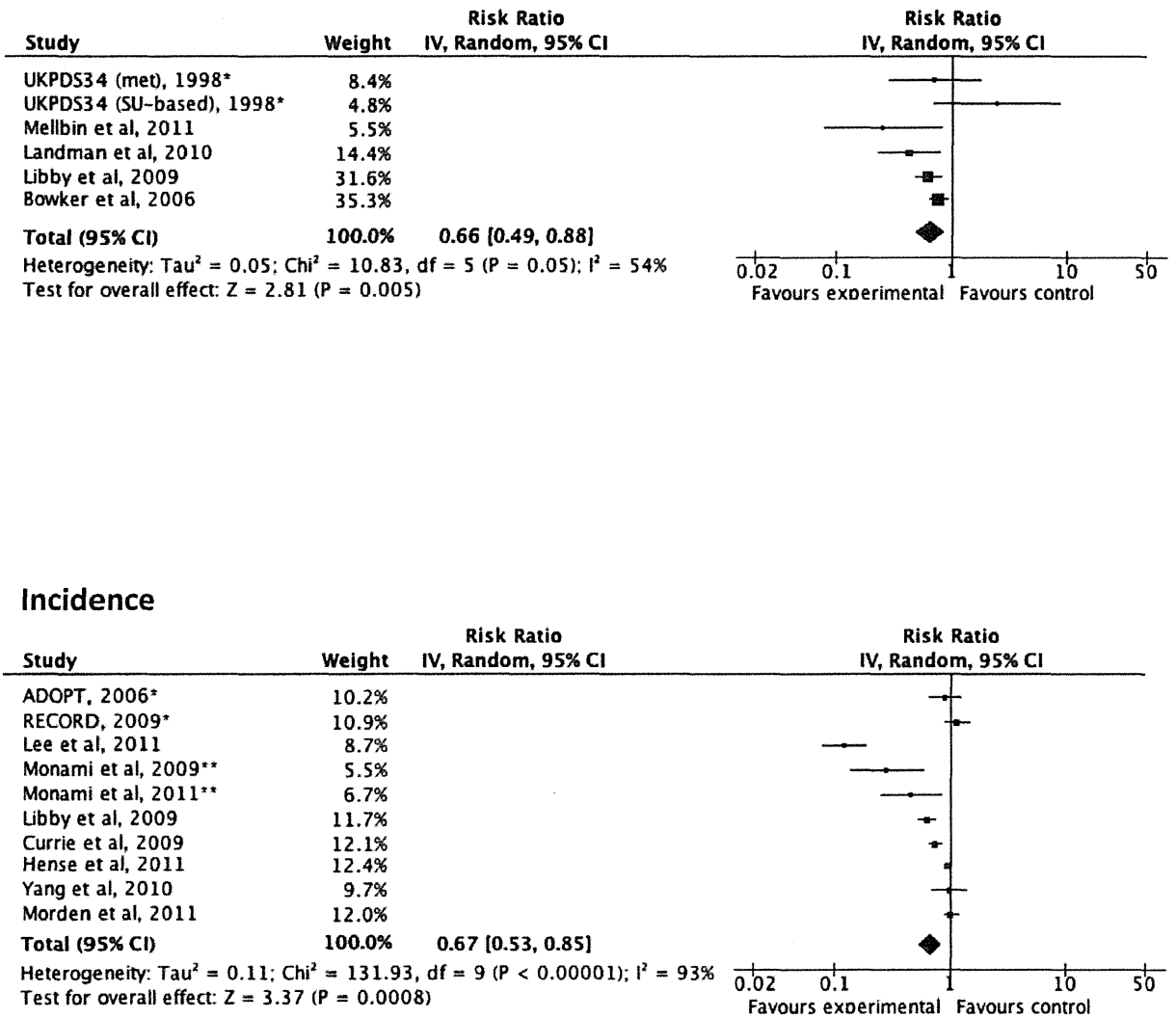

Figure 2. Adjusted risk ratios for all-cancer mortality and incidence among subjects with diabetes taking metformin. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. *, randomized controlled trials; **, case-control studies; IV, inverse-variance.
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The strength of our present study is that the analysis was mainly based on large population-based data originating from multiple nations and was performed with a high level of precision. Compared with recently published studies [18,19], our updated study is novel in that data from RCTs were incorporated and cancer risks for substantially more sites were analyzed. Although the significantly decreased pooled RRs for all-cancer mortality / incidence and cancer at most sites were robust, the results of the component studies were statistically heterogeneous. Of note, all the individual and pooled results of the RCTs were neutral. It seems that each follow-up period in these RCTs is similar to many others in the observational studies and they have power enough to detect the differences in cancer risk. In the analysis of cancer mortality, there was no significant difference in RR between the RCTs and the observational studies. For cancer incidence, on the other hand, the overall RR was significantly reduced but the difference was statistically significant. This discordance may imply that the apparent anti-cancer effect of metformin in observational studies was affected by confounding biases and thus more RCTs are awaited to clarify the effect of metformin on cancer incidence. The large I^2 values indicated that the range of the plausible risk estimates was wide but no evidence in our analysis suggested that metformin may increase the risk of cancer. These findings may reflect the different mechanisms of cancer prevention at different sites and / or different epidemiological characteristics among the diverse populations included in our study.

Evidence has been accumulating to suggest that diabetic patients have a higher risk of cancer than non-diabetic people [12,13]. While the mechanisms are yet to be investigated, insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis, as insulin may have a possible mitogenic effect via its binding to the insulin-like growth factor-1 receptor

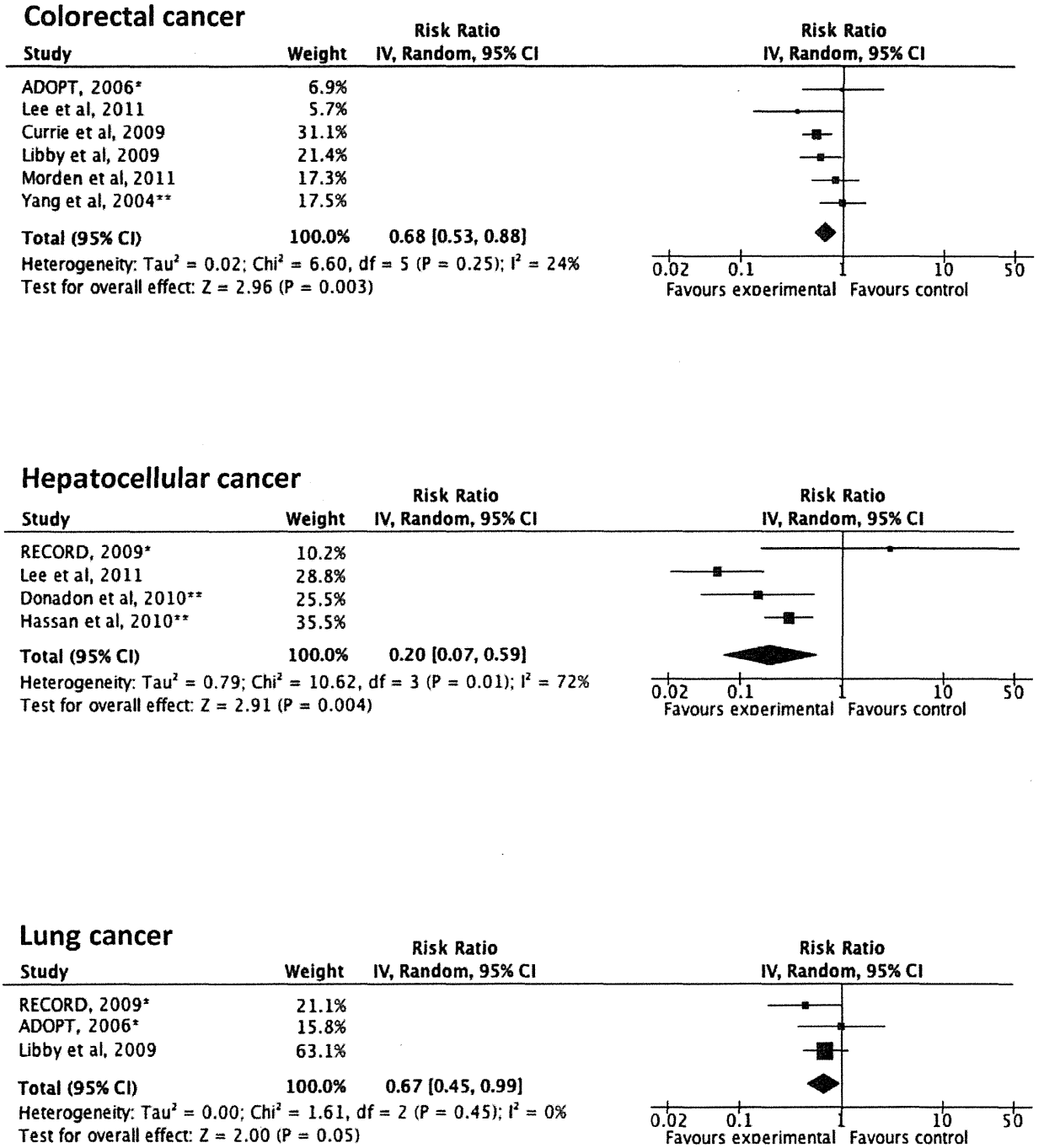

Figure 3. Adjusted risk ratios for site-specific cancer incidence among subjects with diabetes taking metformin. Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. *, randomized controlled trials; **, case-control studies; IV, inverse-variance.
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[60–70]. In addition, hyperglycemia itself may promote carcinogenesis directly [71,72] or indirectly by increasing oxidative stress [73–79]. However, these speculations are derived from retrospective observational studies and may not necessarily demonstrate causality because of possible biases and confounders, such as coexisting obesity and age [15,80,81]. In fact, more recent studies demonstrated no or minimal increments in cancer risk [15,16] and the data from insulin-treated patients are inconclusive [82]. Of interest, diabetes reportedly protects against the development of prostate cancer [8,9], since it is testosterone-dependent and testosterone deficiency is common among men with diabetes secondary to low levels of sex hormone-binding globulin (SHBG)