発表論文

1) **Noto H, Tsujimoto T, Sasazuki T, Noda M: Significantly increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis.**
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Review Article

SIGNIFICANTLY INCREASED RISK OF CANCER IN PATIENTS WITH DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Hiroshi Noto, MD, PhD, FACP[1]; Tetsuro Tsujimoto, MD[1]; Takehiko Sasazuki, MD, PhD[2,3]; Mitsuhiko Noda, MD, PhD[1]

ABSTRACT

Objective: To conduct a review and meta-analysis of the effect of diabetes mellitus on the incidence of and mortality attributable to cancer at any anatomic site.

Methods: We performed a search of MEDLINE and the Cochrane Library for pertinent articles published from the origin of these databases to July 5, 2010, and included them in a qualitative review and meta-analysis of the risk of all-cancer incidence and mortality in patients with diabetes.

Results: Among patients with diabetes (n = 257,222) in 12 cohort studies, the cancer incidence was about 7%. The cancer mortality was approximately 3% among patients with diabetes (n = 152,091) in 19 cohort studies. The pooled adjusted risk ratio (RR) of all-cancer incidence was significantly elevated—RR, 1.10 (95% confidence interval [CI], 1.04 to 1.17) overall; RR, 1.14 (CI, 1.06 to 1.23) for men; and RR, 1.18 (CI, 1.08 to 1.28) for women. Diabetes was also associated with an increased RR of mortality across all cancer types—RR, 1.16 (CI, 1.03 to 1.30) overall; RR, 1.10 (CI, 0.98 to 1.23) for men; and RR, 1.24 (CI, 1.11 to 1.40) for women.

Conclusion: Cancer prevention and early detection by appropriate screening methods in patients with diabetes should be important components of clinical management and investigation, inasmuch as the exponentially increasing prevalence of diabetes will translate into substantial clinical and public health consequences on a global scale. **(Endocr Pract. 2011;17:616-628)**

Abbreviations:
CIs = confidence intervals; **HRs** = hazard ratios; **RR** = risk ratio

INTRODUCTION

Considerable cumulative evidence suggests that diabetes is associated with an increased risk of cancer. The mechanisms are yet to be investigated, but insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis because insulin might have a mitogenic effect by binding the insulinlike growth factor-I receptor (1-11). In addition, hyperglycemia itself may promote carcinogenesis by increasing oxidative stress (12-18).

Meta-analyses have demonstrated that diabetes mellitus is associated with an increased risk of site-specific cancers of the breast (19), endometrium (20), bladder (21), liver (22), colorectum (23), and pancreas (24,25) and also a decreased risk of prostate cancer (26,27). The evidence for kidney cancer and non-Hodgkin lymphoma is still inconclusive. Furthermore, patients with cancer and preexisting diabetes have higher short-term (28) and long-term (29) mortalities. The association of diabetes with all-cancer incidence and mortality, however, remains uncertain.

In light of the current worldwide diabetes epidemic and the higher mortalities in patients with cancer and diabetes (28,29), elucidating the association between these diseases in general populations is crucial for making timely, rational, and informed decisions, not only in the areas of public

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From the [1]Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, Tokyo, Japan, [2]National Center for Global Health and Medicine, Tokyo, Japan, and [3]Institute for Advanced Study, Kyushu University, Tokyo, Japan.
Address correspondence to Dr. Mitsuhiko Noda, Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, Japan 1-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan. E-mail: mnoda@hosp.ncgm.go.jp.
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health and socioeconomy but also for the prevention and targeted management of diabetes in daily clinical practice.

These circumstances prompted us to explore, with more precision, the effect of diabetes on the all-cancer incidence and mortality, by undertaking a scrutiny of the pertinent original reports and combining their data, in an attempt to obtain meaningful clues for the prevention and management of cancer.

MATERIALS AND METHODS

Data Sources and Searches

Searches of MEDLINE and the Cochrane Library from their inception until July 5, 2010, were performed, and articles investigating the cancer incidence and mortality in patients with and without diabetes were extracted. Relevant reports were identified by using a combination of the following medical subject heading terms: "diabetes," "cancer" or "neoplasms," and "risk" or "risk factors." The reference lists of the pertinent articles were also inspected.

We included observational studies evaluating type 2 diabetes, but not those focusing on impaired glucose tolerance, impaired fasting glucose, or solely type 1 diabetes. Cohort, case-control, and cross-sectional studies to evaluate the risk of cancer on the basis of original data analyses were assessed to determine their eligibility for inclusion in a qualitative analysis. Among these investigations, cohort studies reporting hazard ratios (HRs) adjusted for possible confounders and with confidence intervals (CIs) were eligible for inclusion in the meta-analysis. For further elucidation of the magnitude of the risk of all-cancer incidence and mortality in patients with diabetes, subgroup analyses for each sex were performed.

Data Extraction and Quality Assessment

We reviewed each full-text report to determine its eligibility, and we extracted and tabulated all the relevant data independently. The extracted data included the characteristics of the patients (including age, sex, and comorbidities), study design, study years, follow-up period, and methods used for ascertaining the presence or absence of diabetes and cancer. Any disagreement was resolved by consensus among the investigators. For ascertainment of the validity of the eligible studies, the quality of each report was appraised in reference to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (30).

Data Synthesis and Statistical Analysis

If more than one study was published for the same cohort, the report with the information on the most comprehensive population was included, in an effort to avoid overlapping patient populations. This process necessitated exclusion of 2 articles from the systematic review (16,31). One other investigation among patients with diabetes and autopsy-proven nephropathy (32) was also excluded because cohorts with this condition are rare and the generalizability of the study was deemed to be poor.

The reports were summarized both qualitatively and quantitatively. Those studies that did not specify the case numbers were not included in the calculation of the incidence and mortality. In the meta-analysis, the HRs in cohort studies were combined, and the pooled risk ratio (RR) adjusted for possible confounders with 95% CI was calculated by using the random-effects model with inverse-variance weighting. The HR for the combination of men and women was estimated before pooling, if not provided in the original study. The second decimal place of the confidence interval values was estimated as needed. Heterogeneity among studies was evaluated by using I^2 statistics. The possibility of a publication bias, which can result from the nonpublication of small studies with negative findings, was assessed visually with use of a funnel plot for asymmetry. Subgroup analysis stratified by sex was also performed. Review Manager (RevMan) (version 5; the Cochrane Information Management Systems, Baltimore, Maryland) was used for all the calculations. All the procedures were in accordance with the guidelines for the Meta-analysis of Observational Studies in Epidemiology (33) and the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) statement (34).

RESULTS

Search Results

During our search, 1,314 citations were identified; after review of the material, 41 articles were assessed relative to their eligibility for inclusion in our report aimed at determining the influence of diabetes on all-cancer incidence and mortality (Fig. 1). Of these 41 articles, 32 (28 cohort studies, 3 cross-sectional studies, and 1 case-control study) were included in the systematic review and meta-analysis. More than half of the 9 excluded studies at this stage did not provide any pertinent information. Among the 28 cohort studies, 2 reports were excluded from the meta-analysis because the CIs were not provided (35,36).

In Tables 1 (15,36-47) and 2 (15,35,41,48-65) are shown the characteristics of each included study stratified by study design and the year of publication of the study. The 32 selected articles included in the systematic review were moderately heterogeneous in terms of the population demographics and assessment of the confounding factors. The diabetes sample size in these studies ranged from 224 to 109,581. About 7% of the patients with diabetes (total n = 257,222) in the 12 cohort studies developed cancer (Table 1), and approximately 3% of the patients with diabetes (total n = 152,091) in the 19 cohort studies died of cancer during the follow-up period (Table 2).

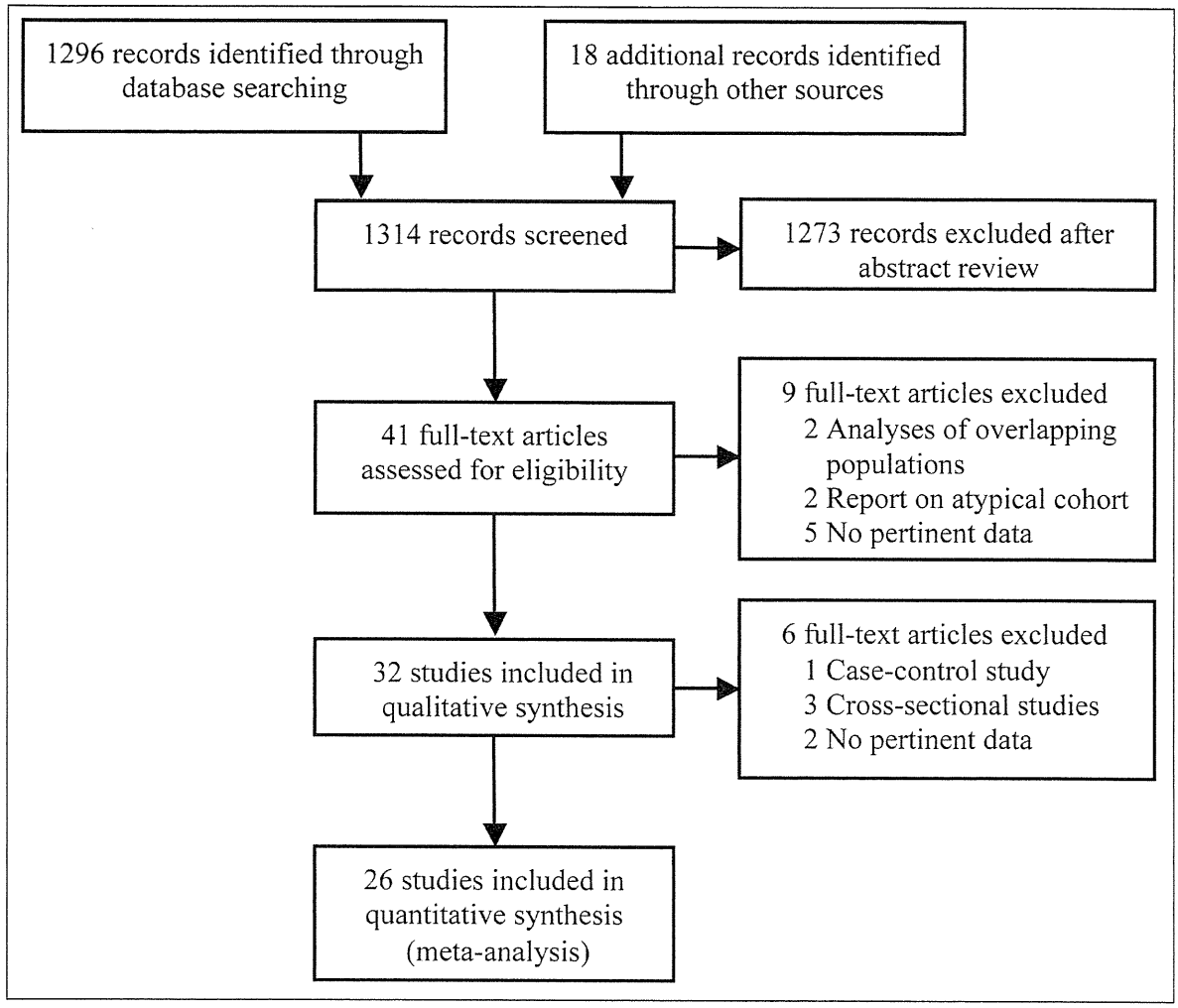

Fig. 1. Summary of the study selection.

The risk of bias among the studies is summarized in Tables 3 and 4. Among the 12 cohort studies and 1 case-control study referring to the cancer incidence, diabetes was diagnosed by using self-reports (n = 4) and prescription databases (n = 2), and 4 satisfied the current diagnostic criteria. All the diagnoses of cancer were confirmed by valid records or registries. Two published reports did not adjust the estimates for potential confounding factors, and 6 studies calculated the standardized incidence ratios. Among the 19 cohort studies and 3 cross-sectional studies on cancer mortality, diabetes was diagnosed by using self-reports (n = 9) and prescription databases (n = 4), and none satisfied the current diagnostic criteria. The diagnoses of cancer in all studies were confirmed by valid methods, except for one case ascertainment by family report. One report did not adjust the estimate for potential confounders, and 11 studies estimated the RR as the standardized mortality ratios.

Qualitative Summary

Most of the studies included were methodologically fair in quality (Tables 3 and 4). A few studies reported a significant decrease in the all-cancer mortality [1 cohort study (52) in men, none in women, and 1 cohort study (52) and 1 cross-sectional study (64) in men and women combined] and none reported a decrease in the all-cancer incidence among patients with diabetes. In contrast, several articles reported a statistically significant elevation in the risk of cancer incidence associated with diabetes [4 cohort studies (15,40,43,44) and 1 case-control study (47) in men, 5 cohort studies (15,38,40,44,45) and 1 case-control study (47) in women, and 1 case-control study (47) overall] and its mortality [3 cohort studies (15,50,57) and 2 cross-sectional studies (48,65) in men, 4 cohort studies (15,57,60,62) and 2 cross-sectional studies (48,65) in women, and 3 cohort studies (59,60,63) and 1 cross-sectional study (65) overall]. The significant increases in

Table 1
Characteristics of the Studies Included in the Systematic Review and Meta-analysis of the Cancer Incidence Risk in Patients With Diabetes[a]

Source	Follow-up (y)	Diabetes mellitus		
		No. (men, %)	Age (y)	Cancer cases (no.)
Cohort studies				
Jee et al (15), 2005	10	62,924 (60)	M: mean, 45 F: mean, 50	NS
Kath et al (36), 2000[b]	Mean, 4.3	2,720 (NS)	NS	28
Ragozzino et al (37), 1982	25	1,135 (NS)	NS	120
Adami et al (38), 1991	Range, 1-19	51,008 (45)	Mean, 45	2,417
Hjalgrim et al (39), 1997	Range, 1-19	772 (48)	≥30	101
Wideroff et al (40), 1997	Range, 1-16	109,581 (50)	M: median, 64 F: median, 69	8,831
Swerdlow et al (41), 2005	Mean, 18.0	5,066 (58)	Range, 30-49	341
Khan et al (42), 2006	9	3,307 (41)	Range, 40-79	215
Inoue et al (43), 2006	Mean, 10.7	4,668 (48)	M: mean, 54 F: mean, 51	470
Rapp et al (44), 2006	M: mean, 8.2 F: mean, 8.6	4,758 (44)	M: mean, 43 F: mean, 43	353
Stattin et al (45), 2007	M: mean, 8.3 F: mean, 8.2	1,706 (52)	M: mean, 46 F: mean, 46	110
Ogunleye et al (46), 2009	Mean, 3.9	9,577 (53)	Mean, 62	661
Case-control study				
Kuriki et al (47), 2007[b]	...	2,191 (33)	Mean, 59	766

Abbreviations: F = female patients; M = male patients; NS = not specified.
[a] The data for men and for women were combined.
[b] Not included in the meta-analysis.

the risk of all-cancer incidence and mortality calculated in these cohort studies ranged from 10% to 51% and from 11% to 88%, respectively.

Quantitative Summary (Meta-analysis)

On the basis of the quality appraisal in our systematic review, a total of 26 reports that provided sufficient information were included in the meta-analysis (Fig. 1). As depicted in Figure 2, patients with diabetes had a significantly increased risk of all-cancer incidence in comparison with those without diabetes (n = 11 studies; adjusted RR = 1.10 [95% CI, 1.04 to 1.17]; I^2 = 79%; P<.00001). The adjusted RRs for both men and women were also significantly elevated (n = 8 studies; RR = 1.14 [CI, 1.06 to 1.23]; I^2 = 81%; P<.00001 for men and n = 8 studies; RR = 1.18 [CI, 1.08 to 1.28]; I^2 = 83%; P<.00001 for women). As shown in Figure 3, diabetes was also associated with an increased RR of mortality across all cancer types (n = 14 studies; RR = 1.16 [CI, 1.03 to 1.30]; I^2 = 82%; P<.00001 overall; n = 13 studies; RR = 1.10 [CI, 0.98 to 1.23]; I^2 = 74%; P<.00001 for men; and n = 10 studies; RR = 1.24 [CI, 1.11 to 1.40]; I^2 = 65%; P = .002 for women). Significant heterogeneity was observed across these studies. No publication bias was apparent, as assessed with use of a funnel plot (data not shown).

DISCUSSION

We found that diabetes is associated with a moderately increased risk of all-cancer incidence and mortality, on the basis of our systematic review and meta-analysis of population-based observational reports of worldwide epidemiologic data. There is a paucity of analyses on the association between diabetes and any-site cancer, and our

Table 2
Characteristics of the Studies Included in the Systematic Review and Meta-analysis of the Cancer Mortality Risk in Patients With Diabetes[a]

Source	Follow-up (y)	Diabetes mellitus		
		No. (men, %)	Age (y)	Cancer deaths (no.)
Cohort studies				
Jee et al (15), 2005	10	62,924 (60)	M: mean, 45 F: mean, 50	NS
Green & Hougaard (35), 1984[b]	7	1,499 (52)	NS	39
Swerdlow et al (41), 2005	Mean, 18.0	5,066 (58)	Range, 30-49	255
Fuller et al (48), 1983[b]	Range, 11-14	5,971 (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	1,772 (45)	Mean, 67	85
Wong et al (52), 1991	5	4,186 (51)	≥15	131
Smith et al (53), 1992	Range, 18-20	224 (100)	Range, 40-64	18
Sievers et al (54), 1996	7.5	1,562 (48)	≥15	27
Gu et al (55), 1998	22	710 (41)	Range, 25-75	61
Adlerberth et al (56), 1998	16	249 (100)	Mean, 56	22
Koskinen et al (57), 1998	5	58,000 (41)	Range, 30-74	1,421
Bruno et al (58), 1999	7	1,967 (68)	M: mean, 64 F: mean, 68	NS
Fujino et al (59), 2001	10	364 (49)	Mean, 59	38
Verlato et al (60), 2003	10	3,659 (47)	M: mean, 63 F: mean, 69	409
Saydah et al (61), 2003	16	427 (39)	Mean, 58	26
Oba et al (62), 2008	7	1,217 (46)	M: mean, 59 F: mean, 63	55
Landman et al (63), 2010	Median, 9.6	1,353 (42)	Mean, 68	122
Cross-sectional studies				
Fuller et al (48), 1983[b]	...	43,336 (42)	NS	3,135
Sasaki et al (64), 1985[b]	...	6,600 (NS)	Mean, 67.1	513
Tierney et al (65), 2001[b]	...	4,287 (NS)	≥18	9.7/y

Abbreviations: F = female patients; M = male patients; NS = not specified.
[a] The data for men and for women were combined.
[b] Not included in the meta-analysis.

current study, to the best of our knowledge, is the first systematic review and meta-analysis on this subject. In light of the facts that cancer is the 2nd and diabetes is the 12th leading cause of death worldwide (66) and that the number of people with diabetes is rapidly increasing, our findings have substantial clinical and public implications on a global scale and emphasize the necessity of further investigation of the interaction between these 2 conditions.

The strengths of the current research are that the analysis relative to overall cancer was mainly focused on large population-based cohorts originating from multiple nations and was performed with high levels of precision. Although the pooled RRs were robust, the results of the component studies were statistically heterogeneous. The large I^2 values indicate that the range of plausible risk estimates is wide, but there was very little evidence in our analysis to

Table 3
Quality Assessments of the Included Studies on Cancer Incidence[a]

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	Standardized incidence ratio
Kath et al (36), 2000[b]	Germany	Hospital-based	Insulin-treated DM, 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	Standardized incidence ratio
Adami et al (38), 1991	Sweden	Population-based	…	Hospital record	Population registries	Standardized incidence ratio
Hjalgrim et al (39), 1997	Denmark	Population-based	Insulin-treated DM	Prescription database	Population registries	Standardized incidence ratio
Wideroff et al (40), 1997	Denmark	Hospital-based	Type 1/type 2 mixed	Hospital record	Population registries	Standardized incidence ratio
Swerdlow et al (41), 2005	United Kingdom	Population-based	Insulin-treated DM	Prescription database	Population registries	Standardized incidence ratio
Khan et al (42), 2006	Japan	Population-based	…	Self-report	Population registries	Age, body mass index, smoking, alcohol
Inoue et al (43), 2006	Japan	Population-based	…	Self-report	Population registries	Age, cardiovascular disease, smoking, alcohol, body mass index, physical activity, green vegetable intake, coffee
Rapp et al (44), 2006	Austria	Population-based	…	Blood test	Population registries	Age, body mass index, 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), 2007[b]	Japan	Hospital-based	…	Self-report	Outpatient registries	Age, body mass index, alcohol, physical activity, bowel movement, family history, diet

Abbreviation: DM = diabetes mellitus.
[a] The data for men and for women were combined.
[b] Not included in the meta-analysis.

Table 4
Quality Assessments of the Included Studies on Cancer Mortality[a]

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	Standardized mortality ratio
Green & Hougaard (35), 1984[b]	Denmark	Population-based	Insulin-treated DM	Prescription database	Population registries	Standardized mortality ratio
Swerdlow et al (41), 2005	United Kingdom	Population-based	Insulin-treated DM	Prescription database	Population registries	Standardized mortality ratio
Fuller et al (48), 1983[b]	United Kingdom	Population-based	…	Self-report	Population registries	Standardized mortality ratio
Levine et al (49), 1990	United States	Employment registry-based	…	Self-report or medical records	Death certificates	Age, body mass index, smoking, systolic blood pressure, cholesterol, education, hypertension treatment
Balkau et al (50), 1991	France	Employment registry-based	…	Blood test	Family report, medical records	Standardized mortality ratio
Moss et al (51), 1991	United States	Population-based	…	Blood test	Death certificates	Standardized mortality ratio
Wong et al (52), 1991	United Kingdom	Clinic-based	Type 1/type 2 mixed	Medical records	Medical records	Standardized mortality ratio
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
Adlerberth et al (56), 1998	Sweden	Population-based	…	Self-report	Population registries	Age, cholesterol, systolic blood pressure, smoking, body mass index, coronary heart disease
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	Standardized mortality ratio
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	Standardized mortality ratio
Saydeh et al (61), 2003	United States	Population-based	…	Self-report or blood test	Death certificates	Age, sex, race, education, smoking, alcohol intake, physical activity, high-density lipoprotein cholesterol, systolic blood pressure, body mass index
Oba et al (62), 2008	Japan	Population-based	…	Self-report	Death certificates	Age, smoking, body mass index, physical activity, education, hypertension, diet, alcohol
Landman et al (63), 2010	The Netherlands	Clinic-based	…	Physician report	Medical records	Standardized mortality ratio
Cross-sectional studies						
Fuller et al (48), 1983[b]	United Kingdom	Death certificates	…	Death certificates	Death certificates	Standardized mortality ratio
Sasaki et al (64), 1985[b]	Japan	Population-based	…	Death certificates	Death certificates	Standardized mortality ratio, age
Tierney et al (65), 2001[b]	United States	Population-based	…	Death certificates	Death certificates	Age

Abbreviation: DM = diabetes mellitus.
[a] The data for men and for women were combined.
[b] Not included in the meta-analysis.

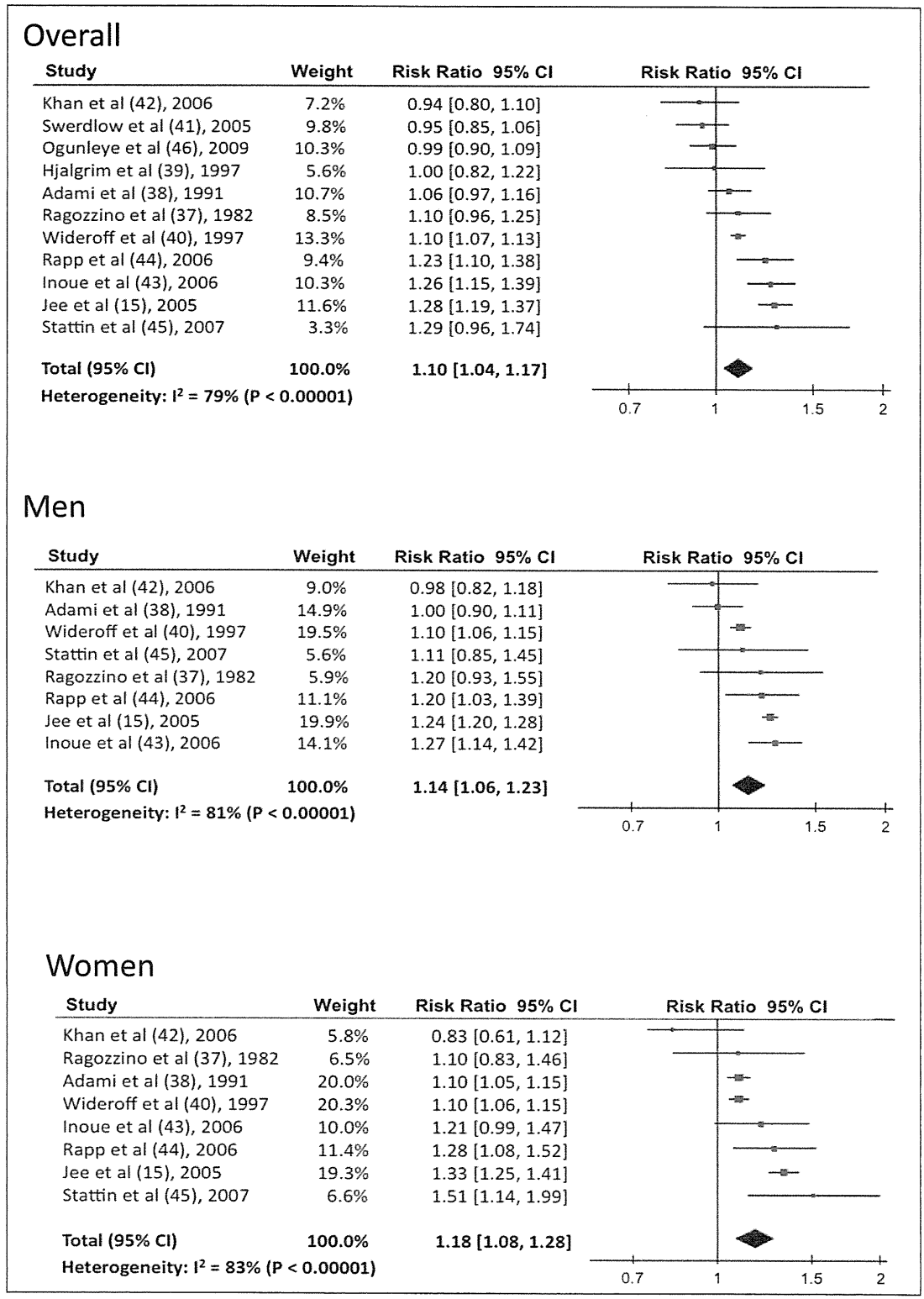

Fig. 2. Adjusted risk ratios (RRs) for the all-cancer incidence among overall patients (as well as stratified by men and women) with diabetes. *Boxes* = estimated RRs; *horizontal bars* = 95% confidence intervals (*CIs*); *diamonds* = RRs; *width of diamonds* = pooled CIs. The size of the box is proportional to the weight of each study in the meta-analysis.

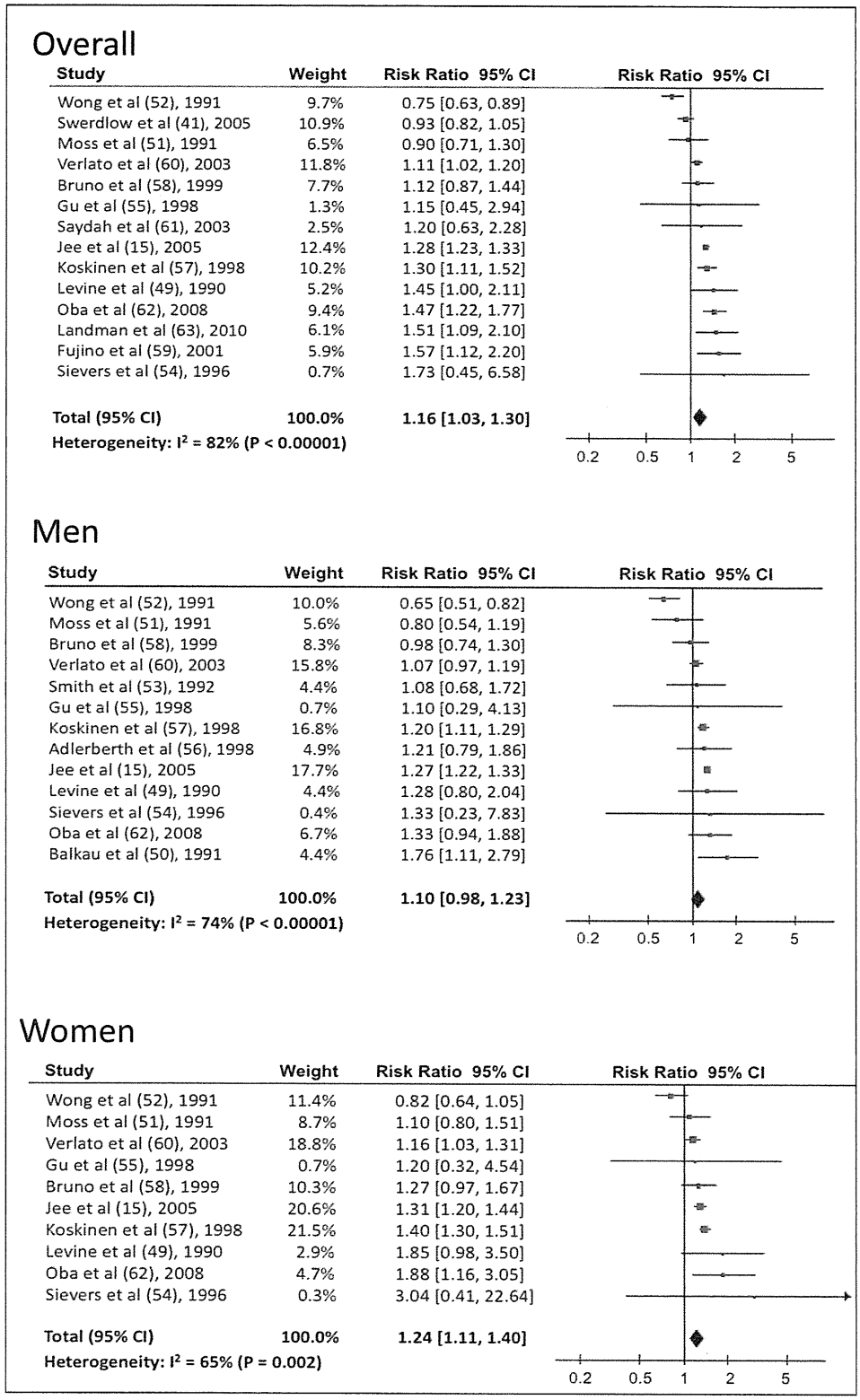

Fig. 3. Adjusted risk ratios (RRs) for the all-cancer mortality among overall patients (as well as stratified by men and women) with diabetes. *Boxes* = estimated RRs; *horizontal bars* = 95% confidence intervals (*CIs*); *diamonds* = RRs; *width of diamonds* = pooled CIs. The size of the box is proportional to the weight of each study in the meta-analysis.

support a protective effect of diabetes on all-cancer incidence and mortality. These findings might reflect the different mechanisms for development of cancer at various anatomic sites or different epidemiologic characteristics among the diverse populations included in our study (or both factors).

Investigators have suggested that insulin might have a potentially mitogenic effect by binding with insulinlike growth factor-I receptor, which is the most frequently proposed hypothesis to explain the apparently elevated risk of cancer in patients with diabetes (1-11). Type 2 diabetes is characterized by insulin resistance with compensatory hyperinsulinemia. Typically, patients with type 2 diabetes are obese and lead sedentary lives, which also contribute to the hyperinsulinemia. In experimental insulin-deficient animals, pancreatic cancer is reportedly induced more effectively with a carcinogen or implantation of cancer cells when they are supplemented with insulin (67,68). In humans, patients with type 1 diabetes, who are deficient in insulin, have a lower risk of cancer than do patients with type 2 diabetes (69,70), although the evidence of the risk in comparison with that in the general population is inconclusive (71,72). Even though these findings might support the insulin supply hypothesis, they are derived from retrospective observational studies, and because of possible confounders and biases, they do not necessarily demonstrate the causality (73,74). In fact, the data from insulin-treated patients are inconclusive (75).

Of interest, some studies have reported that diabetes protects against the development of prostate cancer (26,27), which is testosterone-dependent. Testosterone deficiency is common in men with diabetes or obesity attributable to low levels of sex hormone-binding globulin, and the testosterone level has been shown to be partly influenced by insulin resistance (76-78). The magnitude of the decrease in the cancer risk as a result of testosterone deficiency is likely higher than the magnitude of the increase in cancer risk as a result of insulin resistance. The increase in cancer mortality among men in our worldwide meta-analysis was not significant, whereas our previous meta-analysis on the cancer risk among men with diabetes in Japan, where the prevalence of prostate cancer is relatively low, showed a robust increase in the risk (adjusted RR 1.25) (79). It is speculated that this favorable effect of diabetes on prostate cancer may have contributed to the attenuation of the increase in the mortality risk found in the current study.

Hyperglycemia has also been reported to promote tumor cell proliferation and cancer metastatic involvement in patients with type 2 diabetes (80,81). This hypothesis is supported by evidence that the incidence of cancer is lower in patients with diabetes treated with metformin (82,83). In addition, hyperglycemia itself may promote carcinogenesis by generating oxidative stress (12-18), which is typically observed to be increased in diabetes, in a variety of cells. This situation would result in 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). Our study supports this hypothesis in that the risks of both cancer incidence and mortality are also generally elevated among Japanese (43,47,59,62,79) and Korean (15) patients with diabetes, who are reportedly insulinopenic (84-88). These observations underscore the crucial need for understanding the role of glucose metabolism and insulin resistance in carcinogenesis (89,90).

Alternative explanations for the elevated risk of cancer in patients with diabetes should be assessed, inasmuch as the relationship might not be causal. First, several potential confounders exist. For example, coexisting obesity and a sedentary lifestyle, which induce hyperinsulinemia, may be the true causes, and diabetes might merely be a risk factor. The other confounders include age, sex, diet, alcohol habit, smoking habit, and cirrhosis, factors for which full adjustments were not made in this study. A second possibility is that patients with diabetes might receive medical care more frequently and have more opportunities for cancer detection than those without diabetes. Third, diabetes might develop as a consequence of cancer; generally, cancers cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis factor-α (91,92). Fourth, differences in the cancer treatment between patients with and those without diabetes may have contributed to the increased mortality among patients with diabetes. Often, patients with diabetes have other diabetes-related comorbidities that may influence the prognosis and treatment decisions. For example, diabetes may be accompanied by a high risk of infections, and the diagnosis of cancer may result in inappropriate glucose management.

Several limitations of our investigation should be noted. As with any overview, the possibility that relevant research articles were missed and the inability to adjust fully for confounding factors because of population-based databases must be taken into consideration. It is also important to realize that the populations of the various studies were heterogeneous, most likely attributable to ethnic diversity, and that the risks of site-specific cancers may have varied. Therefore, an analysis for cancer at any site might be overly simplistic and dilute the true associations. Even with these limitations, our analysis should prompt health care providers, policy makers, and patients to devise countermeasures for preventing and managing cancer among patients with diabetes. Another limitation is that the methods used to ascertain the presence of diabetes in the extracted studies included self-reports, which might have eventuated in diagnostic inaccuracies. In addition, the baseline surveillance in most of these studies was conducted when the diagnostic cutoff value for fasting plasma 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 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

2) **Noto H, Tsujimoto T, Noda M:**
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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

Hiroshi Noto[1,2]*, Tetsuro Tsujimoto[1,2], Mitsuhiko Noda[1,2]

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].

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

[1]Department of Diabetes and Metabolic Medicine, Center Hospital, and [2]Department of Diabetes Research, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan
*Corresponding author. Hiroshi Noto Tel.: +81-3-3202-7181 Fax: +81-3-3207-1038
E-mail address: noto-tky@umin.net
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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-

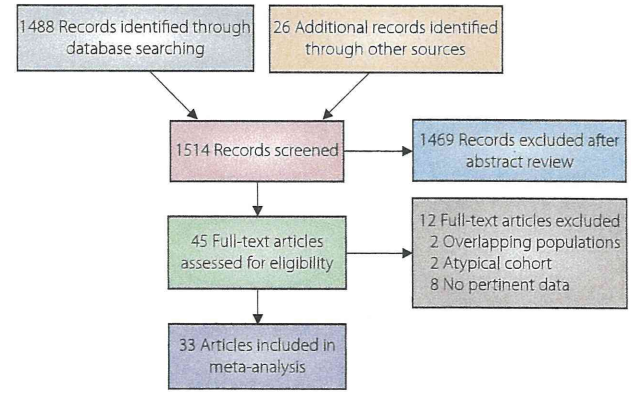

Figure 1 | Summary of the procedure used to select studies for inclusion in the meta-analysis.

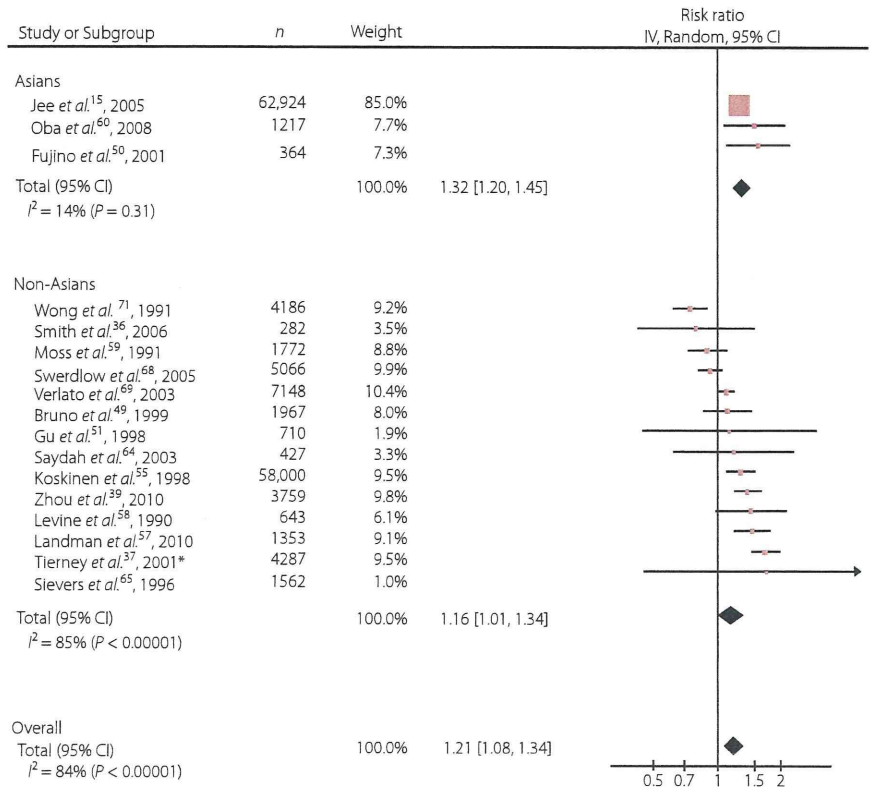

Figure 2 | Adjusted risk ratios (RR) for all-cancer mortality among the subjects with diabetes. *Cross-sectional study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI.

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-

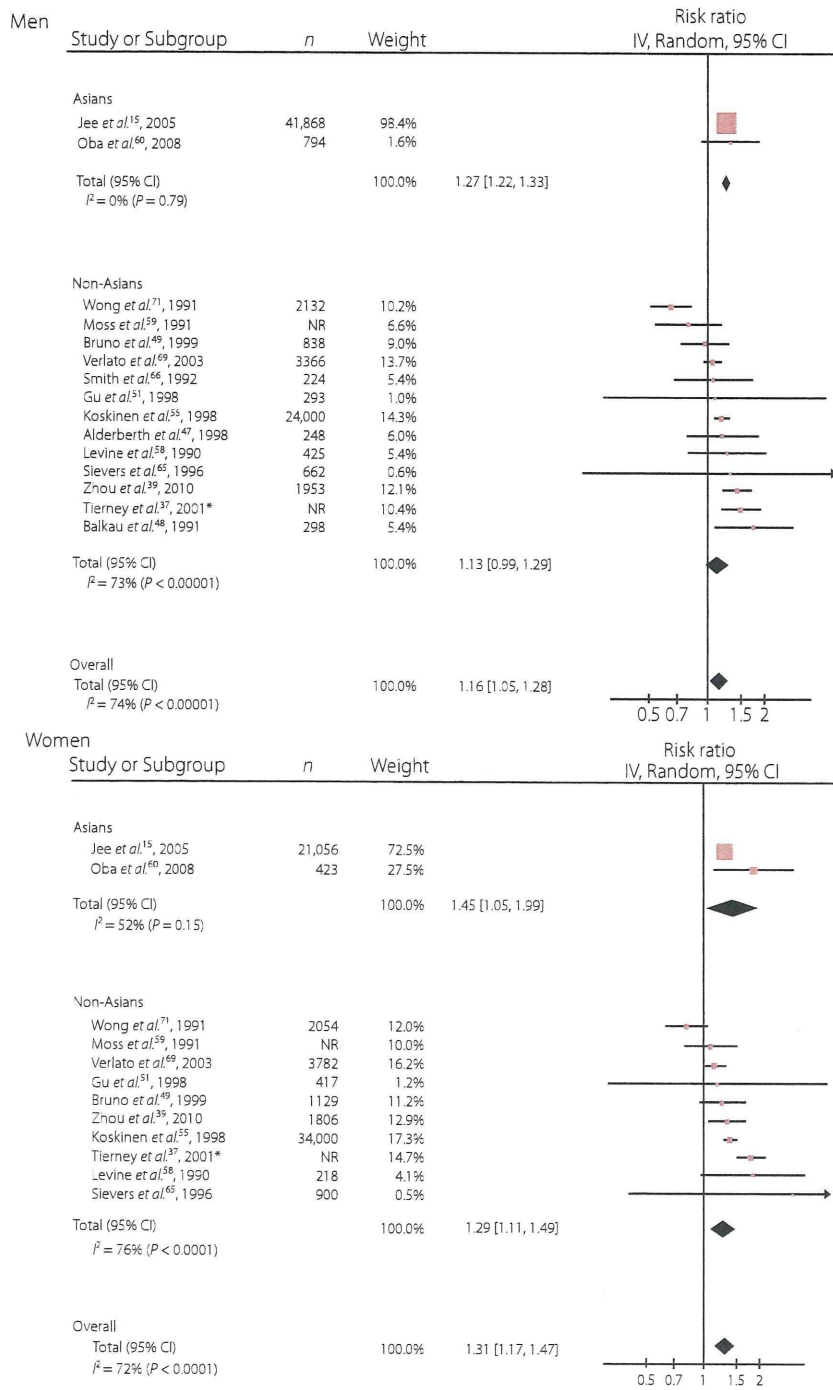

Figure 3 | Adjusted risk ratios (RR) for all-cancer mortality among men and women with diabetes. *Cross-sectional study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI. NR, not reported.

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].

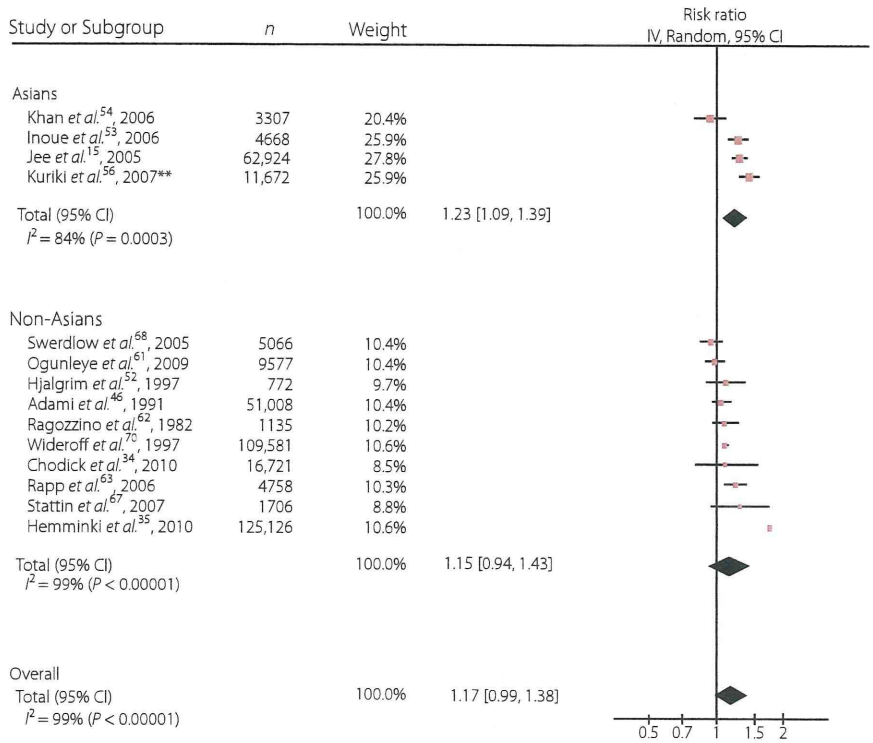

Figure 4 | Adjusted risk ratios (RR) for all-cancer incidence among the subjects with diabetes. **Case–control study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI.

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