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-

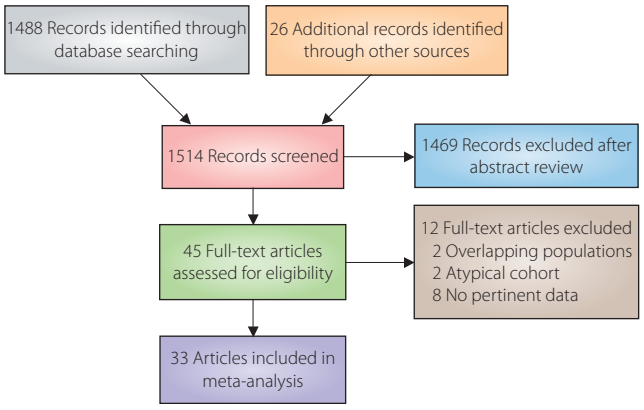

Figure 1 | Summary of the procedure used to select studies for inclusion in the meta-analysis.

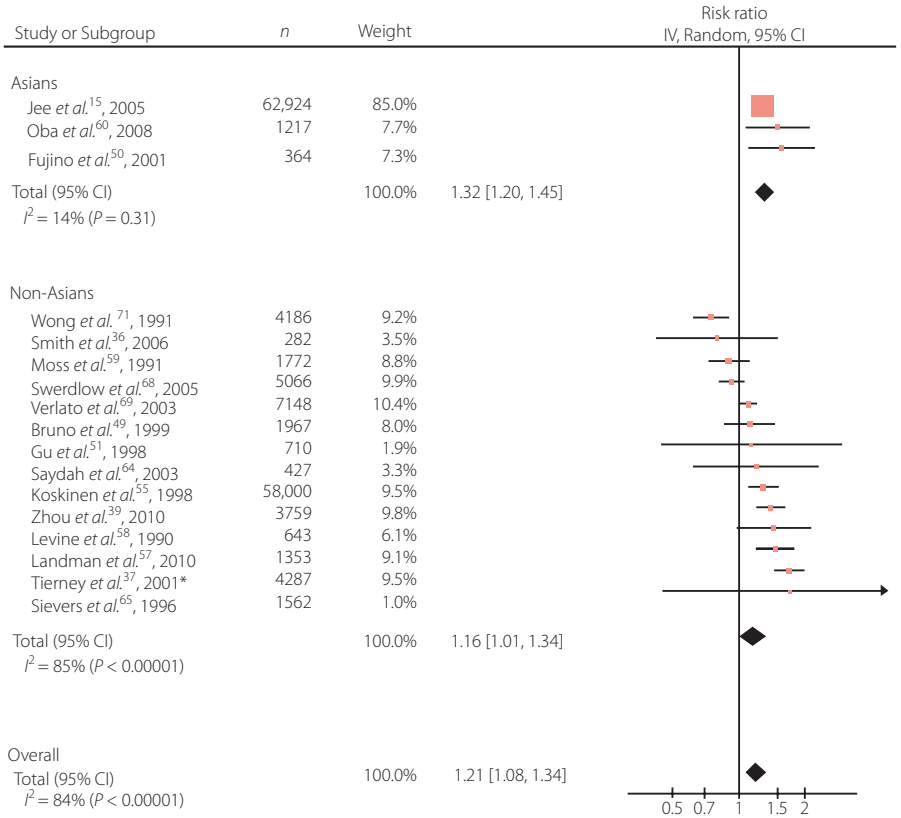

Figure 2 | Adjusted risk ratios (RR) for all-cancer mortality among the subjects with diabetes. *Cross-sectional study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI.

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-

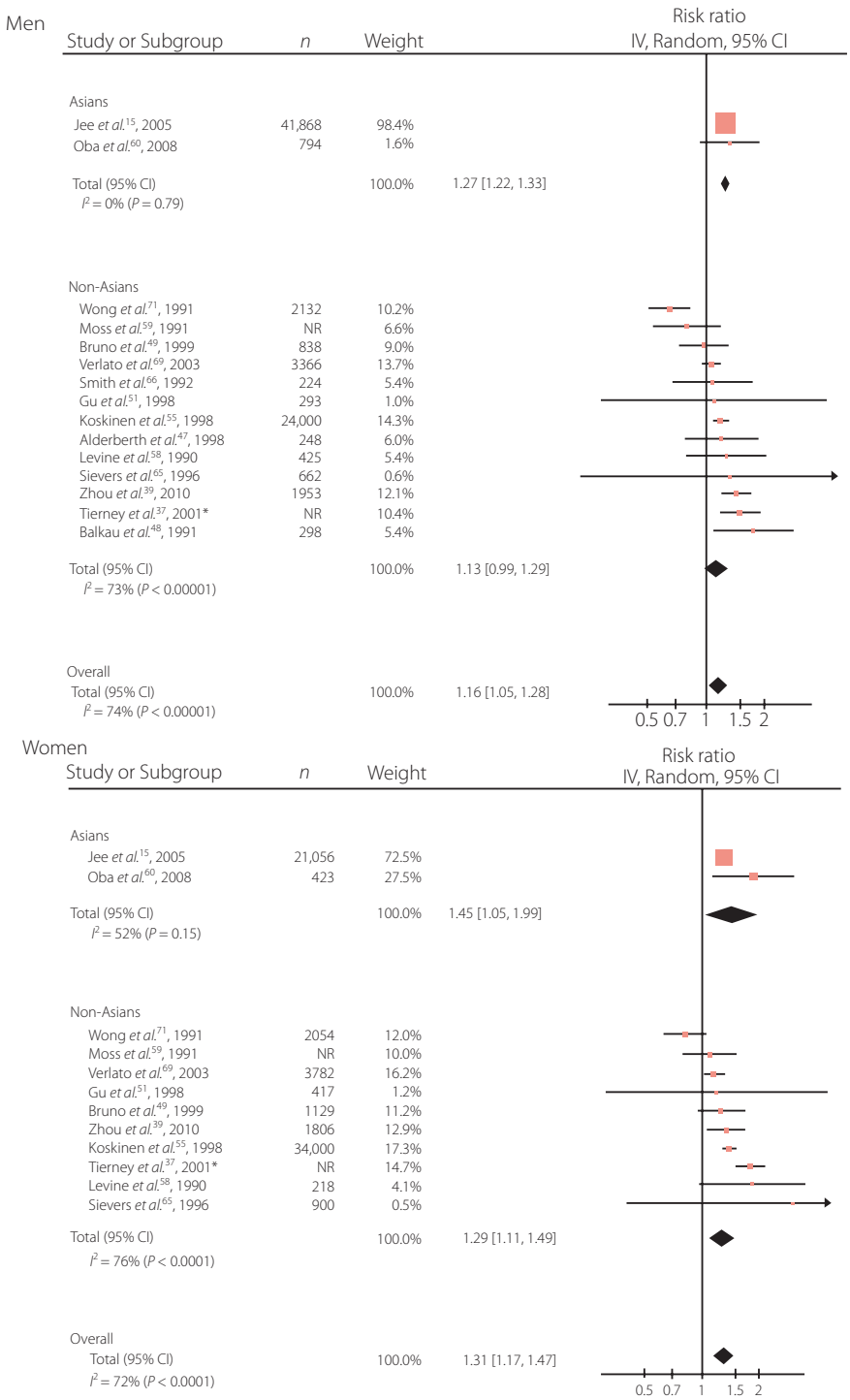

Figure 3 | Adjusted risk ratios (RR) for all-cancer mortality among men and women with diabetes. *Cross-sectional study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI. NR, not reported.

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].

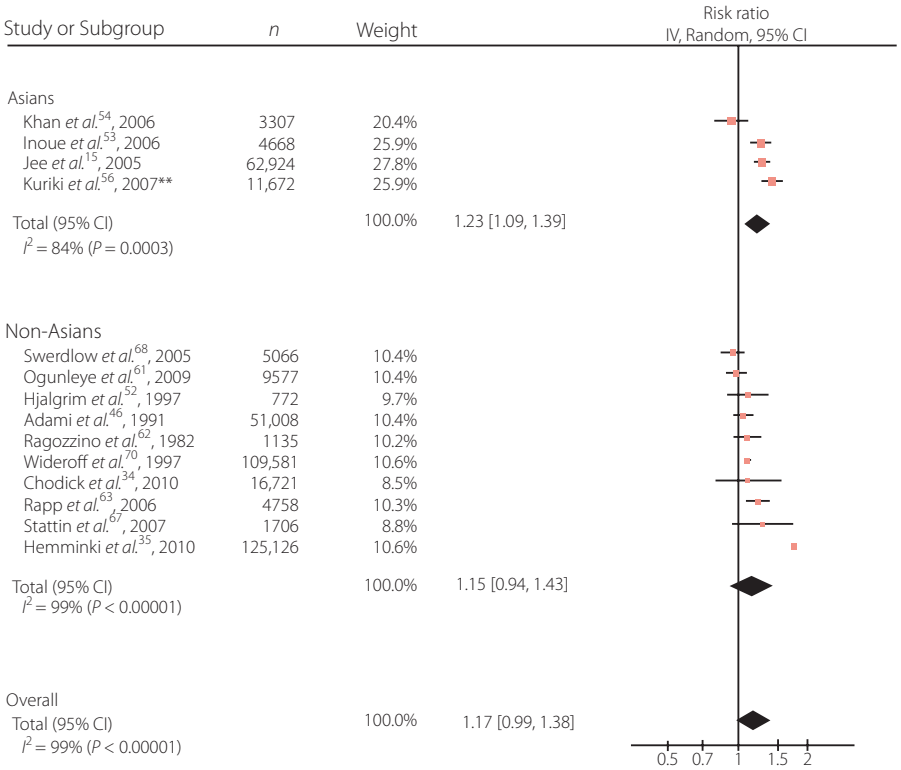

Figure 4 | Adjusted risk ratios (RR) for all-cancer incidence among the subjects with diabetes. **Case–control study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI.

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

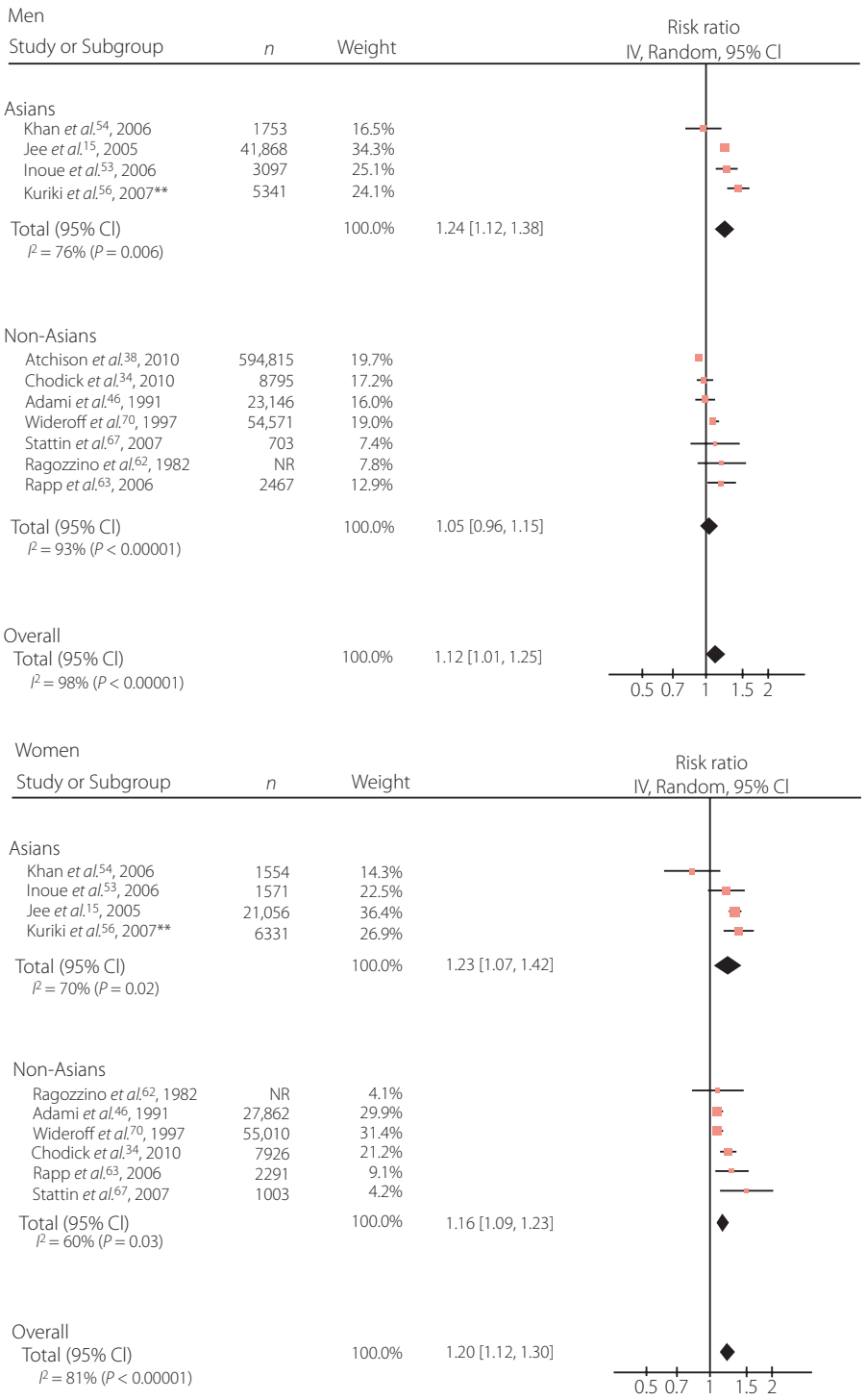

Figure 5 | Adjusted risk ratios (RR) for all-cancer incidence among men and women with diabetes. **Case–control study. Boxes, estimated RR; bars, 95% confidence intervals (CI); diamonds, RR; width of diamonds, pooled CI. NR, not reported.

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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