Results

Search Results

A total of 1314 citations were identified during our search; of these, 41 were assessed in respect of their eligibility for inclusion in our review aimed at determining the influence of diabetes on all-cancer incidence and mortality (Fig. 1). Out of these 41 articles, 32 (28 cohort, 3 cross-sectional and one case-control studies) 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, two reports were excluded from the meta-analysis, because the CIs were not provided (35, 36).

Tables 1 and 2 show the characteristics of each included study according to the 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 diabetic subjects (total n=257,222) in the 12 cohort studies developed cancer and approximately 3% of the diabetic patients (total n=152,091) in the 19 cohort studies died of cancer during the follow-up period.

The risk of bias among the studies is summarized in Tables 3 and 4. Among the 12 cohort studies and one case-control study referring to the cancer incidence, diabetes was diagnosed

using self-reports (n=5) and prescription databases (n=2), and four satisfied the current diagnostic criteria. All the diagnoses of cancer were confirmed by valid records or registries. Two 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 using self-reports (n=8) and prescription databases (n=4), and none satisfied the current diagnostic criteria. The diagnoses of cancer in all the reports were confirmed by valid methods, except in one 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

The majority 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 (one cohort study (52) in men, none in women, and one cohort study (52) and one cross-sectional study (64) in men and women combined) and none reported a decrease in the all-cancer incidence among patients with diabetes. On the other hand, several articles reported a statistically significant elevation in the risk of cancer incidence associated with diabetes (4 cohort studies (15, 18, 40, 44) and one case-control study (47) in men, 5 cohort studies (15, 38, 40, 44, 45) and one case-control study

(47) in women, and one cohort study (37) and one 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 one cross-sectional study (65) overall). The significant increases in the risk of all-cancer incidence and mortality calculated in these cohort studies ranged from 10% to 51% and 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 Fig. 2, subjects with diabetes had a significantly increased risk of all-cancer incidence as compared with non-diabetic subjects (n=11; adjusted RR, 1.10 [95%CI, 1.04 to 1.17]; I^2=79% P<0.00001). The adjusted RRs for both men and women were also significantly elevated (n=8; RR, 1.14 [CI, 1.06 to 1.23]; I^2=81% P<0.00001 for men; n=8; RR, 1.18 [CI, 1.08 to 1.28]; I^2=83% P<0.00001 for women). As shown in Fig. 3, diabetes was also associated with an increased RR of mortality across all cancer types (n=14; RR, 1.17 [CI, 1.05 to 1.31]; I^2=82% P<0.00001 overall; n=13; RR, 1.10 [CI, 0.98 to 1.23]; I^2=74% P<0.00001 for men; n=10; RR, 1.24 [CI, 1.11 to 1.40]; I^2=65% P=0.002 for women). Significant heterogeneity was observed across these studies. No apparent

publication bias was apparent as assessed using a funnel plot (data not shown).

Discussion

We found that diabetes is associated with a moderately increased risk of all-cancer incidence and mortality, based on our systematic review and meta-analysis of population-based observational reports of worldwide epidemiological data. There is a paucity of analyses on the association between diabetes and any-site cancer, and our current study, to the best of our knowledge, is the first systematic review and meta-analysis on this subject. In light of the fact that cancer is the second, 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 point to the necessity of further investigation of the interaction between the two conditions .

The strength of the present research is that the analysis in respect of overall cancer was mainly based 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 support a protective effect of diabetes on all-cancer incidence and mortality. These might reflect the different mechanisms of development of cancer at different sites and/or different epidemiological characteristics among the diverse populations included in our study.

It has been suggested that insulin might have a potentially mitogenic effect via binding with insulin-like growth factor-1 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. People with type 2 diabetes are typically 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 insulin (67, 68). In humans, subjects with type 1 diabetes, who are deficient in insulin, have a lower risk of cancer than subjects with type 2 diabetes (69, 70), although the evidence of the risk as compared with that in the general population is inconclusive (71, 72). Although these findings might support the insulin supply hypothesis, they are derived from retrospective observational studies and they do not necessarily demonstrate the causality due to possible confounders and biases (73, 74). In fact, the data from insulin-treated patients are inconclusive (75).

Of interest, it has been 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 secondary 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 decrease in the cancer risk as a result of testosterone deficiency is likely higher

than that 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 diabetic men 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 increase in the mortality risk found in the current study.

Hyperglycemia has also been reported to promote tumor cell proliferation and cancer metastasis in type 2 diabetes (80, 81). This hypothesis is supported by evidence that the incidence of cancer is lower in diabetic patients treated with metformin, an insulin sensitizer, than in diabetic patients treated with insulin or sulfonylureas (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 would result in DNA damage, the initial step in carcinogenesis (17). Community-based prospective surveys documented associations between plasma glucose levels and the risk of cancer (12-15). Our study would support this hypothesis in that the risk of both cancer incidence and mortality is also generally elevated among Japanese (43, 47, 59, 62, 79) and Korean (15) subjects with diabetes, who are reportedly insulinopenic (84-88). These observations point to 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, as the relation might not be causal. First, several potential confounders exist. For example, co-existing 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, which were not fully adjusted for in this study. A second possibility is that diabetic subjects might receive medical care more frequently and have more opportunities for cancer detection than non-diabetic subjects. Third, diabetes might develop as a consequence of cancer, since cancers generally cause insulin resistance and subsequent hyperglycemia by producing cytokines, such as tumor necrosis-α (91, 92). Fourth, differences in the cancer treatment between patients with and without diabetes may have contributed to the increased mortality in diabetic patients. Diabetic subjects often have other diabetes-related co-morbidities that may influence the prognosis and treatment decisions. For example, diabetes may be accompanied by a higher 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 papers were missed and the inability to adjust fully for confounders based on population-based databases must be taken into consideration. It is also important to realize that the populations of the studies were heterogeneous, most likely secondary to ethnic diversity,

and that the risks of site-specific cancers may have varied. Therefore, an analysis for cancer at any sites might be overly simplistic and dilute the true associations. Even with these limitations, our analysis should stir healthcare providers, policy makers and patients into devising 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 led to diagnostic inaccuracies. In addition, the baseline surveillance in most of these studies was conducted when the diagnostic cutoff 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 may have been underestimated. Lastly, possible modification of carcinogenesis by diabetes medication cannot be completely excluded in descriptive studies, although relevant data are limited at present and further investigation is required (93, 94).

In conclusion, our analysis strongly suggests 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 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. What is also eagerly required is integrated clinical attention and better-designed studies of the complex interactions between diabetes and cancer.

Author contributions

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

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Conflict of interests

The authors have no financial conflict of interests to declare.

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