

Unfolding link between diabetes and cancer

A growing body of evidence has shown that type 2 diabetes is associated with an increased risk of total cancer death and total cancer incidence, including cancers of the liver, endometrium, pancreas, kidney, colorectal, bladder and breast¹. Of interest, the risk of prostate cancer is significantly decreased. Although the majority of the studies on this topic have been carried out in Western countries, those risk ratios of all-cancer mortality and incidence across all cancer types are reportedly even higher in Asians (Table 1)².

Type 2 diabetes is characterized by hyperglycemia secondary to insulin resistance, and compensatory hyperinsulinemia. There are several putative mechanisms involving these factors to account for the higher risk of cancer in diabetes. In addition, it has been shown that hyperglycemia promotes cancer emergence and metastasis. However, high-quality evidence scrutinizing the link between glycemic control and the risk of cancer is scarce³.

More evidence has been accumulating with regard to potential oncogenic effects of diabetes treatment. Of note, it was speculated for a certain period of time that insulin formulation might increase the risk of cancer. Current evidence on the risk of cancer in association with any diabetes treatment to prove the causal relationship between those medications and cancer is limited because of their inadequate adjustment for confounders, not accounting for the degree of exposure to drugs and their short follow-up periods^{1,4}.

Chen *et al.*⁵ recently carried out pooled analyses of 19 prospective population-based cohorts consisting of data

from more than 771,297 Asians, and found that diabetes was significantly associated with an elevated risk of death from overall cancer (hazard ratio 1.26, 95% confidence interval 1.21–1.31). They also reported significant positive associations between diabetes and the risk of mortality from cancers of the endometrium, liver, thyroid, kidney, breast, ovary, pancreas, bile duct, prostate, colorectum, lymphoma, and gallbladder⁵. Although the relative risk is consistent with that in a previous meta-analysis², the strengths of their study design included a huge number of samples with

an adequately long follow-up period, an ability to analyze population subgroups and reduced publication biases. Their findings are clinically meaningful in that they point to the urgent implementation of appropriate cancer screening among diabetes patients, and a greater emphasis on therapeutic lifestyle changes in relation to cancer mortality in Asians with diabetes who have been assumed to be relatively insulin deficient.

Although their findings are compelling, observational studies should be interpreted with caution, because only a minority of associations between diabetes

Table 1 | Cancer risk in diabetes²

	Risk ratio (95% CI)	
	Cancer incidence	Cancer mortality
Men		
Asians	1.24 (1.12–1.38)	1.27 (1.22–1.33)
Non-Asians	1.05 (0.96–1.25)	1.13 (0.99–1.29)
Women		
Asians	1.23 (1.07–1.42)	1.45 (1.05–1.99)
Non-Asians	1.16 (1.09–1.23)	1.29 (1.11–1.49)

Table 2 | Japan Diabetes Society/Japanese Cancer Association joint statements on diabetes and cancer (excerpt)⁴

- Type 2 diabetes is reportedly associated with a higher risk of colorectal, liver, pancreatic, breast, endometrial and bladder cancers. However, it is associated with a lower risk of prostate cancer. Among patients with diabetes in Japan, diabetes is demonstrated to be associated with an elevated risk of cancers of the colorectum, liver and pancreas.
- Diabetes and cancer share some risk factors i.e. aging, obesity and inappropriate diet/exercise, which may partly explain their association.
- Hyperinsulinemia, hyperglycemia and underlying inflammation are deemed to be the plausible mechanisms through which diabetes raises cancer risk.
- To reduce the risk of diabetes and cancer, healthy diet, physical activity, weight control, smoking cessation, and alcohol abstinence are encouraged in light of the fact that inappropriate diets, sedentary lifestyle, smoking, and excessive alcohol intake are risk factors for cancer morbidity.
- It is recommended that patients with diabetes undergo evidence-based cancer screening depending on their sex and age.
- Evidence for determining whether medications for diabetes may modify cancer risk is insufficient at present. Therefore, in choosing drugs, optimizing the benefits of the medications to achieve personalized glycemic control should take priority.

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and cancer risk have robust supporting evidence without bias. The diagnosis of diabetes was partially based on self-reports, and the information on updated glucose management were not available, which might have resulted in misclassification and confounding. Any observational studies are subject to detection bias and confounding by treatment indication, which might have led to overestimation of the risks. In addition, investigation of the diabetes–risk of cancer incidence in their cohort is eagerly awaited.

On the basis of the exploding global epidemic of diabetes, a joint committee was formed composed of professionals from the Japan Diabetes Society and the Japanese Cancer Association to release the recommendations shown in Table 2⁴. The analyses of Chen *et al.*⁵ bring us one step higher on the ladder of research on diabetes-related cancer, and they underscore the need of more attention focusing

on elucidation of the association between diabetes and cancer, which is crucial to making timely and rational decisions for the prevention and appropriate management of diabetes and cancer globally.

DISCLOSURE

The author declares no conflict of interest.

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