# Glycemic control and outcome of cancer patients

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Diabetes mellitus (DM) and cancers are two chronic and complex diseases that have become increasingly prevalent on a global scale and thus pose significant social and economic burderns.[1] DM itself is a group of various metabolic diseases characterized by the presence of hyperglycemia, leasing to the development of microvascular and macrovascular complications (retinopathy, neuropathy, nephropathy, coronary heart disease, peripheral vascular, and cerebrovascular diseases), affects >450 million people in the world.[2–5] Cancers are also a heterogeneous diseases and can be classified based on the site of origin, clinicopathological features, and molecular signature.[2,6,7] Evidence shows the strong association between type 2 DM (T2DM) and many cancers, including risk, prognosis, and treatment, which is supported by numerous epidemiological studies and potential underlying pathophysiological features which propose to explain the causal relationship.[2] Among the pathophysiological features, one of the most important discoveries is the identification of hallmarks of cancers, in which dysregulations of metabolic nature (an essential pathophysiology of T2DM) is involved in cancer, including initiation, development, and progression.[8] Other hormonal imbalances particularly of insulin/insulin-like growth factor (GH) and adiponectin/leptin, as well subsequent hyperinsulinemia (endogenous or exogenous) as well as hyperglycemia, immune response with a dramatical elevation of levels of proinflammatory cytokines as tumor necrosis factor alpha, etc., as chronic inflammatory reaction, oxidative stress-related conditions (overproduction of reactive oxygen species, facilitation of protein oxidation, stimulation of free radical generators, and antioxidative enzymes) and possibly the effect of antidiabetic drugs used to treat T2DM are all contributing to a root cause of this T2DM-cancer association.[2,9] Experimental evidence has shown that insulin and insulin-like GF promote tumor cell mitosis and proliferation and inhibit tumor apoptosis.[2] Leptin mediates multiple signaling cascades involved in cancer cell survival and proliferation, such as induction of interleukin-6, signal transducer, and activator of transcription-3, Src tyrosine kinase, focal adhesion kinase, phosphatidylinositide-3 kinase, extracellular signal-regulated kinase 1/2, and telomerase in different cancer settings.[1] Although the current study pertaining to the exact nature of the pathophysiology linking T2DM with cancer and what is currently known only gives a very complex feature of status quo, latent cancer may also result in the onset of T2DM and hence to reverse causality, contributing to the worse prognosis and increasing morbidity and mortality.[2] However, not all cancers associate positively with T2DM, and some of them, such as prostate cancer, renal cancer, and ovarian cancer, have been reported to be inversely associated with T2DM, although these findings are still highly controversial.[2,10] Therefore, the further research still needs to be done to establish the cause of interaction between T2DM and cancers. Additionally, a better understanding about the linkage between these two diseases and identifying its driving forces are important for the development of novel interventions for both diseases.[1] In the current issue of the *Journal of the Chinese Medical Association,* we are happy to learn this-type research addressing the aforementioned problems. Lin et al[11] tried to investigate whether glycemic control impacts mortality in prostate cancer (PC) patients with T2DM.

The authors retrospectively enrolled 831 patients with PC (690 without T2DM and the other 141 with T2DM) to compare outcome (all-cause, non-PC-specific and PC-specific mortality) of patients with and without T2DM.[11] Additionally, the authors tested whether better glycemic control (defined by hemoglobin A1c [HbA1c] values by <7%, 7%–9%, and ≥9%) was related to outcome of patients with T2DM or not.[11] The authors found that poor glycemic control (HbA1c ≥ 9%) is associated with worse outcome of PC patients with an three-fold increase of all-cause mortality and 5.5-fold increase of non-PC specific mortality, respectively.[11] However, it is interesting to find that PC patients with T2DM, regardless of better, mediate or poor controls (based on HbA1C) did not have a significantly worse prognosis on PC-specific mortality compared to those PC patients without T2DM.[11] The current study is interesting and worthy of further discussion.

Previously, the most common cause of death in people with T2DM is cardiovascular system-related mortality; however, the composition of the mortality burden has changed.[12] Findings from an epidemiological analysis of linked primary care records in England showed that a transition from vascular diseases to cancers as the leading contributor to T2DM-related death.[12] Now cancer is a major cause of death in patients with T2DM, suggesting that clinical and preventative approaches should focus on this finding to reduce the excess mortality risk in patients

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Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2022) 85: 265-267.

Received October 12, 2021; accepted October 15, 2021.

doi: 10.1097/JCMA.0000000000000640.

with T2DM.[12] However, the relationship between T2DM and cancers is much complex. It is well-known that T2DM has been associated with the risk of all-site and some site-specific cancers in several systematic reviews and meta-analysis, and cancer patients (liver, endometrium, pancreas, colon, breast, gastrointestinal tract, bladder, and leukemia) with T2DM have a 15%–225% higher risk of mortality, but conflicted results have also been reported in PC.[1,2,10,12,13] Lin et al[11] showed all-cause mortality was really increased in PC patients with T2DM, regardless whether glycemic control is good or poor compared to that in PC patients without. The trend is more apparent in patients with poor glycemic control (HbA1c ≥ 9%).[11] Additionally, without adjustment, the authors also found the worse prognosis (PC-specific mortality) in PC patients with poor glycemic control (HbA1c ≥ 9% and HbA1c ranged between 7% and 9%) compared to those patients without T2DM.[11] However, after adjusting all confounding factors, PC-specific mortality seemed to be absent of statistically significant difference between PC patients with and without T2DM.[11] Moreover, PC-specific mortality was not influenced by the glycemic control (considering different levels of HbA1c) after adjusting all confounding factors.[11] All suggest that it remains yet to be elucidated why T2DM differentially affects the risk of different cancers and to what extent pathophysiological features are involved.[2] Unfortunately, it is difficult to use one mechanism of action to explain the relationship between T2DM and cancers.

PC is a specific cancer to men, and its pathophysiology is believed to be related to male sex hormone. By contrast, breast cancer occurs frequently in women, and its pathophysiology is related to female sex hormone. The increased incidence and increased mortality of breast cancer patients with T2DM is consistent but it is not always reproducible in PC patients.[2,10] Ohkuma et al[13] performed a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million cancer events, and found although T2DM was associated with all-site cancer in both genders, but with a 6% higher excess risk in women compared with men, and additionally, T2DM conferred a significantly great excess risk in women than men for oral, gastric, and renal cancer and for leukemia, but a lower excessive risk for hepatoma. As shown in the population-based study in England, the prognosis (all-cause mortality) of T2DM seemed to be worse in women than that in men, since death rates declined from 40.7 deaths per 1000 person-years to 27.8 deaths per 1000 person-years in men and from 42.7 deaths per 1000 person-years to 29.5 deaths per 1000 person-years in women with T2DM.[12] All suggest that T2DM contributing to all-cause or cancer-specific mortality is more apparent in female gender compared to male gender population. That is why Dr. Lin's study failed to give the positive correlation between T2DM and PC-specific mortality.

Why the gender difference is associated with incidence and severity of diseases? Attention recently has been focused on understanding the features of gender differences relevant to the physiological, pathological, and pathophysiological features of metabolism-related diseases; however, to date, there is uncertainty as to why gender differences influence physiological, pathological, and pathophysiological changes. The role of sex hormone is frequently discussed and evidence shows that sex hormones play a critical role in the disease from the initiation, development, to progression.[14,15] However, after adjusting all confounding factors, hormone therapy did not influence all-cause or cancer-specific mortality of PC patients in Dr. Lin's study.[11]

Finally, antidiabetic agents and/or cholesterol-lowing medications, such as metformin and/or statins have been long-term considered as a protective factor for prevention and treatment of patients with various kinds of cancers, although the findings are not always consistent.[11,16,17] One study found that hydrophilic statins, and pravastatin in particular, are associated with improved disease free survival (hazard ratio [HR] 0.71, 95% confidence interval [CI] 0.53–0.95) as well as overall survival (HR 0.69, 95% CI 0.50–0.93, as well as HR 0.67, 95% CI 0.47–0.96).[17] Metformin, widely prescribed for T2DM patients, regulate blood sugar by inhibiting hepatic gluconeogenesis and promoting insulin sensitivity to facilitate glucose uptake by cells, mediated by AMP-activated protein kinase (AMPK) and non-AMPK pathways to exert effects beyond those related to T2DM treatment that might ameliorate cancer.[16] Metformin can induce tumor cell death, mediated by nonapoptotic cell death, necroptosis (initiated by interactions between death receptors [TNFR superfamily] and corresponding ligand [FasL and TNF-alpha]), pyroptosis, and ferroptosis.[16] Metformin also modifies the tumor microenvironment (TEM) to influence the behavior of cancer cells, such as invasion, migration, epithelial–mesenchymal transition, and mesenchymal–epithelial transition, and restore the immunosuppression status by cancer.[16] All contribute to revealing the potential role of antidiabetic agents in cancer prevention and therapy. The current study by Dr Lin also included this confounding factor—the use or no-use of metformin in PC patients with T2DM, and in their model 2 which included the use of metformin, all-cause mortality was positively correlated with poor glycemia control of T2DM and Gleason score; non-PC mortality was positively correlated with poor glycemia control of T2DM, and PC-specific mortality was positive correlated with Gleason score.[11]

In conclusion, T2DM and cancer have a multifaceted relationship and may share regulatory mechanisms, although the biological links between T2DM and cancer are not completely understood. Metabolic dysregulation, dyslipidemia, hyperinsulinemia, hyperglycemia, abnormal secretion of local and systemic proinflammatory factors inducing chronic inflammation, excessive production of oxygen-free radicals through oxidative stress, abnormal levels of adipokines, such as leptin and adiponectin, overproduction of insulin-like growth factors, which are all found frequently in patients with T2DM, are also a factor in initiation, development, and progression of cancer.[1] Besides the diseases themselves, treatment for one disease may interact with outcome of the other disease, which may exacerbate or ameliorate the other disease. We congratulate the success of Dr Lin's publication and hope to see more publications addressing this field, since both diseases are a global health issue and associated with heavy burdens of the world. With better understanding of both, prevention or therapeutic approach may be more effective.

## ACKNOWLEDGMENTS

This article was supported by grants from the Taiwan Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 109-2314-B-075B-014-MY2 and MOST 110-2314-B-075-016-MY3), and Taipei Veterans General Hospital (V110C-082, and VGH109E-005-5). The authors appreciate the support from Female Cancer Foundation, Taipei, Taiwan.

## REFERENCES


1. Cao J, Yan W, Ma X, Huang H, Yan H. Insulin-like growth factor 2 mRNA-binding protein 2-a potential link between type 2 diabetes mellitus and cancer. *J Clin Endocrinol Metab* 2021;**106**:2807–18.
2. Durrani IA, Bhatti A, John P. The prognostic outcome of "type 2 diabetes mellitus and breast cancer" association pivots on hypoxia-hyperglycemia axis. *Cancer Cell Int* 2021;**21**:351.
3. Lee WL, Lee FK, Wang PH. Amylin, bariatric surgery and type 2 diabetes mellitus. *J Chin Med Assoc* 2021;84:983–4.
4. Wang JW, Chen PY, Huang HH, Yeh C, Chen SC, Lee WJ, et al. Change of plasma amylin after bariatric surgery challenged by oral glucose is associated with remission of type 2 diabetes mellitus. *J Chin Med Assoc* 2021;84:1001–6.
5. Adiga U, Banawalikar N, Mayur S, Bansal R, Ameera N, Rao S. Association of insulin resistance and leptin receptor gene polymorphism in type 2 diabetes mellitus. *J Chin Med Assoc* 2021;**84**:383–8.
6. Chen YJ, Hou MC, Yang TC, Lee PC, Chao Y, Li CP, et al. The clinical significance of esophagogastric varices in patients with advanced pancreatic cancer. *J Chin Med Assoc* 2021;**84**:917–22.
7. Li YT, Liu CH, Wang PH. Treatment for recurrent epithelial ovarian cancer. *Taiwan J Obstet Gynecol* 2021;**60**:803–4.
8. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;**144**:646–74.
9. Seow KM, Chang YW, Chen KH, Juan CC, Huang CY, Lin LT, et al. Molecular mechanisms of laparoscopic ovarian drilling and its therapeutic effects in polycystic ovary syndrome. *Int J Mol Sci* 2020;**21**:E8147.
10. Tao H, O'Neil A, Choi Y, Wang W, Wang J, Wang Y, et al. Pre- and post-diagnosis diabetes as a risk factor for all-cause and cancer-specific mortality in breast, prostate, and colorectal cancer survivors: a prospective cohort study. *Front Endocrinol (Lausanne)* 2020;**11**:60.
11. Lin CC, Wu MF, Chang YL, Sheu WH, Liou WS. Glycemic control was associated with non-prostate cancer and overall mortalities in diabetic patients with prostate cancer. *J Chin Med Assoc* 2022;**85**: 331-40.
12. Pearson-Stuttard J, Bennett J, Cheng YJ, Vamos EP, Cross AJ, Ezzati M, et al. Trends in predominant causes of death in individuals with and without diabetes in England from 2001 to 2018: an epidemiological analysis of linked primary care records. *Lancet Diabetes Endocrinol* 2021;**9**:165–73.
13. Ohkuma T, Peters SAE, Woodward M. Sex differences in the association between diabetes and cancer: a systematic review and meta-analysis of 121 cohorts including 20 million individuals and one million events. *Diabetologia* 2018;**61**:2140–54.
14. Horng HC, Chang WH, Yeh CC, Huang BS, Chang CP, Chen YJ, et al. Estrogen effects on wound healing. *Int J Mol Sci* 2017;**18**:E2325.
15. Huang BS, Lee WL, Wang PH. The slowing down of renal deterioration but acceleration of cardiac hypertrophy: is the estrogen receptor-α a hero or villain? *Am J Physiol Renal Physiol* 2014;**307**:F1352–4.
16. Hsu SK, Cheng KC, Mgbeahuruike MO, Lin YH, Wu CY, Wang HD, et al. New insight into the effects of metformin on diabetic retinopathy, aging and cancer: nonapoptotic cell death, immunosuppression, and effects beyond the AMPK pathway. *Int J Mol Sci* 2021;**22**:9453.
17. Ceacareanu AC, Jolly SD, Nimako GK, Wintrob ZAP. Statin type and cancer outcomes in patients with diabetes type 2 and solid tumors. *J Res Pharm Pract* 2021;**10**:50–6.