



Diabetes mellitus and cancer

Jae Won Hong

Department of Internal Medicine, Inje University Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea

Diabetes mellitus and cancer are the most common life-threatening illnesses worldwide. Previous epidemiological studies have suggested a strong association between diabetes mellitus and an increased risk of cancer. Potential biological mechanisms underlying this relationship include obesity, hyperglycemia, hyperinsulinemia, chronic inflammation, and oxidative stress. The most common diabetes-related cancers are pancreatic, hepatocellular, breast, endometrial, and colorectal cancer. Special attention should be paid to patients with diabetes through careful cancer screening and preventive anticancer strategies.

Keywords: Neoplasms; Diabetes mellitus; Diagnosis

INTRODUCTION

Diabetes mellitus and cancer are the most common life-threatening illnesses worldwide, and their incidence is increasing. Previous epidemiological studies have suggested that patients with diabetes mellitus have a higher risk of malignancies. While there are shared risk factors for the development of type 2 diabetes mellitus and cancer, the precise connection has yet to be determined. Furthermore, some research suggests that therapeutic agents used to treat diabetes mellitus could either increase or decrease the risk of malignancy. In this article, the author aims to explore the epidemiological relevance, mechanisms, and significance of the relationship of cancer with diabetes mellitus and related therapeutic agents.

EPIDEMIOLOGICAL STUDIES ON DIABETES MELLITUS AND CANCER DEVELOPMENT

It has been reported that individuals with type 2 diabetes mellitus have a twofold higher risk of developing hepatocellular carcinoma (HCC), pancreatic cancer, and endometrial cancer, as well as a 1.2 to 1.5 times higher risk of colon, rectal, breast, and bladder cancer [1]. Since the incidence of cancer increases with age, there are limited studies on the association between type 1 diabetes mellitus and cancer. However, it has been reported that patients with type 1 diabetes mellitus have an elevated risk of developing HCC, pancreatic, renal, endometrial, and ovarian cancer [2].

Diabetes mellitus and colorectal cancer

A meta-analysis of six case-control studies and nine cohort studies found that diabetes mellitus increased the incidence

Received: June 7, 2023; **Revised:** June 22, 2023; **Accepted:** July 17, 2023

Correspondence to Jae Won Hong, MD

Department of Internal Medicine, Inje University Ilsan Paik Hospital, Inje University College of Medicine, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Korea.

Email: hjwcarrot@paik.ac.kr

© 2023 Korean Society of Cardiovascular Disease Prevention, Korean Society of Cardiovascular Pharmacotherapy

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

of colon cancer and rectal cancer by approximately 1.43- and 1.33-fold, respectively [3].

Diabetes mellitus and pancreatic cancer

In a meta-analysis, diabetes mellitus was found to increase the incidence of pancreatic cancer by approximately 1.5 times. A study examining the association of baseline fasting blood glucose levels with cancer incidence and cancer-related mortality over a 10-year period using National Health Insurance Service data revealed a significant association between increased blood glucose levels, even within the prediabetic range, and both the incidence of and mortality from pancreatic cancer [4].

Diabetes mellitus and HCC

Since insulin is produced in the pancreas and transported to the liver via the hepatic portal vein, the liver is naturally exposed to high concentrations of insulin. Furthermore, factors such as diabetes-related fat accumulation, non-alcoholic fatty liver, and liver cirrhosis make individuals more susceptible to HCC. In a US study that analyzed the Surveillance Epidemiology and End-Results Program (SEER)-Medicare database, diabetes mellitus was associated with a twofold to threefold increase in the risk of HCC, even after adjusting for other risk factors such as hepatitis B, hepatitis C, and alcohol consumption [5].

Diabetes mellitus, breast cancer, and endometrial cancer

Diabetes mellitus is known to increase the risk of breast cancer and endometrial cancer in women, which is thought to be related to elevated estrogen levels due to a decrease in sex hormone-binding protein [6,7].

Diabetes mellitus and prostate cancer

Diabetes reduces the incidence of prostate cancer (excluding advanced prostate cancer) in men, and this decrease is believed to be due to a reduction in testosterone levels [8].

Epidemiological studies in Korea

In Korea, a study examined the incidence and mortality

rates of cancer in individuals with diabetes mellitus over a 10-year period using data from the National Health Insurance Service. After adjusting for smoking and alcohol consumption, higher fasting blood glucose levels were associated with an increased incidence of all cancers. Pancreatic cancer demonstrated the strongest association with fasting blood glucose levels. Fasting blood glucose levels were also linked to esophageal cancer, HCC, and colorectal cancer in men, as well as HCC and cervical cancer in women. Furthermore, a study utilizing National Health Insurance Service data from 2002 to 2013 revealed that the leading causes of death among patients with type 2 diabetes mellitus were malignant neoplasm (24.8%), diabetes mellitus (22.0%), cerebrovascular disease (11.2%), ischemic heart disease (6.2%), and other causes (31.3%). This indicates that cancer is the primary cause of death in patients with diabetes mellitus [9].

RISK FACTORS AND MECHANISMS THROUGH WHICH DIABETES MELLITUS INCREASES THE INCIDENCE OF CANCER

Common risk factors for diabetes mellitus and cancer encompass aging, male sex, unhealthy diet (consumption of saturated fatty acids, processed grains, and low fiber), decreased physical activity, smoking, and alcohol use [10]. However, it remains unclear whether the elevated risk of cancer in individuals with diabetes mellitus stems from these shared risk factors or from diabetes-related metabolic disorders, such as hyperglycemia and insulin resistance.

Obesity

Among the common risk factors for diabetes mellitus and cancer, obesity is the most important. Both obesity and cancer are increasingly prevalent worldwide, posing a major threat to human health. Numerous studies have investigated the association between these two diseases, consistently confirming that obesity increases the risk of developing several types of cancer. In 2002, the International Agency for Research on Cancer (IARC) reported that various cancers were associated with obesity, including colon cancer, rectal cancer, postmenopausal breast cancer, endometrial cancer, renal cancer, and esophageal adenocarcinoma [11]. In 2007, the World Cancer Research Fund (WCRF) added pancreatic

cancer to the list of cancers with a clear association with obesity and identified gallbladder cancer as likely being associated with obesity [12].

It has been proposed that obesity significantly increases the risk of developing cholelithiasis, gastroesophageal reflux disease, and nonalcoholic fatty liver. In turn, these conditions may result in a higher incidence of gallbladder cancer, esophageal cancer, and HCC, respectively. Insulin, insulin-like growth factors, sex hormones, and adipokines are believed to link obesity and cancer. It has also been suggested that the chronic inflammatory state induced by obesity may lead to cellular immune dysfunction and alterations in blood hormone levels, potentially accelerating cancer progression.

Hyperglycemia

Hyperglycemia may contribute to the development of cancer, as evidenced by the association between elevated blood glucose levels and a higher incidence of cancer, even within the normal range. Furthermore, hyperglycemia can lead to energy dysregulation in cells and weakened immunity within the body. Numerous studies have discovered that hyperglycemia provides an ample supply of glucose for energy-hungry cancer cells, potentially playing a role in resistance to apoptosis and chemotherapy [13].

Insulin resistance and hyperinsulinemia

When insulin resistance leads to consistently high blood insulin concentrations, insulin-like growth factors and insulin receptors are persistently stimulated. This results in protein synthesis and cell proliferation while inhibiting apoptosis. Moreover, elevated insulin indirectly reduces sex hormone-binding globulin levels, leading to increased estrogen concentrations in both men and women, as well as elevated testosterone concentrations in women. In menopausal women, a rise in endogenous sex hormones has been linked to an increased incidence of breast and endometrial cancer [14,15].

Oxidative stress and inflammatory mediators

Oxidative stress production is highly sensitive to hyperglycemia, leading to the overexpression of intracellular oxida-

tive stress response genes and subsequent DNA damage. Furthermore, numerous inflammatory mediators, such as fatty acids, interleukin-6, plasminogen activator inhibitor-1, adiponectin, leptin, and tumor necrosis factor- α , play a role in the development and progression of cancer [15].

PREVENTION AND SCREENING OF CANCER IN PATIENTS WITH DIABETES MELLITUS

Prevention of cancer

Obesity is associated with breast, colon, rectal, endometrial, pancreatic, esophageal, renal, and gallbladder cancer and HCC. Increased physical activity has been shown to help prevent colon, breast, and endometrial cancer. Studies have also found that smoking can increase the incidence of laryngeal, tracheal, bronchial, lung, upper gastrointestinal, bladder, renal, pancreatic, and cervical cancer, HCC, as well as leukemia. Additionally, excessive alcohol consumption has been associated with a higher incidence of oral, pharyngeal, laryngeal, esophageal, colon, rectal, and breast cancer and HCC. Therefore, to reduce the risk of cancer, it is essential to maintain regular physical activity and an appropriate weight, particularly for patients with diabetes mellitus, while also avoiding smoking and excessive alcohol consumption [16].

Cancer screening

Most patients with type 2 diabetes mellitus are middle-aged or older adults, which is when the incidence of cancer increases. As the life expectancy of patients with diabetes mellitus rapidly improves due to advancements in treatments, it is crucial to emphasize regular cancer screening for these individuals. More frequent screenings should be considered for HCC, pancreatic, endometrial, colon, rectal, breast, and bladder cancer, as these have been found to develop more frequently in patients with type 2 diabetes mellitus than their counterparts in the same age group. In particular, regular screening is strongly recommended for HCC, pancreatic, and endometrial cancer, as these have been reported to have a more than twofold higher relative risk in previous meta-analyses [17].

THERAPEUTIC AGENTS FOR DIABETES MELLITUS AND CANCER

The mitogenic effect of insulin has led to suggestions that insulin secretagogues, including insulin, insulin-like substances, and sulfonylurea, may increase the incidence of cancer. In particular, there have been numerous concerns about the potential association between insulin glargine and cancer [18,19]. However, in the ORIGIN (Outcome Reduction with an Initial Glargine Intervention) trial, which had a mean median follow-up of 6.2 years, no significant difference in incident cardiovascular outcomes and cancer was observed between the insulin-glargine and standard-care groups (hazard ratio, 1.00; 95% confidence interval [CI], 0.88–1.13; $P=0.97$) [20]. Based on these findings, the American Association of Clinical Endocrinology and the US Endocrine Society have reported that currently used medications do not need to be discontinued, as the effect of hypoglycemic agents on cancer development is small or virtually nonexistent.

On the contrary, numerous studies have reported positive findings, indicating that antidiabetic medications that improve insulin resistance, such as metformin, can reduce the risk of cancer development. A Scottish cohort study discovered that the incidence of cancer was lower in metformin users than in nonusers [21]. A retrospective cohort study on patients with breast cancer demonstrated a higher remission rate in the metformin group [22]. A meta-analysis of 11 studies revealed that administering metformin reduced cancer development by approximately 31% (95% CI, 0.61–0.79), with the effect being particularly pronounced in pancreatic cancer and HCC [23]. Furthermore, several studies have verified the anticancer effect of metformin in breast cancer, colon cancer, ovarian cancer, and prostate cancer [21].

The relationship between pioglitazone and bladder cancer remains contentious, but a recent meta-analysis and large-scale randomized controlled trial reported that pioglitazone did not increase the risk of bladder cancer [24,25]. Nevertheless, the European Medicines Agency recommended avoiding the use of pioglitazone in patients with a history of bladder cancer for safety reasons.

Although concerns have arisen regarding the association between incretin-based therapy (glucagon-like peptide-1 receptor agonist and dipeptidyl peptidase-4 inhibitor) and the development of pancreatic and thyroid cancers in pre-

clinical and observational studies, a large-scale prospective clinical study did not find an increased risk for these cancers [26]. Given the prevalence of incretin-based therapy in the treatment of type 2 diabetes mellitus, further research on the potential risk of cancer development is warranted.

Sodium-glucose cotransporter-2 inhibitors did not increase the incidence of cancer in a meta-analysis of 46 randomized controlled trials. However, given their relatively recent introduction to the clinical field, long-term follow-up is necessary [27].

CONCLUSIONS

In individuals with type 2 diabetes mellitus, there is an increased risk of developing HCC, pancreatic, endometrial, colon, rectal, breast, and bladder cancer, while the risk of prostate cancer is reduced. The mechanisms linking diabetes mellitus to cancer development include insulin resistance, hyperglycemia, and inflammatory responses. Additionally, aging, obesity, poor diets, and lack of exercise are common risk factors for both conditions. For those with type 2 diabetes mellitus, more frequent cancer screenings for HCC, pancreatic, and endometrial cancer are recommended, compared to the standard guidelines for the same age group.

ARTICLE INFORMATION

Ethics statements

Not applicable.

Conflicts of interest

The author has no conflicts of interest to declare.

Funding

None.

ORCID

Jae Won Hong, <https://orcid.org/0000-0002-4837-5800>

REFERENCES

1. Wojciechowska J, Krajewski W, Bolanowski M, Krecicki T, Zatonski T. Diabetes and cancer: a review of current knowledge. *Exp Clin Endocrinol Diabetes* 2016;124:263–75.
2. Carstensen B, Read SH, Friis S, Sund R, Keskimaki I, Svensson

- AM, et al. Cancer incidence in persons with type 1 diabetes: a five-country study of 9,000 cancers in type 1 diabetic individuals. *Diabetologia* 2016;59:980–8.
3. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* 2005;97:1679–87.
 4. Kim YJ, Oh CM, Park SK, Jung JY, Kim MH, Ha E, et al. Fasting blood glucose and risk of incident pancreatic cancer. *PLoS One* 2022;17:e0274195.
 5. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005;54:533–9.
 6. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. *Obes Rev* 2007;8:395–408.
 7. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* 2007;50:1365–74.
 8. Gong Z, Neuhaus ML, Goodman PJ, Albanes D, Chi C, Hsing AW, et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev* 2006;15:1977–83.
 9. Kang YM, Kim YJ, Park JY, Lee WJ, Jung CH. Mortality and causes of death in a national sample of type 2 diabetic patients in Korea from 2002 to 2013. *Cardiovasc Diabetol* 2016;15:131.
 10. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33:1674–85.
 11. International Agency for Research on Cancer (IARC). IARC handbooks of cancer prevention volume 6: weight control and physical activity. IARC; 2002.
 12. World Cancer Research Fund; American Institute for Cancer Research (AICR). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. 2nd ed. AICR; 2007.
 13. Ryu TY, Park J, Scherer PE. Hyperglycemia as a risk factor for cancer progression. *Diabetes Metab J* 2014;38:330–6.
 14. Noto H, Goto A, Tsujimoto T, Osame K, Noda M. Latest insights into the risk of cancer in diabetes. *J Diabetes Investig* 2013;4:225–32.
 15. van Kruijsdijk RC, van der Wall E, Visseren FL. Obesity and cancer: the role of dysfunctional adipose tissue. *Cancer Epidemiol Biomarkers Prev* 2009;18:2569–78.
 16. American Diabetes Association. 4. Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes: 2019. *Diabetes Care* 2019;42(Suppl 1):S34–45.
 17. Chuck KW, Hwang M, Choi KS, Suh M, Jun JK, Park B. Cancer screening rate in people with diabetes in the Korean population: results from the Korea National Health and Nutrition Examination Survey 2007–2009. *Epidemiol Health* 2017;39:e2017036.
 18. Colhoun HM; SDRN Epidemiology Group. Use of insulin glargine and cancer incidence in Scotland: a study from the Scottish Diabetes Research Network Epidemiology Group. *Diabetologia* 2009;52:1755–65.
 19. Jonasson JM, Ljung R, Talback M, Haglund B, Gudbjornsdottir S, Steineck G. Insulin glargine use and short-term incidence of malignancies: a population-based follow-up study in Sweden. *Diabetologia* 2009;52:1745–54.
 20. ORIGIN Trial Investigators; Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319–28.
 21. 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;32:1620–5.
 22. Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, Barnett CM, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. *J Clin Oncol* 2009;27:3297–302.
 23. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. *Cancer Prev Res (Phila)* 2010;3:1451–61.
 24. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomized controlled trial. *Lancet* 2005;366:1279–89.
 25. Mehtala J, Khanfir H, Bennett D, Ye Y, Korhonen P, Hoti F. Pioglitazone use and risk of bladder cancer: a systematic literature review and meta-analysis of observational studies. *Diabetol Int* 2018;10:24–36.
 26. Zhang Z, Chen X, Lu P, Zhang J, Xu Y, He W, et al. Incretin-based agents in type 2 diabetic patients at cardiovascular risk: compare the effect of GLP-1 agonists and DPP-4 inhibitors on cardiovascular and pancreatic outcomes. *Cardiovasc Diabetol* 2017;16:31.
 27. Tang H, Dai Q, Shi W, Zhai S, Song Y, Han J. SGLT2 inhibitors and risk of cancer in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Diabetologia* 2017;60:1862–72.