JBUON 2020; 25(5): 2147-2153
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

REVIEW ARTICLE

Distinct effects of anti-diabetic medications on liver cancer risk and patient survival

Pan-Hong Chen[1]*, Guo-Dong Lu[2,3]*, Guang-Zhi Zhu[4], Li Li[5], Yao Chen[1], Hui-Qi Dai[2], Wen-Jing Su[2], Yong Wu[2], Jing Zhou[1,6]

[1]Department of Physiology, School of Preclinical Medicine, Guangxi Medical University, Nanning, Guangxi Province, China, 530021. [2]Department of Toxicology, School of Public Health, Guangxi Medical University, Nanning, Guangxi Province, China, 530021. [3]Cancer Science Institute of Singapore, National University of Singapore, 14 Medical Drive, Singapore, 117599. [4]Department of Hepatobiliary Surgery, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Province, P.R. China, 530021. [5]Department of Endocrinology, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi Province, P.R. China, 530021. [6]Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, 2 Medical Drive, Singapore 117593.

*These authors contributed equally to this work

Summary

Type 2 diabetes mellitus (T2DM) is a pandemic metabolic disease worldwide. Multiple types of cancer, particularly liver cancer, are closely associated with T2DM. As a result, there is growing interest in investigating whether anti-diabetic medications could lower cancer risks in the population and even prolong patient survival among those with concurrent cancer. There are many types of anti-diabetic medications available in the clinic. The present study reviewed how different anti-diabetic drugs affect cancer risk and patient survival. On the one hand, multiple retrospective studies have shown that the different anti-diabetic medications have distinct effects on cancer risks. Insulin-raising drugs, including exogenous insulin, increased cancer risks, while drugs potentiating insulin sensitivity like metformin reduced cancer risks. On the other hand, the effects of anti-diabetic medications on patient survival are relatively less studied, except limited reports in liver cancer and pancreatic cancer. It seems that metformin could extend overall survival in patients of early-stage cancer. In contrast in the advanced cancer with metastasis, metformin has no effect or even worsens cancer mortality. It is yet unknown whether these distinct effects of metformin are attributable to the severity of the cancer staging or to the drug interactions between metformin and other medications. This question warrants reconsideration of the current clinical practice in the control of T2DM. Future large-scale prospective studies are needed to resolve this.

Key words: *anti-diabetic medications, cancer risk, liver cancer, patient survival, T2DM*

T2DM and liver cancer

According to the International Diabetes Federation [1], there are about 463 million diabetic patients (representing 1 of 11 adults) worldwide in 2019, 80-95% of whom are diagnosed with T2DM. Multiple observational studies and meta-analysis have associated T2DM with increased risks to develop different types of cancer, including liver cancer, endometrial cancer, cholangiocarcinoma, gallbladder cancer, colorectal cancer and breast cancer [2,3]. Similar associations were also observed between T2DM and deaths from liver cancer, stomach, colorectum and kidney. In an umbrella review [3], T2DM increased the total cancer risks (odds ratio/OR=1.10, 95%CI=1.04-1.17, N=38010). Among all types of cancer, both hepatocellular carcinoma (HCC) incidence (OR=2.31,

Corresponding author: Dr.Jing Zhou, Department of Physiology, School of Preclinical Medicine, Guangxi Medical University, 22 Shuangyong Rd, Nanning 530021, Guangxi Province, P.R. China.
Tel: +86-0771-5358212, ORCID: 0000-0002-2475-7783, E-mail address: gardenia_zhou@hotmail.com
Received: 01/02/2020; Accepted: 20/02/2020

95% CI=1.87-2.84, N=33765) and HCC mortality (OR=2.43, 95% CI=1.67-3.55, N=292) were the highest to be affected by T2DM (in terms of OR). Furthermore, the umbrella review found the most robust association between T2DM and intrahepatic cholangiocarcinoma. This strong association may be, at least partially, explained by the structural similarity and common risk factors shared by HCC and intrahepatic cholangiocarcinoma. Taken all together, the epidemiological evidence strengthened the importance of T2DM in liver carcinogenesis and patient mortality. It, however, should be noted that most observational studies were conducted retrospectively. These pharmacoepidemiological studies may suffer from time-related bias including immortal time bias, time-window bias, and time-lag bias [4]. Furthermore, these results were limited in diabetic patients, leaving unknown effects for the non-diabetic cancer patients.

Liver is the major organ involved in glucose and lipid metabolism. On the one hand, T2DM and NAFLD (nonalcoholic fatty liver diseases) alone or combined usually predate liver carcinogenesis. Sequentially, disruptions of glucose and lipid homeostasis cause a series of biochemical and histopathological changes in the liver, including hepatic inflammation, insulin resistance, hepatocyte cell death and regeneration, fibrosis, liver cirrhosis and consequent carcinogenesis [5,6]. On the other hand, the patients with chronic liver diseases including HCC can also develop insulin insensitivity, which in turn promotes and/or deteriorates hyperglycemia [7]. Several studies suggested that hyperinsulinemia, rather than hyperglycemia, is the major driving force of the increased cancer risks in patients with T2DM [8,9]. High C-peptide concentration, a marker of endogenous insulin secretion, was associated with colorectal and breast cancer risks, recurrence and mortality [10,11], strengthening the underlying role of T2DM in cancer.

T2DM changes the epidemiology of HCC

Liver cancer is the second leading cause of cancer-related death globally, because of its high incidence rate (854,000 new cases per year) and equal high rate of mortality (810,000 deaths per year) [12,13]. The 5-year survival rate for liver cancer is only 18%, which is one of the lowest among all types of cancer [14]. HCC represents the majority (90%) of liver cancer. Generally, chronic viral hepatitis is the predominant risk factor of HCC. Infection with hepatitis B virus (HBV) accounts for approximately 54% of HCC incidence worldwide, particularly in East Asia, Southeast Asia and Africa [12]. In addition, 31% of HCC incidence (particularly in Western countries and Japan) is attributable to hepatitis C virus (HCV) infection. Environmental toxins including aflatoxin and microcystin-LR also synergize with viral hepatitis to cause HCC.

However, significant alterations of the HCC incidence have been observed in the world. On the one hand, many Western developed countries, namely the USA, Canada, most European countries, Australia and New Zealand have experienced a sharp increase in HCC incidence [12]. For example, both HCC incidence and mortality have been increased by 93% and 71% respectively in the USA during the last 25 years [14]. This unexpected surge of HCC incidence and mortality, comparing with the steady 27% decrease of total cancer mortality, was reported to be associated with the prevalent metabolic diseases such as T2DM, obesity and NAFLD, together with the emergence of chronic hepatitis C [5]. Furthermore, these metabolic disorders have additive effects on patients affected with viral hepatitis [15]. On the other hand, in China and Eastern sub-Saharan Africa where are affected by high HCC incidence, there is a steady decrease of HCC incidence by more than 20% [12,16]. This promising decrease is probably attributed to more than two decades' efforts in preventing hepatitis B through HBV vaccination and in controlling environmental toxicants [17,18]. As a consequence, the heavy burden of metabolic diseases in the developed countries as well as the increasing prevalence in the developing countries [1] may gradually change the epidemiology of HCC. The link between NAFLD and liver cancer has been well reviewed elsewhere [19,20]. The present review focuses on the effect of T2DM medications on liver cancer progression and patient prognosis.

Anti-diabetic drugs: associations with HCC risks and the potential mechanisms involved

A recent big meta-analysis [21] summarized the effect of anti-diabetic drugs on all types of cancer by pooling 83 observational studies (7.6 million diabetic patients) and 182 randomized clinical trials (137,540 diabetic patients). The study pointed out that different anti-diabetic drugs had distinct effects on cancer risks. Particularly, the use of metformin (risk ratio/RR=0.86, 95%CI=0.83-0.90) and thiazolidinediones (RR=0.93, 95% CI=0.91-0.96) decreased cancer risk, while insulin (RR=1.21, 95% CI=1.08-1.36), sulfonylureas (RR=1.20, 95% CI=1.13-1.27) and alpha-glucosidase inhibitor (RR=1.10, 95% CI=1.05-1.15) increased. This raised clinical alarms in selecting the right anti-diabetic medication to avoid the possible oncogenic side-effects (Figure 1).

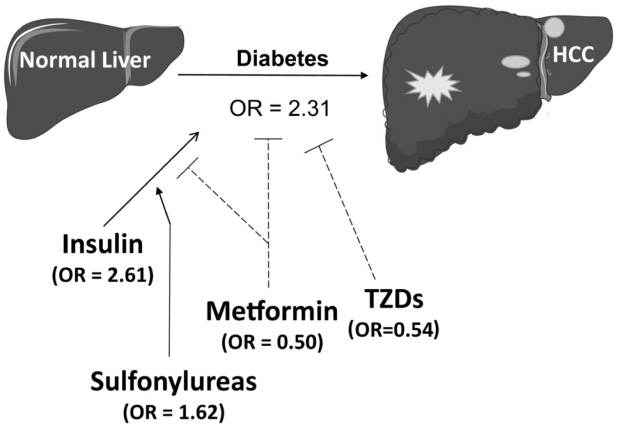

Figure 1. The distinct effects of anti-diabetic medications on HCC risk. Diabetes predisposes liver to the increased risks of HCC. Insulin-stimulating drugs including exogenous insulin may further promote HCC risk, while drugs potentiating insulin resistance like metformin and thiazolidinediones (TZDs) could decrease HCC risk. The levels of OR are summarized below.

Insulin

The increased carcinogenic risk of T2DM was attributable to a number of factors, including hyperglycemia, insulin resistance, hyperinsulinemia, increased level of insulin-like growth factor-1 (IGF-1) and inflammatory cytokines [22]. Insulin production is physically secreted from pancreatic beta-islet cells into the circulation to mobilize glucose metabolism after meals. In type 1 diabetes, insulin production is impaired through autoimmune mechanisms. Thus, exogenous insulin is commonly prescribed to control hyperglycemia. But in T2DM, major glucose-metabolizing organs including liver, muscle and adipose tissues become resistant to insulin. As a result, there are gradually increasing concentrations of insulin relative to the level of glucose, which may aggravate hyperinsulinemia. Insulin belongs to the IGF family. Substantial clinical and experimental evidence has confirmed that receptors of insulin and IGF1 are highly expressed in cancer cells to mediate the activation of Akt, MAPK (mitogen-activated protein kinase) and mTOR (mammalian target of rapamycin) signaling [22]. Stimulations of these prosurvival pathways have important roles in carcinogenesis.

According to a Taiwanese population-based study, insulin usage in each incremental year could cause 13% increase of HCC risk (OR=1.13, 95% CI=1.10-1.06) [23]. Another meta-analysis based on 7 observational studies concluded that administration of insulin increased HCC risk by 161% (OR=2.61, 95% CI=1.46-4.65) [24]. After adjusting the uses of other anti-diabetic drugs, insulin was still associated with higher HCC risk. Note that the oncogenic effect of insulin was more apparent in the Asian populations (OR=4.36, 95% CI=4.16-4.58, p=0.05) than in the Western populations (OR=2.01, 95% CI=1.17-3.44), although the epidemic of obesity and diabetes is more severe in Western population. Why there is a preference to the Asian population by insulin is yet unknown.

Sulfonylureas

Sulfonylurea is the oldest drug class available for diabetes treatment, working by promoting insulin secretion. As same as insulin, sulfonylurea could increase HCC risk by 62% (OR=1.62, 95% CI=1.16-2.24) [24]. But sulfonylureas differ from insulin because sulfonylureas promote HCC risk only in the Western population (OR=1.84, 95% CI=1.20-2.82), but not in the Asian population (OR=1.25, 95% CI=0.78-2.02).

Metformin

Metformin, an oral biguanide medication, is the first-line treatment for T2DM by reducing glucose in the circulation and improving insulin resistance. Metformin mechanically activates AMPK (adenosine monophosphate-activated protein kinase) signaling and thus inhibits hepatic gluconeogenesis to control hyperglycemia [25]. It was suggested that partial inhibition of oxidative phosphorylation by metformin results in the increase of AMP/ATP ratio and consequently activate AMPK [26,27]. This in turn represses mTOR and the downstream signaling pathways. AMPK also represses NF-κB (nuclear factor kappa light chain enhancer of activated B cells). Lower AMPK phosphorylation was correlated with the clinicopathological characteristics of advanced HCC and with poorer patient survival [28]. Thus, activation of AMPK by metformin could inhibit HCC cell proliferation *in vitro* and experimental HCC xenograft growth [28]. It is noteworthy that liver specifically expresses organic cation transporter 1 (OCT1), a membrane transporter of metformin [29]. Therefore, metformin accumulates in the liver. This may be the reason why metformin has a greater effect on liver and liver cancer cells [3]. Another possible mechanism has been proposed that metformin may decrease insulin and mTOR activity in the host microenvironment [30]. However, the exact molecular targets of metformin are yet unclear.

Metformin can reduce cancer risks in many types of cancer including HCC [2]. The aforementioned Taiwanese population-based study suggested that metformin usage in each incremental

year could lower 7% of HCC risk (OR=0.93, 95% CI=0.91-0.94) [23]. A subsequent meta-analysis [24] confirmed that metformin usage is associated with 50% reduction of HCC incidence (OR=0.50, 95% CI=0.34-0.73). Even after adjusting the other anti-diabetic drugs, the protective effect of metformin against HCC incidence was still significant (OR=0.78, 95% CI=0.75-0.83). Furthermore, this effect is independent of the medication duration and diabetes severity. It is worth noting that the suppressive effect of metformin was more evident in the Western population than in the Asian populations (OR=0.42 *vs.* 0.79, p=0.04).

Thiazolidinediones (TZDs)

Two TZDs, namely rosiglitazone and pioglitzone, are available for the treatment of T2DM. TZDs work as agonists of peroxisome proliferator activated receptor γ (PPARγ) to promote adipocyte differentiation and combat insulin resistance. But experimental studies showed that TZDs may inhibit HCC cell growth, invasion and preclinical animal HCC independent of PPARγ [31]. The aforementioned Taiwanese population study (23) showed that TZDs usage could decrease 9% HCC risk with each incremental year (OR=0.91, 95% CI=0.87-0.95). However, the meta-analysis study [24] failed to confirm it with insufficient statistical power (OR=0.54, 95% CI=0.28-1.02), possibly due to the heterogeneity across different studies. There are also concerns over the increased risk of bladder cancer using pioglitazone [32].

There are other types of medications available for T2DM, e.g. glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporter type 2 inhibitors. These medications are relatively new in the market. Whether they affect cancer incidence or even mortality is yet unclear, although there are some inconsistent results from a few small reports.

Anti-diabetic drugs and cancer patient survival

Overall, T2DM itself increases both cancer incidence and cancer-related mortality. However, whether anti-diabetic medications affect cancer mortality is comparatively less studied.

Insulin

Although T2DM is characterized by insulin resistance, insulin is still frequently used in the clinic particularly during the perioperative period when the patients are requested to fast before and after surgery. This practice is chosen mainly because of the convenient delivery mode of insulin by injection. Another reason to use insulin is that metformin may cause lactic acidosis in patients with liver and renal dysfunctions. However, it was recently found that patients with cirrhosis could tolerate metformin well without major side efforts [33]. More importantly, metformin significantly improved the survival among these cirrhotic patients. A recent population-based study conducted in Shanghai, China [34] found that insulin use could worsen mortality of four cancer types including colorectal [HR (hazard ratio)=2.60, 95% CI=1.90 to 3.54), gastric (HR=1.45, 95% CI=0.99 to 2.10), breast (HR=1.94, 95% CI=1.05 to 3.56) and lung cancer (HR=1.43, 95% CI=1.06 to 1.94), respectively. Unfortunately, this study did not include HCC.

Sulfonylureas

To the best of our knowledge, only one report [34] has linked the use of sulfonylureas with poorer survival in patients with breast cancer (HR=2.87; 95% CI=1.22 to 6.80) and gastric cancer (HR=2.05; 95% CI=1.09 to 3.84), respectively.

Metformin

Because of the promising results of metformin against cancer incidence, there are substantial interests in the hypothesis that metformin may also inhibit existing cancer (including HCC), improving patient survival. However, the results from several retrospective HCC clinical studies are inconsistent. A Korean population-based cohort study [35] showed that metformin use could lower HCC-specific mortality (OR=0.38, 95% CI=0.30-0.49) and tumor recurrence (OR=0.41, 95% CI=0.30-0.49) in the early-stage HCC patients after curative resection. Another small clinical study conducted in Taiwan [36] reported that metformin treatment increased the survival in HCC patients undergoing radiofrequency ablation (OR=0.24, 95% CI=0.07-0.80).

In contrast, the beneficial effect of metformin was lost in the advanced-stage HCC patients. A US report [37] demonstrated no effects of using metformin (OR=1.0, 95% CI=0.8-1.3) among advanced-stage HCC (59.2% BCLC-C and 12.9% BCLC-D). Furthermore, a small Italian study [38] even found that metformin worsens patient survival (overall survival: 6.6 months of metformin-users *vs.* 16.6 months of insulin-users) among the sorafenib-treated patients (73% BCLC-C). Finally, a recent

German study [39] reiterated that metformin usage promoted longer median overall survival (22 *vs.* 15 months, p=0.019) among HCC patients. The authors further found that the beneficial effect of metformin was most significant in early-stage HCC patients after curative resection or liver transplantation [median overall survival (mOS): 32 *vs.* 10 months, p=0.016). But the protective effect was unobservable in patients undergoing local ablation (mOS: 41 *vs.* 26 months, p=0.059) and transarterial (chemo)embolization (mOS: 19 *vs.* 18 months, p=0.417). Furthermore, metformin tended to cause poorer survival in the sorafenib-treated HCC patients (mOS: 7 *vs.* 11 months, p=0.088). Thus, it seems that the effect of metformin may be dependent on HCC staging and/or the relevant primary treatments (Figure 2).

Similar results were observed in pancreatic cancer [40]. Metformin improved overall survival in early-stage pancreatic cancer patients after resection (OR=0.79, 95% CI=0.69-0.91) and in patients with locally advanced tumors (OR=0.68, 95% CI=0.55-0.84). But for the advanced-stage patients with metastatic tumors, the use of metformin had no effect. Furthermore, there are two independent phase-II randomized clinical trials (RCT) studies conducted on advanced pancreatic cancer patients who were simultaneously treated with standard chemotherapies. The first RCT [41] failed to demonstrate the benefits of metformin in advanced pancreatic cancer patients who were also treated with gemcitabine and erlotinib (HR=1.056, 95% CI=0.72-1.55, p=0.78). The second RCT study [42] assessed the efficacy of adding metformin to a standard chemotherapy cocktail (cisplatin, epirubicin, capecitabine, and gemcitabine) in patients with metastatic pancreatic cancer. This RCT also failed to observe significant changes in neither overall survival (HR=0.92, 95% CI=0.54-1.56) nor progression-free survival (HR=0.728, 95% CI=0.43-1.22) between metformin-users and non-users. Furthermore, multivariate Cox regression analysis even suggested a worse outcome. These two RCT studies however may be limited by the inadequate dose of metformin in the target tumor sites and by the advanced stage of cancer. The combination of multiple drugs may further complicate the drug efficacy.

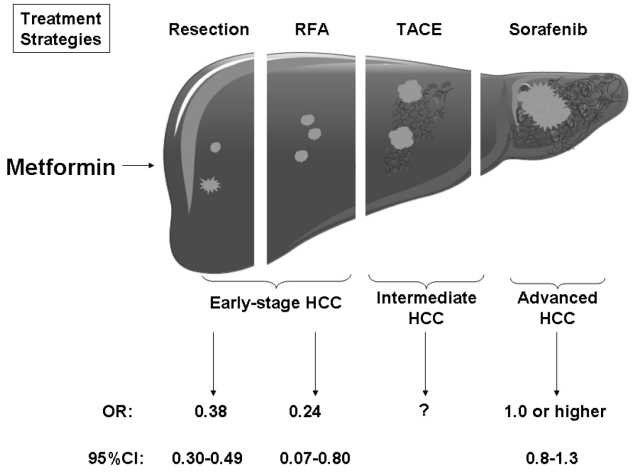

Figure 2. The different effects of metformin on HCC patient survival. HCC with different Barcelona Clinic Liver Cancer stages were treated with relevant clinical practice options. The effects of metformin on the patient survival seem to be related with the different HCC staging or the relevant treatment options. The respective OR and 95% CI are listed below.

Inconsistent results were also reported in other types of cancer. On the one hand, metformin use was linked to better patient survival in colorectal and cervical cancer. The use of metformin could lower cancer-specific mortality in colon cancer by 35% (HR=0.65, 95% CI=0.56-0.76) [43] and in cervical cancer by 21% (HR=0.79, 95% CI=0.63-0.98) [44]. The aforementioned Shanghai population-based study [34] supported that metformin was associated with reduced mortality in patients with colorectal cancer (HR=0.55, 95% CI=0.34-0.88). On the other hand, some studies found no observable differences between patients with or without metformin. Two separate population-based studies conducted in UK [45] and Canada [46] found that there were no benefits of using metformin in controlling breast cancer-specific mortality. Another meta-analysis study tried to investigate the protective effect of metformin against endometrial hyperplasia (a precancerous endometrial disease). This small cohort also failed to make a clear conclusion [47].

It is yet unknown whether these distinct effects of metformin resulted from the severity of disease (cancer staging) or from the interactions between metformin and the applied primary medication. Metformin may be given in too low dose to achieve a reasonable concentration in the target organs or given too late to intervene the advanced cancer. For many T2DM patients, the usual dose of oral metformin is around 2 g per day. Metformin reached its peak plasma concentration of 18 μM after 1.5 g oral dose in 3 h [48], which is substantially lower than those applied in most *in vitro* cellular studies and in experimental animal models. Thus, whether metformin could inhibit cancer development in the clinical settings is questionable. If the dose of metformin is critical to cancer treatment, liver cancer should be the primary cancer affected by metformin, given the fact that metformin specifically accumulated in the liver through the trans-

porter OCT1 [29,49]. If the cancer staging is critical, recent phase-3 large-scale RCT studies like MA.32 study [50] might be able to resolve it.

Conclusions

With the epidemic of T2DM and other metabolic disorders worldwide, the resultant cancer will be steadily increased. Because of the clear association between T2DM and cancer, it is tempting to control cancer risk by applying anti-diabetic drugs. Metformin and Thiazolidinediones (TZD) rather than insulin-raising drugs including insulin, are useful for reduction of cancer risks. Although less studied, experience from HCC and pancreatic cancer suggested that metformin may improve the survival of cancer patients with early-stage cancer. But for the advanced cancer, metformin showed no effect or even worsening the patient outcome. Therefore, it is important to carefully choose the right anti-diabetic medication and the right therapeutic window in cancer prevention and cancer treatment.

Author contributions

P.H. Chen, HQ Dai, WJ Su, and Y Wu searched the literature; G.Z. Zhu and L. Li provided clinical suggestions and organized the data; P.H. Chen drafted the manuscript; Y. Chen prepared the figures; J. Zhou and G.D. Lu designed the research, summarized the data and finalized the paper.

Funding acknowledgements

This work was supported by the National Natural Science Foundation of China (31601120) awarded to J. Zhou; and by the National Natural Science Foundation of China (81672370, 81972291), the Guangxi Natural Science Foundation Key Grant (2018GXNSFDA050006) and the Hundred-Talent Program (2016) awarded to G.D. LU.

Conflict of interests

The authors declare no conflict of interests.

References

1. International Diabetes Federation. IDF Diabetes Atlas (9th Edn). International Diabetes Federation; Brussels, Belgium: 2019.
2. Shlomai G, Neel B, LeRoith D, Gallagher EJ. Type 2 Diabetes Mellitus and Cancer: The Role of Pharmacotherapy. J Clin Oncol 2016;34:4261-9.
3. Tsilidis KK, Kasimis JC, Lopez DS, Ntzani EE, Ioannidis JP. Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies. BMJ 2015;350:g7607.
4. Suissa S, Azoulay L. Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 2012;35:2665-73.
5. Marengo A, Rosso C, Bugianesi E. Liver Cancer: Connections with Obesity, Fatty Liver, and Cirrhosis. Annu Rev Med 2016;67:103-17.
6. Furman D, Campisi J, Verdin E et al. Chronic inflammation in the etiology of disease across the life span. Nat Med 2019;25:1822-32.
7. Baig NA, Herrine SK, Rubin R. Liver disease and diabetes mellitus. Clin Laboratory Med 2001;21:193-207.
8. Singh S, Earle CC, Bae SJ et al. Incidence of Diabetes in Colorectal Cancer Survivors. J Natl Cancer Inst 2016;108:djv402.
9. Onitilo AA, Stankowski RV, Berg RL et al. Breast cancer incidence before and after diagnosis of type 2 diabetes mellitus in women: increased risk in the prediabetes phase. Eur J Cancer Prev 2014;23:76-83.
10. Jenab M, Riboli E, Cleveland RJ et al. Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2007;121:368-76.
11. Ahern TP, Hankinson SE, Willett WC, Pollak MN, Eliassen AH, Tamimi RM. Plasma C-peptide, mammographic breast density, and risk of invasive breast cancer. Cancer Epidemiol Biomark Prev 2013;22:1786-96.
12. Akinyemiju T, Abera S, Ahmed M et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol 2017;3:1683-91.
13. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
14. Sengupta R, Honey K. AACR Cancer Progress Report 2019: Transforming Lives Through Innovative Cancer Science. Clin Cancer Res 2019;25:5431.
15. Yu MW, Lin CL, Liu CJ, Yang SH, Tseng YL, Wu CF. Influence of Metabolic Risk Factors on Risk of Hepatocellular Carcinoma and Liver-Related Death in Men With Chronic Hepatitis B: A Large Cohort Study. Gastroenterology 2017;153:1006-17.e1005.
16. Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. CA A Cancer J Clin 2016;66:115-32.
17. Chang MH, Chen CJ, Lai MS et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. New Engl J Med 1997;336:1855-9.
18. Yu SZ, Chen G, Zhi XL, Li J. Primary liver cancer: natural toxins and prevention in China. J Toxicol Sci (23 Suppl) 1998;2:143-7.

19. Dyson J, Jaques B, Chattopadyhay D et al. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014;60:110-7.
20. Younossi ZM, Otgonsuren M, Henry L et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology (Baltimore, Md.) 2015;62:1723-30.
21. Wu L, Zhu J, Prokop LJ, Murad MH. Pharmacologic Therapy of Diabetes and Overall Cancer Risk and Mortality: A Meta-Analysis of 265 Studies. Sci Rep 2015;5:10147.
22. Giovannucci E, Harlan DM, Archer MC et al. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674-85.
23. Chen HP, Shieh JJ, Chang CC et al. Metformin decreases hepatocellular carcinoma risk in a dose-dependent manner: population-based and in vitro studies. Gut 2013;62:606-15.
24. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. Am J Gastroenterol 2013;108:881-91; quiz 892.
25. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. Cell Metabol 2014;20:953-66.
26. Bridges HR, Jones AJ, Pollak MN, Hirst J. Effects of metformin and other biguanides on oxidative phosphorylation in mitochondria. Biochem J 2014;462:475-87.
27. Andrzejewski S, Gravel SP, Pollak M, St-Pierre J. Metformin directly acts on mitochondria to alter cellular bioenergetics. Cancer Metabol 2014;2:12.
28. Zheng L, Yang W, Wu F et al. Prognostic significance of AMPK activation and therapeutic effects of metformin in hepatocellular carcinoma. Clin Cancer Res 2013;19:5372-80.
29. Jonker JW, Schinkel AH. Pharmacological and physiological functions of the polyspecific organic cation transporters: OCT1, 2, and 3 (SLC22A1-3). J Pharmacol Experim Ther 2004;308:2-9.
30. Pollak MN. Investigating metformin for cancer prevention and treatment: the end of the beginning. Cancer Discov 2012;2:778-90.
31. Wu CW, Farrell GC, Yu J. Functional role of peroxisome-proliferator-activated receptor gamma in hepatocellular carcinoma. J Gastroenterol Hepatol 2012;27:1665-9.
32. Tang H, Shi W, Fu S et al. Pioglitazone and bladder cancer risk: a systematic review and meta-analysis. Cancer Med 2018;7:1070-80.
33. Zhang X, Harmsen WS, Mettler TA et al. Continuation of metformin use after a diagnosis of cirrhosis significantly improves survival of patients with diabetes. Hepatology (Baltimore, Md.) 2014;60:2008-16.
34. Baglia ML, Cui Y, Zheng T et al. Diabetes Medication Use in Association with Survival among Patients of Breast, Colorectal, Lung, or Gastric Cancer. Cancer Res Treat 2019;51:538-46.
35. Seo YS, Kim YJ, Kim MS et al. Association of Metformin Use With Cancer-Specific Mortality in Hepatocellular Carcinoma After Curative Resection: A Nationwide Population-Based Study. Medicine 2016;95:e3527.
36. Chen TM, Lin CC, Huang PT, Wen CF. Metformin associated with lower mortality in diabetic patients with early stage hepatocellular carcinoma after radiofrequency ablation. J Gastroenterol Hepatol 2011;26:858-65.
37. Bhat M, Chaiteerakij R, Harmsen WS et al. Metformin does not improve survival in patients with hepatocellular carcinoma. World J Gastroenterol 2014;20:15750-5.
38. Casadei Gardini A, Faloppi L, De Matteis S et al. Metformin and insulin impact on clinical outcome in patients with advanced hepatocellular carcinoma receiving sorafenib: Validation study and biological rationale. Eur J Cancer 2017;86:106-14.
39. Schulte L, Scheiner B, Voigtlander T et al. Treatment with metformin is associated with a prolonged survival in patients with hepatocellular carcinoma. Liver Int 2019;39:714-26.
40. Li X, Li T, Liu Z, Gou S, Wang C. The effect of metformin on survival of patients with pancreatic cancer: a meta-analysis. Sci Rep 2017;7:5825.
41. Kordes S, Pollak MN, Zwinderman AH et al. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol 2015;16:839-47.
42. Reni M, Dugnani E, Cereda S et al. (Ir)relevance of Metformin Treatment in Patients with Metastatic Pancreatic Cancer: An Open-Label, Randomized Phase II Trial. Clin Cancer Res 2016;22:1076-85.
43. Lega IC, Shah PS, Margel D, Beyene J, Rochon PA, Lipscombe LL. The effect of metformin on mortality following cancer among patients with diabetes. Cancer Epidemiol Biomark Prev 2014;23:1974-84.
44. Han K, Pintilie M, Lipscombe LL, Lega IC, Milosevic MF, Fyles AW. Association between Metformin Use and Mortality after Cervical Cancer in Older Women with Diabetes. Cancer Epidemiol Biomark Prev 2016;25:507-12.
45. Redaniel MT, Jeffreys M, May MT, Ben-Shlomo Y, Martin RM. Associations of type 2 diabetes and diabetes treatment with breast cancer risk and mortality: a population-based cohort study among British women. Cancer Causes Control 2012;23:1785-95.
46. Lega IC, Austin PC, Gruneir A, Goodwin PJ, Rochon PA, Lipscombe LL. Association between metformin therapy and mortality after breast cancer: a population-based study. Diabetes Care 2013;36:3018-26.
47. Clement NS, Oliver TR, Shiwani H, Sanner JR, Mulvaney CA, Atiomo W. Metformin for endometrial hyperplasia. The Cochrane database of systematic reviews 2017;10:Cd012214.
48. Tucker GT, Casey C, Phillips PJ, Connor H, Ward JD, Woods HF. Metformin kinetics in healthy subjects and in patients with diabetes mellitus. Br J Clin Pharmacol 1981;12:235-46.
49. Wilcock C,Bailey CJ. Accumulation of metformin by tissues of the normal and diabetic mouse. Xenobiotica; the fate of foreign compounds in biological systems 1981;24:49-57.
50. Goodwin PJ, Parulekar WR, Gelmon KA et al. Effect of metformin vs placebo on and metabolic factors in NCIC CTG MA.32. J Natl Cancer Inst 1072015.