JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
REVIEW

Cancer biology in diabetes update: Focusing on antidiabetic drugs

Emi Kawakita[1], Keizo Kanasaki[1,2]*

[1]Department of Internal Medicine 1, Faculty of Medicine, Shimane University, Izumo, Japan, and [2]The Center for Integrated Kidney Research and Advance, Faculty of Medicine, Shimane University, Izumo, Japan

Keywords
Antidiabetic drugs, Cancer, Diabetes

***Correspondence**
Keizo Kanasaki
Tel.: +81-853-20-2183
Fax: +81-853-23-8650
E-mail address:
kkanasak@med.shimane-u.ac.jp

J Diabetes Investig 2024; 15: 525–540

doi: 10.1111/jdi.14152

ABSTRACT

The association of type 2 diabetes with certain cancer risk has been of great interest for years. However, the effect of diabetic medications on cancer development is not fully understood. Prospective clinical trials have not elucidated the long-term influence of hypoglycemic drugs on cancer incidence and the safety for cancer-bearing patients with diabetes, whereas numerous preclinical studies have shown that antidiabetic drugs could have an impact on carcinogenesis processes beyond the glycemic control effect. Because there is no evidence of the safety profile of antidiabetic agents on cancer biology, careful consideration would be required when prescribing any medicines to patients with diabetes and existing tumor. In this review, we discuss the potential influence of each diabetes therapy in cancer 'initiation', 'promotion' and 'progression'.

INTRODUCTION

Accumulating evidence suggests the association of type 2 diabetes with an increased risk of cancer incidence and poor prognosis in certain types of cancers[1–3]. Common metabolic abnormalities of type 2 diabetes, such as hyperglycemia, hyperinsulinemia, insulin resistance and chronic inflammation, are known to contribute to cancer development. In addition, long-term use of diabetes medications potentially affects cancer cell biology and the tumor microenvironment. However, the possible cancer risk associated with diabetic medicine has been overlooked by clinicians. Also, treatment algorithms for patients with diabetes and existing cancer are lacking.

When considering the risk of diabetic medicine for malignancies, the carcinogenesis phase must be discussed. Carcinogenesis consists of multiple steps known as cancer initiation, promotion and progression (Figure 1). Cancer 'initiation' is characterized by irreversible genetic damage in cells. In the next 'promotion' step, initiated cells with certain deoxyribonucleic acid damage selectively proliferate, and further additional critical mutations are accumulated in this preneoplastic lesion. Continuous genetic instability induces further mutations, and these cell populations finally acquire malignant phenotypes, such as uncontrolled growth, invasiveness and metastatic capacity, in the 'progression' phase. Randomized controlled trials (RCTs) have been carried out to evaluate the safety profile of diabetic medications; however, such clinical trials were generally performed with a short-term period to observe certain cancer incidence. In addition, individuals with diabetes and existing tumor or active cancer history were excluded in these trials. Therefore, the diabetic agent-mediated risks for cancer promotion and progression are also unknown (Figure 1). Some observational studies showed the cancer progression risk of specific diabetic therapy; however, several methodological limitations cannot be avoided in these retrospective analyses. Furthermore, it is impossible to carry out RCTs evaluating the impact of diabetes treatment on cancer outcomes for ethical reasons, except for metformin, which has shown anticancer potency in several basic and clinical studies. Hence, experimental data are also indispensable to discuss the possible influence of diabetes therapy on the cancer progression process.

The present review focused on the cancer risk of each diabetic treatment. Diabetologist should update the knowledge and be aware the possible effects of diabetic medicines for the cancer 'initiation', 'promotion', and 'progression'.

INSULIN AND INSULIN ANALOGS ON CANCER

Hyperinsulinemia is most relevant to tumor progression in type 2 diabetes. Mechanistically, insulin has been reported to promote cell proliferation, survival and invasiveness in both

Received 20 November 2023; revised 25 December 2023; accepted 8 January 2024

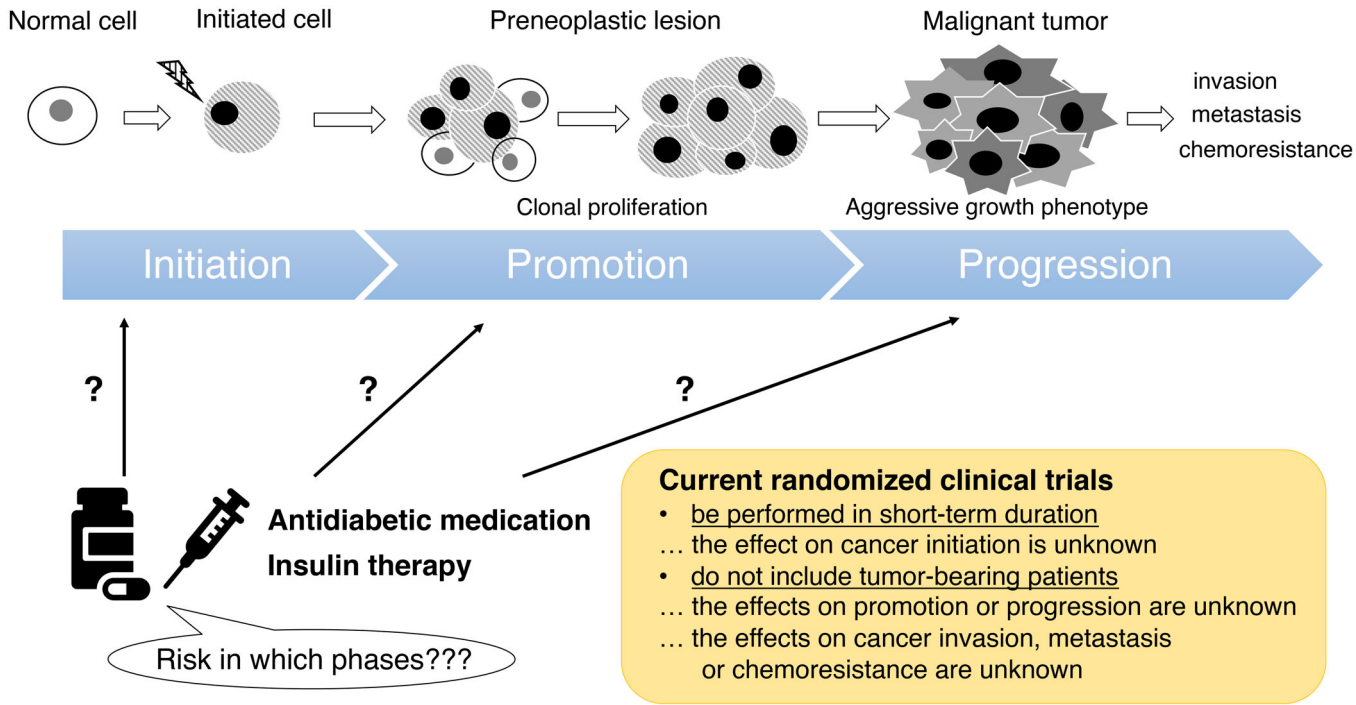

Figure 1 | Cancer risk assessment against each carcinogenesis phase in the current randomized trials of antidiabetic drugs. Cancer is developed through multiple steps including cancer initiation, promotion and progression. In the cancer 'initiation' phase, certain genetic damage irreversibly occurs in a normal cell. This initiated cell clonally proliferates, and this cell population forms a preneoplastic lesion in the next cancer 'promotion' phase. In the final step, known as the cancer 'progression' phase, cell populations with further critical mutations acquire an aggressive growth phenotype, and cancer cells spread throughout the body by invasion and metastasis. Current prospective studies of antidiabetic agents did not evaluate the cancer risk in each carcinogenesis phase.

normal cells and cancer cells. In contrast, a recent preclinical study showed that insulin might act on the gut insulin receptor and modulate intestinal barrier function to attenuate the progression of nonalcoholic steatohepatitis-associated hepatocellular carcinoma[4]. However, there are no clear answers as to whether the exogenous administration of insulin influences cancer development similar to endogenous insulin signals.

The association between insulin therapy and an increased risk of cancer incidence has been debated for years. A retrospective cohort study[5] showed that the incidence of colorectal cancer was higher in insulin users compared with that in non-insulin users among patients with type 2 diabetes. Another meta-analysis of observational studies[6] also supported this result. In addition, another concern is that long-acting insulin analogs might increase some types of cancer incidence compared with neutral protamine Hagedorn insulin. Indeed, insulin analogs were reported to exert cell proliferative and anti-apoptotic effects through their higher binding affinity to insulin-like growth factor-1 receptor than that of human insulin in many types of cancer cell lines[7]. In 2009, two observational studies[8,9] reported that insulin analogs did not increase the risk of cancer incidence, whereas others[10,11] showed the increased risk of cancer occurrence in patients with diabetes treated by insulin glargine compared with human insulin. Regarding the risk for site-specific cancer, some retrospective data represented the insulin glargine-associated breast cancer risk[12–19]. However, several methodological limitations have been pointed out in these observational investigations[18].

For a long-term RCT, the Outcome Reduction with Insulin Glargine (ORIGIN) trial, including a total of 12,537 participants, was carried out to compare the effect of insulin glargine on cardiovascular events with standard care[20]. Safety analysis in this study showed no significant signals in any cancer, death from cancer or cancer at specific sites between the glargine group and standard-care group after a median follow-up period of 6.2 years[20]. The data from follow-up analysis of the ORIGIN trial[21] and meta-analyses[22–24] also represented no association between increased cancer risk and short-term glargine use. However, it must be noted that previous studies did not recruit patients who are typically eligible for insulin therapy in clinic. For instance, the ORIGIN trial included participants with impaired fasting glucose, impaired glucose tolerance or very early/mild type 2 diabetes, who are basically considered for treatment with oral glucose-lowering drugs for first-line therapy. The insulin would be initiated >10 years after the onset of type 2 diabetes; patients with type 2 diabetes often have

suffered from endogenous hyperinsulinemia before initiating insulin therapy.

Regardless of these concerns, there is no doubt about the criticalness of insulin treatment, especially in patients with type 1 diabetes or advanced type 2 diabetes. The appropriate interpretation of these clinical studies is required when considering the necessity of insulin therapy for diabetes.

SULFONYLUREAS, GLINIDE AND CANCER

Increased levels in circulating insulin as a result of the use of sulfonylureas and glinides, insulin secretagogues, have potential effects on cancer biology. Cohort studies showed that the use of sulfonylureas increases the risk of cancer incidence and cancer-related mortality in patients with type 2 diabetes[8,25]. However, this cancer risk associated with sulfonylureas use was found when compared with metformin treatment. In 2012, a study using a Taiwan database also suggested that sulfonylureas and glinides significantly increased the overall cancer incidence in patients newly diagnosed with type 2 diabetes[26]. In contrast, Zhao *et al.*[27] recently showed no relationship between sulfonylureas use and any cancer risk.

Although some retrospective studies have shown the possible association of insulin secretagogues with cancer incidence risk, there are several limitations, as there are with the clinical research of insulin. In addition, prospective studies exploring the safety of insulin secretagogues for carcinogenesis are lacking. Therefore, from current evidence, it is unknown whether the use of sulfonylureas and glinides could have an influence on cancer initiation, promotion and progression in type 2 diabetes.

THIAZOLIDINEDIONES, PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR-γ AND CANCER

Thiazolidinediones (TZDs) act as an insulin sensitizer and a selective agonist of peroxisome proliferator-activated receptor-gamma (PPARγ), which is expressed in many types of cancer cell lines[28–30]. TZDs could modulate cellular differentiation, proliferation and apoptosis both in normal cells and cancer cells[31–36]. In addition, the systemic influence of TZDs treatment, such as improvement of insulin resistance and adipocyte differentiation, potentially plays a protective role in carcinogenesis. Indeed, clinical studies have shown the association of TZDs use with the decreased risk for liver, colorectal, lung, lymphatic, prostate, stomach, kidney, breast and brain cancer[37–44] in patients with diabetes.

Conversely, a preclinical study showed that a TZD, pioglitazone, increases the incidence of bladder cancer in male rats. Also, in a human study, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial including 5,238 participants with type 2 diabetes showed a higher trend of bladder cancer incidence among pioglitazone users compared with placebo (14 vs 6)[45]. A similar imbalance of bladder cancer events was observed in another other RCT (12 vs 8, for the pioglitazone and placebo group, respectively)[46]. As a consequence to the publication of the PROactive trial, the US Food and Drug Administration requested that clinical research defining the safety profile of pioglitazone for bladder cancer development be carried out. A large cohort study[47] showed that pioglitazone use of >2 years is associated with an increased risk of bladder cancer occurrence in patients with diabetes. Tuccori *et al.*[48] also reported the elevation in bladder cancer occurrence by 63% among patients with diabetes prescribed pioglitazone in a large population-based cohort study, whereas rosiglitazone did not exert an increased trend of bladder cancer cases. Observational studies also supported these findings[49–54], whereas others reported no statistically significant increased risk of bladder cancer after treatment with pioglitazone[38,55–63]. Although the concern about bladder cancer incidence in pioglitazone users is still discussed, little is known about the molecular mechanism of how pioglitazone activates bladder cancer initiation or promotion.

Regarding the other types of cancers, several meta-analyses have shown the neutral effect of TZDs on any cancer incidence[40,43,64,65]. In contrast, Lewis *et al.*[55] reported the increased risk of prostate and pancreatic cancer associated with ever use of pioglitazone in cohort and nested case control analyses among patients with diabetes. Recently, the result of a Mendelian randomization analysis exploring the pharmacological perturbation of diabetic medications on cancer risk was published[66]. The authors used *PPARG* as the genetic instrument of the PPARγ agonist target and analyzed a link between *PPARG* variants and the risk of breast, colorectal and prostate cancer. It was found that genetically proxied *PPARG* perturbation is associated with a higher risk of prostate cancer and lower risk of estrogen receptor-positive breast cancer[66].

Altogether, no clear conclusion about the TZDs-associated cancer risk has been drawn to date. However, as uncertainty remains in bladder cancer, careful consideration is needed when using TZDs for the treatment of patients with type 2 diabetes and active bladder cancer or a history of bladder tumor. It is also worth carrying out regular urine testing in patients prescribed pioglitazone as bladder cancer screening. Furthermore, previous research has mainly discussed the risk of cancer initiation or promotion; therefore, it is also necessary to investigate the effect of TZDs and PPARγ activation on cancer 'progression' in cancer-bearing patients with diabetes.

METFORMIN AND CANCER

Metformin has been well established as an anticancer agent. Mechanically, previous basic investigations reported the tumor suppressive effect of metformin through various molecular mechanisms including repression of insulin and insulin-like growth factor-1, the mammalian target of rapamycin (mTOR) pathway inhibition with or without the activation of adenosine monophosphate-activated protein kinase, the accumulation of nicotinamide adenosine dinucleotide and modulation of the immune response or gut microbiota. Metformin also has an indirect influence on cancer biology through the improvement

of glycemic control and insulin resistance. The detailed biological functions of metformin in cancer development have been extensively reviewed elsewhere[67–69].

Several epidemiological data have identified the link between metformin use and the risk reduction in cancer incidence and mortality of patients with diabetes[70–74]. However, in these retrospective studies, time-related biases, such as immortal time bias, cannot be avoided[75,76], thus the clinical efficacy of metformin for cancer was possibly overestimated due to such a limitation. In fact, some large cohort studies and meta-analyses showed no significant benefit of metformin for cancer incidence and outcomes[77–79]. In addition, it has been pointed out that the concentration of metformin used in most previous basic experiments is much higher than that in patients with type 2 diabetes treated by a clinical dose of metformin[80,81]; therefore, whether the results from basic research of metformin can apply to the clinical setting is unknown. From this background, appropriate RCTs are absolutely required to confirm the clinical benefit of metformin in cancer-bearing patients.

A large number of randomized clinical studies of metformin were carried out in patients with multiple types of cancers. The completed phase II or III RCTs evaluating the efficacy of metformin with standard cancer therapy for tumor-bearing patients without diabetes are summarized in Table 1. Despite the metformin's antitumor potential, most phase III trials failed to show favorable outcomes in the metformin treatment group (Table 1). For instance, Goodwin *et al.*[82] carried out a phase III study to confirm whether the adjuvant metformin treatment improves outcomes of patients without diabetes who received standard therapy for breast cancer. A total of 3,649 participants were randomly assigned to the metformin (850 mg of oral metformin twice a day for 5 years) or placebo group. Although metformin significantly improved bodyweight and metabolic factors[83,84], adjuvant metformin did not ameliorate invasive disease-free survival in high-risk operable breast cancer patients[82]. This finding is consistent with the results from previous randomized phase II studies examining metformin's effect in patients with metastatic breast cancer[85–87]. In contrast, there are some phase II RCTs showing that metformin improved clinical outcomes in hormone receptor-positive breast cancer patients[88,89].

Heterogeneity of cancer outcomes has been found in clinical trials for lung cancer patients. Some studies showed the improved progression-free survival in non-small cell lung cancer (NSCLC) patients with standard chemotherapy plus metformin[90,91], whereas other studies reported no survival benefit of NSCLC patients with metformin treatment[92–94]. Neutral effects, as well as unfavorable cancer outcomes associated with metformin prescription, were also published. In a phase II study, 2,000 mg daily treatment of metformin with standard chemoradiotherapy for 1 year was associated with worse outcomes in patients with NSCLC[95]. Furthermore, a higher trend of adverse events, such as esophagitis and lung infection, in the metformin group was observed in this trial[95]. Another study also showed the addition of metformin to gefitinib remarkably increases incidence of diarrhea compared with the gefitinib plus placebo group in NSCLC participants[92]. We must know the specific features of patients who are potentially sensitive to the antitumor effect of metformin without critical adverse events. In regard to this, Lee *et al.*[94] reported that chemotherapy with metformin significantly decreased progression and death in squamous lung cell carcinoma patients with higher fluorodeoxyglucose uptake on positron emission tomography imaging.

A prospective study showing the antitumor efficacy of metformin was also published. Higurashi *et al.*[96] carried out a RCT to evaluate the preventive effect of metformin against colorectal cancer. This study included a total of 498 Japanese participants without diabetes who had single or multiple colorectal adenomas or polyps resected by endoscopy. Treatment of 250 mg daily metformin for 1 year significantly reduced the prevalence and number of metachronous adenomas or polyps after polypectomy[96]. A systematic review and meta-analysis also showed the significant benefit of metformin for cancer outcomes in colorectal cancer patients with curative-intent treatment[97]. Some phase II clinical trials also supported the benefit of metformin against colorectal cancer prognosis[98,99]. As the accumulation of metformin in the gastrointestinal tract was reported, as well as in the liver and kidneys[100–103], metformin might exert a protective effect on gastrointestinal cancer. In contrast, no beneficial impact of metformin on overall survival or relapse-free survival in resected colon cancer-bearing patients treated with adjuvant chemotherapy was published[104].

Randomized efficacy trials evaluating the clinical benefit of metformin were also carried out in patients with bladder[105], cervical[106], esophageal[107], liver[108], ovary[109,110], pancreas[111,112] and prostate cancer[113–115]. Although some human studies have shown the protective effect of metformin on cancer development, many prospective studies failed to show the improvement in primary endpoints, such as disease-free survival (DFS) and overall survival, in cancer-bearing patients treated with metformin plus standard cancer therapy. This heterogeneity in the outcomes of previous RCTs potentially depends on the differences in clinical background, such as cancer type, clinical stage and the presence or absence of combined therapy. It is estimated that appropriate selection of therapeutic target patients is necessary to see the clinical benefit of metformin treatment for cancer-bearing patients. Also, the influence of metformin on patients with diabetes and cancer remains to be elucidated.

INCRETIN-BASED THERAPIES AND CANCER

Incretin-based drugs, such as dipeptidyl peptidase (DPP)-4 inhibitors (DPP-4is) and glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs), are commonly used antitherapeutics for the treatment of patients with type 2 diabetes. Incretin hormones induce glucose-dependent insulin secretion from the islet β-cells. DPP-4is improve glycemic control through the inhibition of incretin hormones degradation; whereas

Table 1 | Phase II and III randomized clinical trials examining the clinical impact of metformin in cancer progression

Tumor type	Study design	Primary endpoint and results		Ref.
Phase II randomized trials evaluating the impact of metformin on clinical cancer outcome as a primary endpoint				
Early HER2$^+$ breast cancer	Metformin with trastuzumab plus chemotherapy	pCR rate	Succeed: Higher pCR rate in metformin	88
HER2$^+$ stage 2/3 breast cancer	Neoadjuvant therapy plus ganitumab ± metformin	pCR rate	Succeed: Higher pCR rate in ganitumab and metformin	89
Advanced hormone receptor$^+$ breast cancer	Aromatase inhibitor plus metformin or placebo	PFS	Failed: No differences in PFS	86
Advanced HER2$^-$ breast cancer	Chemotherapy ± metformin	PFS	Failed: No differences in PFS	87
Metastatic breast cancer	1st to 4th line chemotherapy plus metformin or placebo	PFS	Failed: No difference in PFS	85
Advanced NSCLC with EGFR mutation	Gefitinib plus metformin or placebo	PFS	Failed: No difference in PFS at 1 year metformin group increased toxicity	92
Locally advanced NSCLC	Chemoradiation ± metformin	PFS	Failed: No difference in PFS at 1 year	93
Locally advanced NSCLC	Chemoradiotherapy ± metformin	Proportion of patients who experienced a failure event	Failed: The addition of metformin associated with worse treatment efficacy and increased toxic effects	95
Advanced NSCLC with EGFR-ALK wild type	Chemotherapy ± metformin	Survival benefit	Failed: No differences in progression and death	94
Advanced non-squamous NSCLC	Chemotherapy ± metformin	PFS	Succeed: Higher 1-year PFS with metformin	90
Advanced lung adenocarcinoma with EGFR mutation	EGFR-TKIs ± metformin	PFS	Succeed: Longer PFS with metformin (HR 0.60)	91
Metastatic CRPC	Docetaxel plus metformin or placebo	PSA response	Failed: No differences in PFS-response rate	113
Hormone sensitive prostate cancer	Standard androgen deprivation therapy ± metformin	CRPC-free survival	Succeed: Longer CRPC-free survival with metformin (29 vs 20 months)	114
Prostate cancer with overweight or obesity	Bicalutamide ± metformin	The number of patients with undetectable PSA	Failed: No improvement in achieving undetectable PSA (<0.2 ng/mL) at 32 weeks	115
Advanced pancreatic cancer	Gemcitabine and erlotinib with metformin or placebo	OS	Failed: No differences in OS at 6 months	111
Metastatic pancreatic cancer	Chemotherapy ± metformin	PFS	Failed: No differences in PFS at 6 months	112
Epithelial ovarian cancer	Chemotherapy ± metformin	PFS and DFS	Failed: No differences in PFS and DFS	109
Phase III randomized trials metformin vs placebo in tumor-bearing patients				
Early breast cancer	Adjuvant metformin or placebo	Invasive DFS in ER/PgR$^+$ breast cancer	Failed: No difference in DFS	82
Atypical hyperplasia or endometrial cancer	Metformin or placebo for 1–5 weeks until hysterectomy	Post-treatment IHC expression of Ki-67	Failed: No difference in Ki67 expression	187
Advanced endometrial cancer	Paclitaxel and carboplatin with metformin or placebo	OS	Failed: No difference in OS	188
Colorectal adenomas or polyps resected by endoscopy	Metformin or placebo until 1-year follow-up colonoscopy	The number and prevalence of adenomas or polyps	Succeed: Metformin reduced the number and prevalence of adenomas or polyps after polypectomy	96

CRPC, castration-resistant prostate cancer-free survival; DFS, disease-free survival; EGFR, epidermal growth factor receptor; ER/PgR, estrogen receptor and/or progesterone receptor; HER2, human epidermal growth factor receptor type 2; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival; PSA, Prostate-Specific Antigen; TKIs, tyrosine kinase inhibitors.

GLP-1RAs mimic incretin activity. An increasing number of patients with type 2 diabetes are treated with these medications; however, the safety profile of incretin-based drugs for cancer risk is still debated. In particular, the effect on pancreatic β-cells and thyroid cells when the GLP-1 receptor is activated has often been discussed. Furthermore, DPP-4 plays diverse roles in cancer development, thus, DPP-4is treatment possibly has an unexpected impact on cancer-bearing patients beyond the incretin-mediated action.

In the GLP-1RAs part, we mainly focused on possible common risk for cancers in incretin therapy; whereas, in the DPP-4is part, we discussed the molecular mechanism of DPP-4 deficiency in cancer progression processes, including our recent basic data.

EFFECTS OF GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS ON CANCER: FOCUSING ON CLINICAL EVIDENCE

In 2011, the increased risk for pancreatitis, pancreatic cancer and thyroid cancer in patients with diabetes prescribed DPP-4i sitagliptin or GLP-1RA exenatide was reported by analyses of the US Food and Drug Administration adverse events reporting database[116]. For the concerns about pancreatic cancer, Butler *et al.*[117] showed that incretin therapy induces proliferation and dysplasia of exocrine and endocrine pancreatic mass in patients with type 2 diabetes. In contrast to this concern, the large multicenter population-based cohort study reported that incretin drugs were not associated with an increased risk of pancreatic cancer when compared with sulfonylurea treatment, regardless of the treatment duration[118]. In fact, the cardiovascular outcomes trials (CVOTs) of DPP-4is[119–122] and GLP-1RAs[123–129] showed no significant relationship between incretin treatment and the increased number of pancreatic cancer events, even though a slight, but numerically higher, number of pancreatic cancers were observed with DPP-4is[119,122,130]. The meta-analysis of CVOT studies and other RCTs also reported no elevated risk of pancreatic cancer incidence in patients with type 2 diabetes receiving incretin-based therapy[131–133]. However, these CVOTs were carried out with short drug exposure time; therefore, the risk of long-term use of incretin drugs is not fully elucidated. Indeed, chronic activation of the GLP-1 receptor by 12 weeks of exendin-4 injection to $Kras^{G12D}$ mice was reported to induce chronic pancreatitis with increased dysplastic lesions, known to be a precursor for pancreatic cancer[134]. It was also published that DPP-4i treatment increases the risk of acute pancreatitis occurrence by 75%[131]. Pancreatitis is an important risk factor of pancreatic cancer initiation and promotion. Hence, the impact of long-term use of incretin therapy on pancreatic cancer development also remains a topic of interest.

The increased risk of thyroid cancer incidence in incretin users has also been debated. Mechanistically, the expression of GLP-1 receptor was observed in human medullary thyroid carcinoma and C cell hyperplasia[135,136]. Dore *et al.*[137] explored the data form active safety surveillance system and found that a GLP-1RA exenatide treatment modestly increased the number of inpatient and outpatient claims for thyroid malignancies. Also, the elevated incidence of all thyroid cancer and medullar thyroid cancer associated with the 1–3 years' use of GLP-1RAs was shown by analysis of the database including type 2 diabetes in French[138]. Conversely, other observational research established no relationship between the use of GLP-1RAs and thyroid cancer occurrence[139].

It was also reported that the elevated level of GLP-1 or GLP-1RA induces tumor proliferation and anti-apoptotic response in cholangiocytes[140–142]. In this regard, Abrahami *et al.*[143] found a significant association between incretin drugs prescription and an increased risk of cholangiocarcinoma in patients with type 2 diabetes. This population-based cohort study showed a 77% increased risk of cholangiocarcinoma incidence among DPP-4is users compared with other antidiabetic drugs. Although retrospective studies often include a methodological shortness, such as a prescription bias, cholangiocarcinoma is a progressive cancer type, like pancreatic cancer, thus the possible risk of incretin therapy for these rare types of cancer cannot be ignored.

Despite these findings suggesting the cancer incidence risk associated with incretin drugs use, there is strong evidence showing the clinical benefit of GLP-1RAs treatment against renal–cardiovascular diseases in patients with diabetes[123–129]; however, all RCTs with DPP-4is never showed such an organ protective influence[119–122]. Therefore, when prescribing these incretin-based drugs, clinicians should consider their benefits versus risk, such as the influence on cancer biology.

DPP-4 INHIBITORS AND CANCER BIOLOGY

DPP-4 is a multifunctional glycoprotein and expressed in various types of cells, including cancer cells[144]. For enzymatic action, DPP-4 cleaves not only incretin hormones, but also numerous polypeptides, such as chemokines, neuropeptide and growth factors. Several preclinical studies have reported DPP-4 plays multiple roles in cancer biology, thus, an inhibition of DPP-4 could have an influence on cancer itself, the tumor microenvironment and the immune system. In fact, many basic data have raised concerns about DPP-4 suppression in patients with existing tumors.

In regard to the risk of cancer initiation, a prospective controlled study including 5,969 Japanese patients with type 2 diabetes showed that the incidence of cancer was higher in the DPP-4i alogliptin treatment group than in the other types of oral hypoglycemic agents group for a 3-year period[145]. However, the association between alogliptin use and site-specific cancer risk was not found. Also, the alogliptin usage group included more elderly participants and smokers than that of the other oral hypoglycemic agents group; this imbalanced patient distribution might contribute to the increased number of cancer events in DPP-4is users[145]. Caution is required to evaluate the risk for cancer incidence from clinical data of antidiabetic drugs.

Several basic studies have addressed the influence of DPP-4is on cancer progression. Suppression of DPP-4 was reported to induce cancer cell adhesion, migration and invasion[146,147]. Wang *et al.*[148] showed that DPP-4is, saxagliptin and sitagliptin increase tumor metastasis of multiple cancers through activation of the nuclear factor E2-related factor 2-mediated antioxidant response. For another possible mechanism, we have previously elucidated that DPP-4 inhibition accelerates breast cancer progression through its substrate C-X-C motif chemokine 12-mediated pathway. C-X-C motif chemokine 12 binds to C-X-C chemokine receptor 4 (CXCR4) and plays significant role in several physiological processes[149]. CXCR4 is expressed in many cancers and its overexpression in human tumor tissues was reported to be associated with poor

prognosis in various types of cancer[150]. We found that DPP-4 suppression increases the level of C-X-C motif chemokine 12 through inhibition of its cleavage, that consequently activates the CXCR4–downstream mTOR pathway and induces epithelial–mesenchymal transition (EMT) in breast cancer[151]. EMT is believed to be an important process, in which cancer cells acquire mesenchymal features to promote cancer progression. Indeed, the induction of EMT by DPP-4 inhibition in breast cancer cells resulted in primary tumor metastasis and chemoresistance (Figure 2)[151,152]. These undesirable effects of DPP-4i were canceled by the CXCR4 inhibitor, AMD3100, and mTOR inhibitor, rapamycin, showing that DPP-4 suppression accelerates breast cancer progression through the CXCR4/mTOR dependent mechanism. More recently, we detected the CXCR4/mTOR-mediated autophagic regulation by DPP-4i as a breast cancer cell survival mechanism. In $CXCR4^{+}$ breast cancer cells, DPP-4 knockdown and pharmacological inhibition of DPP-4 induce autophagy and anti-apoptotic reaction in a CXCR4/mTOR/hypoxia-inducible factor-1α dependent manner; the antidiabetic agent, metformin, could cancel DPP-4i-induced breast cancer progression by suppressing mTOR pathway activation (Figure 2)[153]. In contrast to breast cancer cells, DPP-4 suppression showed no impact on normal breast cell autophagy and apoptosis[153]. In this line, it was reported that DPP-4i suppresses the mTOR pathway and autophagic response in a non-cancer animal model[154]. As the significance of DPP-4 inhibition in cell biology might be different depending on cell types and host conditions, DPP-4 suppression might act protectively in cancer progression under different experimental conditions.

For clinical evidence, some retrospective analyses showed that DPP-4i treatment has a neutral or protective impact on cancer outcome in patients with diabetes[155,156], whereas a nationwide study in Hungary showed that DPP-4i users have higher mortality from cancer compared with the sodium–glucose cotransporter 2 (SGLT2) inhibitors cohort[157]. It is difficult for these studies to match patients' profiles associated with cancer and diabetes; hence, we cannot conclude the real risk of DPP-4i treatment for cancer progression in type 2 diabetes patients. In addition, there are few clinical studies exploring the impact of DPP-4is on cancer outcome in specific conditions, such as postoperation, chemotherapy and radiotherapy. In this regard, Saito *et al.*[158] retrospectively examined the postoperative outcome of colorectal cancer in patients with type 2 diabetes prescribed DPP-4i. Treatment with DPP-4i was associated with significantly lower postoperative DFS compared with that in DPP-4i nonusers (5-year DFS, 73.7% vs 87.4%; hazard ratio 1.98; $P = 0.035$). Also, the DFS of patients who have continued DPP-4i after colectomy was shorter than those not treated with DPP-4i (hazard ratio 2.44; $P = 0.0090$). In mechanistic exploration, immunostaining of tumors showed that DPP-4i users have

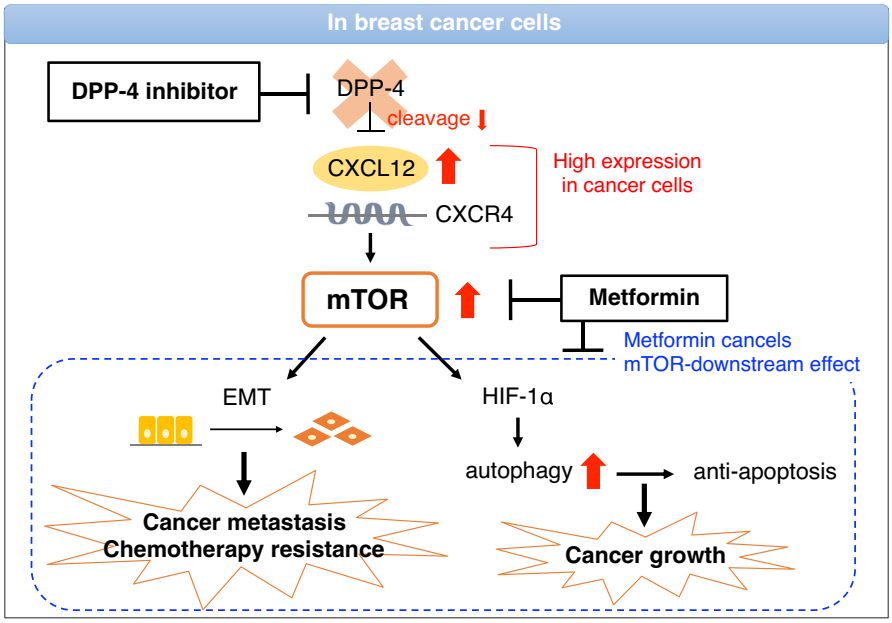

Figure 2 | Dipeptidyl peptidase (DPP)-4 inhibitor accelerates C-X-C motif chemokine 12 (CXCL12)/mammalian target of rapamycin (mTOR)-mediated breast cancer progression; metformin mitigates DPP-4 inhibitor-induced undesirable effects through mTOR suppression. C-X-C chemokine receptor 4 (CXCR4) is known to highly express in multiple cancers, including breast cancer. DPP-4 inhibitor suppresses the cleavage of CXCL12 by DPP-4, which induces a downstream CXCL12/CXCR4/mTOR pathway. DPP-4 suppression-mediated mTOR activation results in breast cancer metastasis and chemotherapy resistance by induction of the epithelial–mesenchymal transition (EMT) process. Also, mTOR induces an autophagic response to promote breast cancer cell survival in a hypoxia-inducible factor-1α (HIF-1α)-dependent manner. Metformin could abolish these mTOR-downstream effects induced by DPP-4 inhibitor.

an increased number of EMT marker Zeb1-positive tumor cells and reduced density of tumor-infiltrating immune cells compared with nonusers[158]. Interestingly, they also showed combination use of metformin canceled such deleterious influence of DPP-4i on postoperative colon cancer patients with diabetes. Importantly, Saito's data raised the concern that DPP-4 inhibition affects the cancer outcome in certain types of cancer and in specific patients' conditions. We require future investigation evaluating not only the overall cancer risk of DPP-4i treatment, but also the cancer progression risk in more specific patient populations.

Altogether, there is no clear evidence showing that DPP-4is worsen the cancer outcome in patients with diabetes and malignancy. However, DPP-4 suppression could have unexpected effects on cancer biology through its numerus molecular functions. Diabetologists need to carefully choose the target patients for treatment, especially in tumor-bearing individuals with type 2 diabetes.

SODIUM–GLUCOSE COTRANSPORTER 2 INHIBITORS AND CANCER

Growing evidence has shown the protective effect of SGLT2 inhibitors (SGLTis) on cardiovascular, renal, and mortality events in patients with[159–163] and without type 2 diabetes[164–168]. Although almost more than a decade was passed since SGLT2is were first put on the market, there is no clear evidence suggesting an increased risk of cancer incidence associated with SGLT2is treatment in individuals with diabetes. However, the numbers of patients taking SGLT2i are increasing due to its clinical benefit, thus, clinicians need to update the information about the possible influence of this class of drug on cancer initiation, promotion and progression.

Inhibition of SGLT2 induces exposure to the urinary tract in the high glucose condition, thereby, the long-term effect of SGLT2is for the urinary tract has been a controversial topic. Animal studies showed the long-term use of high-dose SGLT2is possibly induces the carcinogenicity[169,170]; however, it is unknown whether these data are relevant to humans. In a premarketing RCT[162] of a SGLT2i, dapagliflozin, the numeric imbalances in cases of bladder and breast cancer between the dapagliflozin group and control group were pointed out (bladder cancer, 9 vs 1; breast cancer, 10 vs 3 for dapagliflozin and control, respectively), whereas the post-marketing CVOT study showed a lower rate of bladder cancer incidence in the dapagliflozin treatment group compared with that in the placebo group. In other RCTs of SGLT2is, the imbalance in bladder cancer cases was also observed a empagliflozin trial[159], but not in a canagliflozin trial[160]. There was a small number of bladder cancer patients in these SGLT2is trials, thus, the number of cancer events was possibly overestimated. Indeed, a pooled analysis[171] and meta-analyses[172] of RCTs showed no significant association of SGLT2is use with an increased risk of overall cancer incidence. A large cohort study also showed that short-term use of SGLT2is was not associated with an increased risk of bladder cancer compared with GLP-1RAs or DPP-4is[173]. However, in a subgroup analysis of prespecified types of cancer, SGLT2is were found to be significantly associated with the increased risk of bladder cancer incidence than comparators (odds ratio 3.87, 95% confidence interval 1.48–10.08), especially with empagliflozin treatment (odds ratio 4.49, 95% confidence interval 1.21–16.73)[172]. Further prospective studies and meta-analyses with long duration are needed in the future to evaluate the influence of SGLT2is treatment on initiation of certain types of cancers.

Contrary to the possible risk of SGLT2is for cancer incidence, many preclinical studies have shown the protective effects of SGLT2 inhibition in cancer progression. Several basic and clinical investigations have elucidated that SGLT2is could mitigate the development of nonalcoholic steatohepatitis[108], which is one of the important risk factors of liver cancer initiation or promotion. In this line, animal studies showed that a SGLT2i canagliflozin attenuates the development of hepatocellular carcinoma through the suppression of hepatic steatosis, inflammation, fibrosis and pro-angiogenic activity[174–176]. Another possible mechanism of SGLT2i's antitumor activity is targeting the extrarenal expression of SGLT2. In addition to glucose transporters, SGLT2 was found to express in human pancreatic, prostate and lung tumors[177,178]. Scafoglio *et al.* showed the expression of SGLT2 is mainly detected in early-stage and well-differentiated lesions of lung adenocarcinoma; whereas glucose transporter 1 is highly expressed in poorly differentiated tumor cells. They found that treatment with canagliflozin attenuates tumor growth and improves survival through suppression of SGLT2 in lung adenocarcinoma model mice[178]. This study raised the possibility of SGLT2 expression in cancer as the therapeutic target of early lung adenocarcinoma. More recently, Ding *et al.*[179] found that SGLT2 is colocalized with programmed death-ligand 1 at the plasma membrane and prevents proteasome-dependent degradation of programmed death-ligand 1. SGLT2 inhibition by canagliflozin and gene silencing both modulated anti-tumor immunity through restoring programmed death-ligand 1 expression and significantly suppressed tumor progression in a mouse model[179]. The expression of SGLT2 and its role in multiple types of cells and organs are of future interest.

Taken together, the possible risk of long-term use of SGLT2is for cancer incidence remains to be elucidated. In contrast, several findings implied the protective effect of SGLT2is for cancer promotion and progression through diverse pathways. Accumulation of further data is needed in future to evaluate the effect of SGLT2 inhibition on cancer promotion and progression of patients with diabetes.

OTHER ORAL HYPOGLYCEMIC AGENTS AND CANCER

There are a few retrospective studies investigating the association between cancer risk and alpha-glucosidase inhibitors (AGIs) use in patients with type 2 diabetes. A large cohort study of diabetes patients in Taiwan showed that an AGI,

acarbose, use reduces the risk of colorectal cancer incidence[180]. Some meta-analysis of observational studies also supported these data[181], whereas the other represented the increased cancer risk associated with AGIs treatment[182]. To date, no serious concern about certain cancer risk with AGIs prescription has been published.

Imeglimin is a new class of antidiabetic agent, which was approved in 2021 for type 2 diabetes treatment in Japan. This drug exerts a glucose-lowering effect by targeting mitochondria biogenesis to ameliorate β-cell function and insulin sensitivity. In addition, imeglimin is known to induce the gene expression of nicotinamide phosphoribosyl transferase, which results in an increase in cellular nicotinamide adenine dinucleotide[183,184]. Nicotinamide phosphoribosyl transferase is often expressed in various tumor tissues, and its inhibition has been established to be a therapeutic target of cancer[185,186]. Therefore, careful observation is needed to conclude the long-term effect of imeglimin-mediated nicotinamide phosphoribosyl transferase modulation on cancer development.

CONCLUSION

Great advances in diabetes medication have significantly improved the prognosis of type 2 diabetes patients. Although current evidence suggests the association between type 2 diabetes and the increased risk of certain cancer incidence and poor prognosis, the possibility that long-term use of antidiabetic agents influences carcinogenesis has not been fully discussed yet. For cancer initiation risk, uncertainty remains with some drugs, such as insulin glargine and pioglitazone. Also, cancer progression risk is hypothesized for drugs with pleiotropic effects on cancer biology, such as DPP-4is. However, there are no prospective studies evaluating the influence of antidiabetic drugs on tumor progression, hence, we cannot draw any conclusions about the possible risk of diabetes treatment in cancer-bearing patients. As an exception, the clinical efficacy of metformin as cancer treatment has been well investigated for recent years; however, most results have been disappointing to date.

Further investigations are required to elucidate the possible effect of each diabetic agent for cancer initiation, promotion and progression. A certain treatment algorithm for patients with diabetes and cancer is also needed in the future.

ACKNOWLEDGMENTS

This study was partially supported by a Grant for JSPS KAKENHI awarded to EK (23K14567). KK is supported by a grant from the Japan Society for the Promotion of Science (22K08330), and the grant from The Ministry of Health Labor and Welfare (202112004A). KK is under a consultancy agreement with Boehringer Ingelheim. KK collaborated with Boehringer Ingelheim, Taisho Pharma and Kowa for a project not related to this manuscript. The author's department in Shimane University was supported by funds from Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Taisho Pharmaceutical, Ono Pharmaceutical, Bayer, Kowa, Nipro and Life Scan Japan. KK received lecture honoraria from Dainippon-Sumitomo Pharma, Astellas, Astra Zeneca, Ono, Otsuka, Taisho, Tanabe-Mitsubishi, Eli Lilly, Boehringer-Ingelheim, Novo Nordisk, Bayer, Sanofi and Kowa. KK is the recipient of the Japan Diabetes Society Carrier Development Award supported by Sanofi.

DISCLOSURE

KK is an Editorial Board member of *Journal of Diabetes Investigation* and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication. The authors declare no conflict of interest.
Approval of the research protocol: N/A.
Informed consent: N/A.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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