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INCRETIN-BASED THERAPY AND CANCER: ARE THEY ENEMIES OR ALLIES?

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The link between cancer and diabetes is established but not fully understood. Incretin-based therapy has been increasingly used in the past decade for the management of type 2 diabetes mellitus (T2DM). A link between incretin pathway and cancer has been proposed. Still a debate in the scientific committee is rising whether incretin-based therapy has beneficial or harmful effects on patients with malignant diseases or at risk of malignancy. This review summarizes the published preclinical and clinical research discussing incretin-based therapy and cancer. Except for pancreatic cancer, thyroid cancer, and cholangiocarcinoma, the published data agree that incretin-based therapy has either a beneficial or zero effect on the risk of malignancy. Regarding pancreatic cancer, there are case reports of pancreatic cancer after receiving incretin-based drug therapy but the lag time for tumorigenesis is questionable. To date, meta-analyses agreed that no increased incidence of pancreatic cancer was observed among users of incretin-based therapy. Whether incretin-based therapy increases the risk of thyroid cancer is controversial therefore it is advisable to avoid prescribing glucagon-like peptide-1 receptor agonists (GLP-1RAs) for patients with high risk for thyroid cancer. Despite the numerous studies published about incretins and cancer, it is still a rich area for further research

Keywords: *Cancer; Incretin; Glucagon-like peptide-1; Dipeptidyl peptidase 4 inhibitors; Type 2 diabetes mellitus*

INTRODUCTION

Cancer is one of the leading causes of death worldwide as it was reported to be responsible for about 10 million deaths in 2020 by the international agency for research on cancer [1]. It is worth mentioning that around 18% of cancer patients worldwide are diabetics but the percentage can vary depending on the population and cancer type[2].

Diabetes mellitus is an alarming growing health problem that affects around 540 million people worldwide and this number is expected to increase to 783 million by the year 2045. About 90% of those patients suffer from type 2 diabetes mellitus (T2DM)[3]. Studies have observed an increased risk of different types of cancer in diabetic patients including breast, lung, endometrial, bladder, stomach, pancreas, liver, and colorectal cancer with 11% higher mortality compared to non-diabetics[4]. Several studies have investigated the underlying mechanisms associated with increased risk of cancer in diabetic patients including hyperinsulinemia, insulin resistance, increased oxidative stress and inflammation[4].

Incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) released from L-cells and K-cells, respectively, are peptides that potentiate meal-stimulated insulin secretion, in addition to other effects as summarized in **Fig. 1**. These peptides have a very short half-life owing to their degradation by dipeptidyl-peptidase 4 (DPP-4) enzyme and their renal clearance[5].

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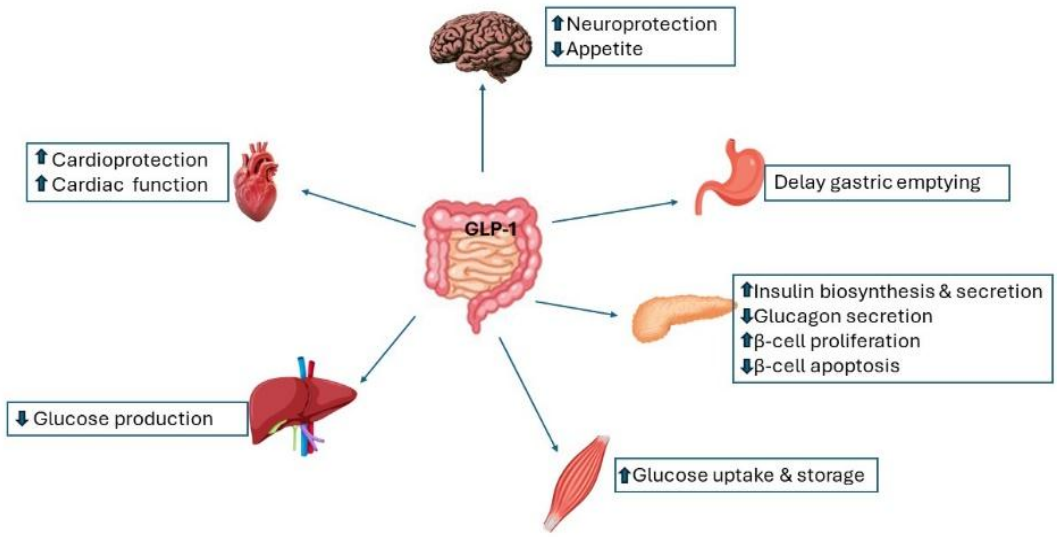

Fig. 1: Effect of glucagon-like peptide-1 in different organs, modified from[5].

In the past decade, incretin-based therapy has been increasingly used for the management of T2DM. Incretin-based therapy includes potentiation of endogenously secreted incretins by inhibiting DPP-4 and using glucagon-like peptide-1 receptor agonists (GLP-1RAs). These drugs were introduced into clinical practice starting from 2006 after FDA approval of exenatide and sitagliptin[6, 7]. They are widely used because of their beneficial effect on glycemic control, beta-cell functions, blood lipids level and blood pressure in addition to their few side effects and low risk of hypoglycemia[8].

GLP-1 receptors are widely expressed in many tissues besides the pancreas including kidneys, lungs, cardiovascular and central nervous systems, gastrointestinal tract, as well as the skin[9]. In addition,, GLP-1R is also found in some tumors such as thyroid cancer, pheochromocytoma, insulinoma, and brain tumors [10]. Regarding expression of DPP-4, it is found in kidneys, vascular endothelial cells, hepatocytes, and intestinal mucosal cells. It is also found in a soluble form in plasma, bile, cerebrospinal fluid, seminal fluid, and synovial fluid. In addition, it is expressed on immune cells as natural killer cells, T-cells, B-cells, and macrophages. For its role in the immune system, it is also known as CD-26 [11]. Studies have found that DPP-4 expression is increased in some cancers such as acute leukemia [12], lung papillary adenocarcinoma, prostate cancer, hepatocellular carcinoma, brain tumors, thyroid cancer, and breast cancer, while decreased in some other types of cancer as melanoma, endometrial adenocarcinoma, Sezary syndrome and squamous cell carcinoma [13].

Incretin-based therapy and pancreatic cancer

GLP-1R activation can lead to pancreatic cancer, where the hypothesis came from, and is it true?

Since the use of GLP1RAs such as liraglutide and exenatide have been linked to clinical cases of pancreatitis[27, 28], a hypothesis suggesting that activation of GLP1Rs can cause pancreatitis and may even lead to pancreatic cancer after long-term use has come to the surface. This was based on the studies linking chronic pancreatitis with an increased risk of developing pancreatic cancer[29]. Chronic inflammation and pancreatic duct stenosis with increased intraductal pressure can lead to pancreatic cancer [30]. This has been established in chronic pancreatitis, but not in cases of acute pancreatitis. This finding is in favor of GLP1RAs as most cases of pancreatitis reported with the use of GLP1RAs were acute not chronic[31]. In this review, we will discuss the studies both preclinical and clinical that either prove or decline the hypothesis that incretin-based therapy can increase the risk of developing cancer.

Table 1: Approved and under-investigations glucagon-like peptide-1 receptor agonists (GLP1RAs).

GLP-1RA	Trade Name	Half-life	Dose	Approval Date	Administration
Exenatide [6]	Byetta®	2.4 h	5 µg-10 µg	28 April 2005 (FDA)	Before meal BID (S.C)
Exenatide-extended release[14]	Bydureon®	2 weeks	2 mg	27 Jan 2012 (FDA)	Once weekly (S.C)
Exenatide-osmotic mini-pump[15]	Itca-650®	———	20-60 µg/day	Not approved yet	subcutaneous delivery via an osmotic mini pump surgically placed under the skin
Liraglutide[16]	Saxenda® Victoza®	13 h	0.6mg, 1.2mg, 1.8mg, 2.4mg, 3mg	**For obesity:** 23 Dec 2014(FDA) 23 March2015(EMA) **For T2DM:** 25 Jan 2010 (FDA) 30 June 2009 (EMA)	Once daily (S.C)
Albiglutide[17]	Tanzeum®	6-8 days	30 mg, 50 mg	15 April 2014 (FDA)	Once weekly (S.C)
Dulaglutide[18, 19]	Trulicity®	5.5 days	0.75 mg, 1.5 mg, 3 mg, 4.5 mg	18 Sep 2014 (FDA) 21 Nov 2014 (EMA)	Once weekly (S.C)
Semaglutide[20]	Ozempic® Wegovy®	7 days	0.25 mg, 0.5mg,1mg, 2mg 0.25mg, 0.5mg,1mg,1.7m, 2.4mg	**For T2DM:** 5 Dec 2017 (FDA) 8 Feb 2018 (EMA) **For obesity:** 4 June 2021 (FDA) 6 Jan 2022 (EMA)	Once weekly (S.C)
Semaglutide[20]	Rybelsus®	7 days	3mg, 7mg, 14mg	20 Sep 2019 (FDA) 3 April 2020 (EMA)	Oral (on empty stomach)
Geniposide[21]	———	———	———	Not approved	———
Efpeglenatide[22]	———	5.6-7.5 days	———	Not approved yet	Once weekly (S.C)
Lixisenatide[23, 24]	Lyxumia® Adlyxin®	3 h	10 µg-20 µg	31 Jan 2013 (EMA) 28 July 2016 (FDA)	Once daily (S.C)
Tirzepatide (dual agonist for GIP and GLP1 receptors)[25, 26]	Mounjaro®	5 days	2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg	13 May 2022 (FDA) 15 Sep 2022 (EMA)	Once weekly (S.C)

Preclinical studies

Inconsistent findings were observed when different cell lines or different GLP-1 agonists were used. Both exendin-4 and liraglutide induced proliferation of INS-1 cells[32, 33], while in human pancreatic cancer cell lines, liraglutide showed an anti-proliferative effect and exenatide had no effect [34-36]. Since liraglutide induced apoptotic cell death of malignant cells both *in vitro* and *in vivo* (in human pancreatic cancer cell line and mouse xenograft model), treatment with liraglutide may even be beneficial in diabetic patients with pancreatic cancer. It also increased the chemosensitivity of pancreatic cancer to gemcitabine in addition to its antiproliferative effect[35-37]. Many causes may contribute to this discrepancy including different types of cells used, different cell origins (rodents vs. human), and different agonists.

It is worth mentioning that studies by Vrang et al.[38] and Nyborg et al.[39] failed to observe any preneoplastic pancreatic lesions or increased risk of pancreatitis even after using much higher doses of liraglutide than those

used clinically. Regarding sitagliptin, Matveyenko et al.[40] observed that sitagliptin induced ductal proliferation and metaplasia. However, Aston-Mourney et al.[41] reported no evidence of pancreatitis, altered ductal proliferation or metaplasia after much longer duration (1 year vs. 12 weeks). Their results were later confirmed by Forest et al.[42] who reported that neither pancreatitis nor any adverse pancreatic effects were associated with treatment with sitagliptin.

The previously described pathological changes in some rodent studies were not supported by nonhuman primate studies as treatment with either liraglutide or semaglutide, for 87 weeks and 52 weeks, respectively, was not associated with any adverse effects on the pancreas[43].

Clinical studies

In 2020, a case report of pancreatic cancer after using liraglutide was published. However, the causality could not be confirmed as the patient had many other risk factors for pancreatic cancer including uncontrolled diabetes, smoking, alcohol consumption, and chronic pancreatitis. In addition, the patient used other medications and also used liraglutide for only 20 months, which seems a short time for developing cancer[44].

Gokhale et al.[45], after analyzing data from US Medicare claims, concluded that no increased risk of pancreatic cancer was associated with DPP4 inhibitors after 18 month follow-up period compared to sulfonylureas (SU) and thiazolidinediones. Furthermore, the risk was even lower when compared to SU users. Similar results were obtained from the Korean health insurance services revealing no increased risk of pancreatic cancer among DPP4I users after 8 years of follow-up[46].

Monami et al. conducted two meta-analyses evaluating the safety of DPP4 inhibitors and GLP-1R agonists, analyzing results of 53 randomized controlled trials (RCT) (24 weeks or longer) and 113 RCT (11 weeks or longer), respectively, enrolling more than 20,000 DPP4Is users and more than 33000 GLP-1R agonist users. They concluded that neither the use of GLP-1RAs nor DPP-4 inhibitors increased the risk of developing pancreatitis or pancreatic cancer[47, 48]. Later in 2023, in collaboration with other investigators, they published an updated meta-analysis evaluating the risk of pancreatitis and pancreatic cancer in GLP-1RAs users analyzing 43 RCT (only those with 52 weeks duration or longer were included) and drew the same conclusion[49].

Pinto et al. [50] conducted a meta-analysis to evaluate the risk of pancreatic cancer associated with DPP4Is use, they found no association between DPP4Is and pancreatic cancer, but observed a trend towards increased risk of acute pancreatitis, but the sample size was not enough to draw a conclusion. Another meta-analysis enrolling 11 cardiovascular outcome trials (CVOTs) agreed with Nreu et al. [49] that both GLP-1R agonist users and DPP4Is users did not show an increased risk for pancreatic cancer but disagreed with them in estimating the risk of pancreatitis as they reported an increased risk of acute pancreatitis among DPP4 inhibitor users [51] as previously reported by Pinto et al.

Cao et al. published a meta-analysis in 2020 stating that treatment with GLP-1RAs did not increase the risk of pancreatitis or pancreatic cancer[52]. Conclusively, after reviewing till date published data, regarding pancreatic cancer, despite the published cases of pancreatic cancer after incretin-based drug therapy, it remains uncertain if these cases are due to incretin-based therapy as the time between exposure and diagnosis is not enough for tumorigenesis. In addition, all meta-analyses and population-based cohort studies reported no increase in pancreatic cancer among users of GLP-1RAs and DPP4Is. It remains controversial if incretin-based therapy can induce acute pancreatitis. Meta-analyses agreed that no increased incidence of acute pancreatitis was associated with GLP-1RAs, but they disagreed on the risk of pancreatitis associated with DPP4Is as Abd El Aziz et al. and Pinto et al.[50, 51] observed an increased risk of acute pancreatitis after DPP4Is therapy while Monami et al.[47] reported no increased risk so it remains controversial and further studies are needed to confirm or reject the hypothesis that incretin-based therapy can induce acute pancreatitis. However, the benefits of using incretin-based therapy still outweigh any risk reported.

Incretin-based therapy and thyroid cancer

Preclinical studies

It was reported that there is a difference between human and rat thyroid cells as the latter express more GLP-1R[53, 54]. Contrarily, Gier et al. [55] reported observing GLP-1R expression in normal human thyroid tissue in addition to C-cell hyperplasia, medullary and papillary thyroid cancer, raising concerns about the risk of developing thyroid cancer after long-term incretin-based therapy. However, Pyke et al.[56] using specific antibodies reported that GLP-1R was not expressed in normal thyroid cells in humans. These different observations may be explained by lack of specificity of the used antibodies. Bjerre Knudsen et al.[53] reported that 20 months liraglutide treatment was not associated with any change in plasma calcitonin level or C-cell hyperplasia in monkeys (even with doses 60 times greater than the human dose) in contrast to what was observed in rodents. Additionally, sitagliptin induced apoptosis and reduced the proliferation of thyroid carcinoma both *in vitro* and *in vivo*[57, 58].

Clinical studies

Hegedüs et al. reported that no correlation was observed between serum calcitonin level, which is a marker for C-cell hyperplasia and medullary thyroid carcinoma, and liraglutide treatment after reviewing clinical trials enrolling more than 5000 patients receiving liraglutide (both diabetic patients and non-diabetic obese subjects) [59].

In a case-control study conducted in the French population, an increased risk of thyroid cancer was observed after 1-3 years of treatment with GLP-1R agonists[60]. However, this study has limitations that may influence the interpretation of its result in clinical practice, including over diagnosis and detection bias, lack of adjustment for family history and obesity which are established risk factors for developing thyroid cancer, and short latency period [61]. Additionally, a pharmacovigilance study found an association between GLP-1RAs use and thyroid tumors; GLP-1RAs use was associated with increased risk of thyroid tumors but the causality could not be confirmed, further studies are needed to confirm a cause-and-effect relationship between GLP-1RAs and thyroid tumors[62].

On the other hand, a meta-analysis of RCTs concluded that the risk of thyroid disorders including thyroid cancer was not increased with GLP-1RAs[63]. In addition, a prospective study evaluating the safety of alogliptin reported that no increased risk of any malignancy including thyroid cancer was observed after 3 years [64].

Conclusively, the clinical decision of whether to use or not to use incretin-based therapy should be based on risk-benefit ratio especially since the incidence of thyroid cancer remains rare and is associated with low mortality. However, it may be more prudent to avoid the use of GLP-1RAs in patients with risk factors of thyroid cancer while encouraging more research to further understand the relation between thyroid cancer and incretin-based therapy.

Incretin-based therapy and colorectal cancer

GLP-1Rs are expressed in the GIT of humans and monkeys[10]. Jin hypothesized that GLP-1R overactivation may increase the risk of colon cancer in diabetic patients [65]. However, later preclinical and clinical studies negated his hypothesis. *In vitro* and *in vivo* studies conducted on liraglutide, exendin-4, sitagliptin, and vildagliptin showed beneficial effects of incretin-based therapy on colorectal cancer as it decreased tumorigenesis, angiogenic ability, invasiveness, and metastasis [66-71]. In addition, clinical studies[72] proved that both GLP-1RAs and DPP4Is did not increase the risk of colorectal cancer. Further, clinical studies revealed that DPP4Is were associated with better prognosis and improved survival[73-75]. It is worth mentioning that in a nested case-control study, the risk of colorectal cancer in diabetic patients receiving DPP4Is was dependent on the dose as low doses were associated with reduced risk, while higher doses increased the risk this may be explained by the anti-angiogenic effect of DPP4Is, which resembles the J-shaped dose-response curve of other anti-angiogenic agents, by modulating plasminogen activator inhibitor-1. In addition, this complex response may also be related to the wide variety of DPP4 substrates such as stromal cell-derived factor 1 (SDF-1), and substance P and the role of DPP4 enzyme in the immune system

as severe inhibition of the enzyme may help cancerous cells evade the immune detection[76].

Incretin-based therapy, hepatocellular carcinoma (HCC) and cholangiocarcinoma

In vitro and *in vivo* studies conducted on liraglutide showed that liraglutide enhanced the antitumor immune response and protected against nonalcoholic steatohepatitis (NASH) and HCC[77, 78]. It also showed antiproliferative effects against HCC[79], the same antiproliferative effect was also observed using exenatide [80]. In addition, DPP4Is increased the chemotaxis of natural killer cells and T-lymphocytes, and suppressed the angiogenesis[81]. Sitagliptin showed an antitumor effect against diethyl nitrosamine-induced liver cancer[82]. Vildagliptin also prevented high-fat diet induced HCC[83]. The same antitumor effect was observed using a pan DPP inhibitor, ARI-4175[84]. Further, anagliptin protected against liver fibrosis and HCC independent of its effect on glucose and lipid metabolism in genetically obese mice[85]. Clinically, users of DPP4Is showed lower risk of developing HCC in the presence of chronic hepatitis B and hepatitis C[86, 87].

On the other hand, the incidence of cholangiocarcinoma, bile duct cancer, was higher among users of incretin-based therapy compared to SU and thiazolidinediones[88].

Incretin-based therapy and breast, endometrial, ovarian, and cervical cancer

Liraglutide increased the proliferation of breast cancer cells *in vitro* and *in vivo*[89, 90] while exendin-4 inhibited the growth of breast cancer both *in vitro* and *in vivo* and may even have a therapeutic benefit as it may also modulate invasion and migration[91, 92]. Sitagliptin inhibited the proliferation of MCF7 cells and suppressed the tumor development *in vivo*[93] while inhibition of DPP4 by KR62436 promoted the survival of breast cancer cells[94]. In addition, studies by Li et al. showed that sitagliptin and saxagliptin may facilitate the metastasis of breast cancer using murine cell line [95]. However, in a population-based cohort study, GLP-1RAs did not increase the risk of breast cancer[96]. The same result was proved later in the meta-analysis by Piccoli et al. after analyzing 52 RCTs enrolling more than 48 thousand GLP-1RA users[97]. To date, all available clinical data reveal that incretin-based therapy does not increase the risk of developing breast cancer; however, caution must be taken when prescribing incretin-based therapy to breast cancer patients due to concerns of increased survival and metastasis of malignant cells observed in preclinical studies.

Regarding female reproductive system cancers, incretin-based therapy has mostly a beneficial rather than harmful effect. Exendin-4 prevented the growth of cervical cancer induced by hyperglycemia *in vivo* and *in vitro*[98], it also decreased the resistance of endometrial cancer to cisplatin chemotherapy[99]. Exenatide also decreased the migration and induced apoptosis of ovarian cancer [100]. Similar results were obtained by He et al. as they showed that exendin-4 may have antitumor effects on ovarian cancer both *in vitro* and *in vivo*[101]. Sitagliptin suppressed the growth of endometrial carcinoma *in vitro* and *in vivo*[102, 103] while enhancing the migratory ability of cervical cancer cells *in vitro*[104]. It also improved the response of ovarian cancer cells to paclitaxel chemotherapy *in vitro*[105].

Incretin-based therapy and prostate cancer

In preclinical studies, exendin-4 showed antiproliferative effects on prostate cancer cells expressing GLP-1R *in vivo* and *in vitro* [106] and when it was combined with metformin, it produced a synergistic effect [107]. Later, the same effect was obtained by Li et al. by using exenatide and liraglutide[108]. In addition, exendin-4 also enhanced the radiosensitivity of prostate cancer cells[109]. In clinical studies, GLP-1RAs showed protective effect against prostate cancer compared to SU and basal insulin[110, 111]. Additionally, DPP4Is reduced the risk of prostate cancer compared to SU [110] but failed to improve the progression-free survival in patients with advanced stage prostate cancer compared to metformin [112].

Incretin-based therapy and lung cancer

A previous *in vivo* study showed that vildagliptin suppressed the growth of lung cancer[113]. In another *in vivo study*, anagliptin increased the efficacy of PD-L1 antibody against non-small cell lung cancer[114]. In addition, DPP4Is improved the clinical outcomes in patients receiving immune

checkpoint inhibitors without increasing the adverse effects[115].

Other cancers

The beneficial effects of incretin-based therapy have been reported in many tumors; exendin-4 suppressed the migration of glioma cells GLP-1R-dependent pathway[116], sitagliptin suppressed the growth of gastric cancer cells, as well as melanoma[117, 118], it also decreased the number of intestinal tumors[119].

It was found that the aggressiveness of urothelial carcinoma was correlated with DPP4 expression and DPP4 knockdown induced apoptosis of urothelial carcinoma cells [120]. Therefore, inhibition of DPP4 by different available DPP4Is may be of a therapeutic benefit but this is still a gap for further research.

In a cohort study conducted in the UK, GLP-1RAs did not increase the risk of developing skin cancer[121]. On the other hand, a case study was published in 2015 linking saxagliptin usage and serotonin level and indicating a possible relation between DPP4Is use and the activity of carcinoid tumors[122].

Incretin-based therapy in preclinical and clinical studies

a-Glucagon-like peptide-1 receptor agonists in preclinical studies.

Study	Agent used	Cancer type	Outcomes
In vitro study using NCI-H661 and LOVO cell lines [66]	Liraglutide	Colorectal cancer	Liraglutide resulted in inhibition of cell proliferation as well as migration and invasion. Also, it induced apoptotic cell death. These effects were mediated by modulating PI3K/Akt/mTOR signaling pathway.
In vivo study[90]	Liraglutide	Breast cancer	High dose liraglutide increased the proliferation and migrative ability of breast cancer cells. These effects were owing to the observed overexpression of GLP1R in breast cancer.
In vitro study[99]	Exendin-4	Endometrial cancer	Exendin-4 decreased resistance to cisplatin chemotherapy induced by hyperglycemia
In vivo and *in vitro* study[98]	Exendin-4	Cervical cancer	Hyperglycemia may promote cervical cancer growth this effect was blocked by exendin-4.
In vitro study[89]	Liraglutide	Breast cancer	Liraglutide may promote or inhibit the growth of triple negative breast cancer cells depending on the concentration
In vivo and *in vitro* study[77]	Liraglutide	Hepatocellular carcinoma	Liraglutide enhances the antitumor immune response both *in vivo* and *in vitro*; this antitumor effect was mediated by natural killer cells.
In vivo study[78]	Liraglutide	Hepatocellular carcinoma	Liraglutide has a protective effect against NASH and HCC.
In vivo and *in vitro* study[37]	Liraglutide	Pancreatic cancer	GLP1RAs may be beneficial for diabetic patients with pancreatic cancer, especially those with gemcitabine-resistant pancreatic cancer. As it enhances the chemosensitivity of malignant cells to gemcitabine and possesses antiproliferative and proapoptotic effects.
In vitro study[80]	Exenatide	Hepatocellular carcinoma	Exenatide possesses antiproliferative effects against hepatocellular carcinoma.
In vitro study[116]	Exendin-4	Glioblastoma	Exendin-4 suppressed the migration and invasion of glioma cells via GLP1R/SIRT3 pathway.
In vivo and *in vitro* study[109]	Exendin-4	Prostate cancer	Exendin-4 enhanced the radiosensitivity of prostate cancer
In vivo and *in vitro* study[91]	Exendin-4	Breast cancer	Exendin-4 inhibited the growth of breast cancer through inhibiting NF-κB activation.
In vitro study[100]	Exenatide	Ovarian cancer	Exenatide decreased migration and induced apoptosis via activation of caspases. It may also be beneficial in terms of metastasis.

In vitro study[79]	Liraglutide	Hepatocellular carcinoma	Liraglutide showed antiproliferative effect and induced autophagy and cellular senescence by inducing TGF-β1
In vivo and *in vitro* study[123]	Exendin-4	Colon cancer	GLP1R was not expressed in human colon cancer cells. Exendin-4 neither increased the proliferation of colon cancer cells nor decreased anticancer effect of cytotoxic agents.
In vitro study[108]	Exenatide and liraglutide	Prostate cancer	GLP1RAs possess antiproliferative effect on prostate cancer cells.
In vivo and *in vitro* study[101]	Exendin-4	Ovarian cancer	Exendin-4 may have antitumor effects on ovarian cancer as it induced apoptotic death of cancer cells in addition to inhibiting cellular proliferation, and invasion.
In vivo and *in vitro* study[107]	Exendin-4	Prostate cancer	Exendin-4 inhibited prostate cancer growth. In addition, it also possessed a synergistic effect when combined with metformin.
In vitro study[92]	Exendin-4	Breast cancer	Exendin-4 may have a therapeutic benefit in treatment of breast cancer as it possesses anticarcinogenesis effect by modulating apoptosis, invasion, and migration.
In vivo and *in vitro* study[106]	Exendin-4	Prostate cancer	Exendin-4 has an antiproliferative effect on prostate cancer.
In vivo and *in vitro* study [36]	Liraglutide	Pancreatic cancer	Liraglutide induced apoptosis of cancer cells and inhibited the growth of pancreatic cancer both *in vitro* and *in vivo*.
In vivo and *in vitro* study [35]	Liraglutide	Pancreatic cancer	Liraglutide has anticarcinogenesis effect and inhibits metastasis of pancreatic cancer through PI3K/Akt pathway

b-Dipeptidyl peptidase 4 inhibitors in preclinical studies.

Study	**Agent used**	**Cancer type**	**Outcomes**
In vivo study using LLC and H460 cell lines in mice[113]	Vildagliptin	Lung cancer	Vildagliptin ameliorated lung cancer growth
In vitro and *in vivo* study[67]	Sitagliptin and vildagliptin	Colon cancer	DPP4Is decreased the *in vitro* angiogenic ability of HUVECs which led to *in vivo* reduction in tumor size and micro vessel density
In vitro study [57]	Sitagliptin	Thyroid cancer	Sitagliptin reduced cell proliferation of thyroid carcinoma *in vitro* in addition to stimulating the apoptosis
In vitro study[120]	No drug used	urothelial carcinoma	DPP4 expression was found to be correlated with aggressiveness of UC, enhanced invasive ability and worse clinical outcomes. In addition, DPP4 knockdown induced apoptosis in UC cell lines.
In vitro study[71]	Sitagliptin	Colorectal cancer	Sitagliptin reduced the invasiveness of CRC cell lines
In vivo study[114]	Anagliptin	Non-small cell lung cancer	Anagliptin increased the efficacy of PD-L1 antibody0020
In vitro study[105]	Sitagliptin	Ovarian cancer	Sitagliptin improved the ovarian cancer cells response to paclitaxel
In vivo study[68]	Vildagliptin	Colorectal cancer	Vildagliptin decreased not only the incidence but also the growth of lung metastasis
In vivo study using mouse xenograft model[58]	Sitagliptin	Thyroid cancer	Sitagliptin reduced tumor growth.

In vivo and *in vitro* study[81]	Anagliptin and vildagliptin	Hepatocellular carcinoma	DPP4 inhibitors showed antitumor effects via increasing the chemotaxis of natural killer cells and T-lymphocytes. They also decreased tumor angiogenesis. In addition, the researchers reported the correlation between serum DPP4 activity and bad prognosis in HCC patients.
In vivo study using diethyl nitrosamine to induce liver cancer in rats[82]	Sitagliptin	Liver cancer	Sitagliptin showed antitumor effect by inhibiting the expression of NF-κB
In vitro study[104]	Sitagliptin	Cervical cancer	Sitagliptin enhanced the migratory ability of cervical cancer cells
In vivo and *in vitro* study[93]	Sitagliptin	Breast cancer	Sitagliptin inhibited the proliferation of MCF7 cells. Further, inhibiting DPP4 enzyme using sitagliptin suppressed the tumor development in the *In vivo* model
In vitro study[117]	Sitagliptin	Gastric cancer	DPP4 may function as a growth factor for stimulating the proliferation of scirrhous gastric cancer (SGC) cells while sitagliptin suppressed this growth promoting effect
In vivo study [83]	Vildagliptin	Hepatocellular carcinoma	Treatment with vildagliptin prevented high-fat diet induced HCC.
In vitro and *in vivo* study[102]	Sitagliptin	Endometrial carcinoma	Inhibition of DPP4 with sitagliptin suppressed endometrial carcinoma progression
In vivo study[84]	ARI-4175 (pan DPP inhibitor)	Hepatocellular carcinoma	Pan DPP inhibitor may have antitumor effect against HCC
In vitro and *in vivo* study[94]	KR62436	Breast cancer	DPP4 inhibition promotes the survival of breast cancer cells by enhancing autophagy via CXCL12/CXCR4/mTOR/HIF-1α pathway while cotreatment with metformin counteracts this undesirable effect
In vitro study on colorectal cell line[69]	Sitagliptin and vildagliptin	Colorectal cancer	Both sitagliptin and vildagliptin showed a significant anti-cancer effect against colorectal cancer. Further, sitagliptin was more potent than vildagliptin.
In vivo study[118]	Sitagliptin	Melanoma	Inhibition of DPP4 activity by sitagliptin reduced tumor growth. It also decreased the number of metastatic lesions into the lung.
In vivo and *in vitro* study[95]	Sitagliptin and saxagliptin	Breast cancer	Sitagliptin and saxagliptin may facilitate the metastasis of breast cancer.
In vitro study[103]	Sitagliptin	Endometrial carcinoma	Sitagliptin inhibited the growth of endometrial cancer cells.
In vivo study using genetically obese melanocortin 4 receptor-deficient (MC4R-KO) mice[85]	Anagliptin	Hepatocellular carcinoma	Anagliptin prevented the development of liver fibrosis and hepatocellular carcinoma independent on its effect on glucose and lipid metabolism.
In vivo study[119]	Sitagliptin	Intestinal tumors	Sitagliptin treatment numerically decreased the number of intestinal tumors in high-fat diet fed $Apc^{Min/+}$ mice.
In vivo study[70]	Sitagliptin	Colorectal cancer	Sitagliptin treated mice showed suppressed colon cancer tumorigenesis

c-Glucagon-like peptide-1 receptor agonists in clinical studies.

Study	Agent used	Cancer type	Outcomes
Retrospective cohort study[110]	Albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, oral semaglutide, and semaglutide	Prostate cancer	Compared to sulfonylureas, GLP1RAs showed a decreased risk of developing prostate cancer
Retrospective cohort study[72]	GLP1RAs	Colorectal cancer	GLP1RAs use did not increase the risk of colorectal cancer
Meta analysis[51]	lixisenatide, liraglutide, exenatide, dulaglutide, albiglutide, and semaglutide	Pancreatic cancer and any other malignancy	No increased risk of pancreatic cancer, nor any other malignancies nor even acute pancreatitis were observed (in both individual studies and meta-analysis)
Cohort study in UK[121]	Exenatide, dulaglutide, liraglutide, lixisenatide, and semaglutide	Skin cancer	In comparison to SU users, patients receiving GLP1RAs did not show any increased risk for developing skin cancer.
Cohort study in Denmark[111]	Exenatide, dulaglutide, liraglutide, lixisenatide, and semaglutide	Prostate cancer	After 5-year-follow up period, GLP1RAs may have a protective effect against prostate cancer, compared to basal insulin use; this protective effect was more prominent in older age patients and those with CVD.
Disproportionality analysis based on FAERS[124]	GLP1RAs	All types	No increase in all tumor cases was caused by GLP1RAs use. However, notable relation was observed between GLP1RAs and certain tumors such as thyroid cancer, islet cell neoplasm and neuroendocrine tumors.
Nested case-control study[60]	GLP1RAs	Thyroid cancer	After 1-3 years of treatment with GLP1RAs, an increased risk of thyroid cancer was observed in the French population covered by the national insurance system.
Meta-analysis of randomized controlled trials[63]	GLP1RAs	Thyroid cancer	GLP1RAs neither increased nor decreased the risk of thyroid cancer or other thyroid disorders.
Analysis of real-world databases[125]	GLP1RAs	Several types	Compared to metformin users, GLP1RA users showed decreased risk of prostate, colon, and lung cancers. On the other hand, it showed higher risk of thyroid cancer.
Case report[44]	Liraglutide	Pancreatic cancer	It is possible that liraglutide use may be related to pancreatic cancer.
Systematic review and meta-analysis[97]	GLP1RAs	Breast cancer	GLP1RAs did not increase the risk of breast tumors.
A case-non case pharmacovigilance study[62]	Exenatide, liraglutide and dulaglutide	Thyroid cancer	An association between GLP1RAs use and thyroid tumors was observed but the causality cannot be confirmed.
Meta analysis of randomized clinical trials[49]	Albiglutide, exenatide, liraglutide, lixisenatide, dulaglutide, and semaglutide	Pancreatic cancer	After analyzing 43 clinical trials, no evidence for pancreatitis was observed while available data on pancreatic cancer was not enough to draw a conclusion.

Meta analysis[52]	GLP1RAs	Pancreatic cancer	GLP1RAs use did not increase the risk of developing pancreatitis or pancreatic cancer.
Meta-analysis[126]	GLP1RAs (Albiglutide, exenatide, liraglutide, lixisenatide, dulaglutide, and semaglutide)	All types	Among GLP1RAs users, no increased risk of any malignancy was reported. Further, albiglutide showed a lower risk of cancer, however more studies are needed to confirm this observation. In addition, the risk of neither thyroid nor pancreatic cancer was increased among GLP1RAs users.
Meta-analysis[127]	Liraglutide, exenatide, semaglutide, and albiglutide	All types	No increased risk of malignancy was reported among GLP1RAs users.
Population based cohort study[88]	GLP1RAs	Cholangiocarcinoma	The use of GLP1RAs may be associated with an increased hazard of bile duct cancer compared to SU and thiazolidinediones
Meta-analysis[48]	Albiglutide, exenatide, liraglutide, lixisenatide, dulaglutide and semaglutide	Pancreatic cancer	GLP1RAs did not increase the risk of pancreatic cancer nor pancreatitis but increased the risk of cholelithiasis
UK-Population based cohort study[96]	Exenatide, liraglutide and lixisenatide	Breast cancer	GLP1RAs users did not exhibit an increased risk of breast cancer.

d-Dipeptidyl peptidase 4 inhibitors in clinical studies.

Study	**Agent used**	**Cancer type**	**Outcomes**
3-year-prospective study in T2DM patients[64]	Alogliptin	Several types including lung cancer, pancreatic cancer, gastric cancer, prostate cancer, thyroid cancer, and others.	The use of alogliptin was safe and no significant increase in incidence of any cancer type was observed in ALO-treated group
Retrospective study[73]	Sitagliptin, linagliptin, vildagliptin, saxagliptin	Colorectal cancer	DPP4Is were associated with better 5-year-prognosis compared to metformin.
Retrospective cohort study[110]	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	Prostate cancer	Compared to sulfonylureas, DPP4Is were associated with lower risk of prostate cancer
Epidemiology study[74]	Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin	Colorectal cancer and lung cancer	DPP4Is showed improved survival
Cohort study[45]	DPP4Is	Pancreatic cancer	No increased risk of developing pancreatic cancer with DPP4Is (18months study)
Population-based cohort study[128]	DPP4Is	Metastatic lesions after various primary malignancies	DPP4Is use was not associated with increased risk of metastasis except for primary thyroid cancer

Retrospective study[72]	DPP4Is	Colorectal cancer	DPP4Is use did not increase the risk of colorectal cancer
Meta-analysis of clinical trials[50]	DPP4Is	Pancreatic cancer	No association was found between DPP4Is and pancreatic cancer. On the other hand, a smaller increase in acute pancreatitis was observed, however this finding is not definitive as the sample size was small.
Retrospective study[75]	Sitagliptin, saxagliptin, linagliptin	Colorectal, lung, head, and neck cancer	Patients treated with DPP4Is showed improved progression-free survival
Population-based cohort study of diabetic patients[46]	DPP4Is	Pancreatic cancer	with a relatively long follow-up (around 8 years), DPP-4 inhibitor use was not associated with an increased risk of pancreatic cancer
Nested case-control study of diabetic patients [76]	DPP4Is	Colorectal cancer and liver cancer	There was no association between DPP4Is use and the risk of liver cancer. However, regarding the risk of colorectal cancer, the results were controversial depending on the dose; the usage of low dose of DPP4Is were associated with reduced risk while medium and high dose showed increased risk of colorectal cancer in J-shaped dose response curve.
Retrospective study[112]	DPP4Is	Prostate cancer	Treatment with DPP4Is failed to improve the progression-free survival in diabetic patients with advanced stage prostate cancer compared to metformin group.
Retrospective study[115]	DPP4Is	Non-small cell lung cancer	DPP4Is together with metformin improved the clinical outcomes in patients receiving immune checkpoint inhibitors without increasing the risk of adverse effects.
Meta analysis based on CVOTs[51]	saxagliptin, sitagliptin, alogliptin, and linagliptin	Pancreatic cancer and any other malignancy	The use of DPP4Is were not associated with any change in the risk of pancreatic cancer or any other malignant tumor while showed a nonsignificant trend in individual studies towards increased risk of acute pancreatitis that showed statistical significance in meta-analysis
Retrospective study[129]	DPP4Is	Several types	No increased risk of malignancies was observed in DPP4I users compared to metformin users.
Retrospective study on T2DM patients with HBV infection in Taiwan[86]	Alogliptin, sitagliptin, saxagliptin, vildagliptin, and linagliptin	Hepatocellular carcinoma	DPP4I users showed reduced risk of developing HCC in patients with HBV infection compared to non-users
Case study[122]	Saxagliptin	Carcinoid tumor	A correlation was found between saxagliptin usage and serotonin level which may indicate a possible relation between DPP4Is use and the activity of carcinoid tumors.

Retrospective cohort study on T2DM patients with chronic hepatitis C in Taiwan [87]	DPP4Is	Hepatocellular carcinoma	Compared to non-users, DPP4I users showed a reduced risk of developing HCC.
Population based cohort study [88]	DPP4Is	Cholangiocarcinoma	Among users of DPP4Is, the incidence of cholangiocarcinoma was higher compared to sulfonylureas and thiazolidinediones.
Meta-analysis [47]	DPP4Is (vildagliptin, sitagliptin, alogliptin, saxagliptin, linagliptin and dutogliptin)	Any malignancy including pancreatic cancer	No increased risk of cancer or pancreatitis was observed in DPP4Is

Conclusion

Different studies, both preclinical and clinical, have investigated the relation between cancer and incretins. While interpreting these studies, some points must be considered; differences between species, differences in expression of GLP-1R and DPP4 enzyme in tissues and the pleiotropic effects of GLP-1RAs and DPP4Is, especially as it is known that DPP4 enzyme works on numerous substrates which may influence cell survival, proliferation and immune response. Whether there is a role for genetic factors and ethnicity differences in the risk of malignancy, especially thyroid and pancreatic cancer, among incretin-based drug users is worth future research. Different meta-analyses and retrospective studies stated the safety of incretin-based therapy in terms of cancer risk[47, 126, 127, 129]. Other studies have even investigated the risk of metastasis in patients receiving incretin-based therapy, and found that except for primary thyroid cancer, the risk of metastasis was not increased[128]. To date, the reported benefits of incretin-based therapy outweigh the concerns about increased risk of pancreatitis and thyroid cancer, especially in light of low incidence, good prognosis, and low mortality of thyroid cancer. Future research is still needed to help us fully understand the complex connection between incretins and cancer considering studies that have supposed a protective effect of incretin-based therapy against adverse effects induced by different chemotherapy.

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العلاجات القائمة على الإنكريتين والسرطان: هل هم أعداء أم حلفاء؟

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قسم الأدوية والسموم ، كلية الصيدلة ، جامعة المنيا

العلاقة بين السرطان ومرض السكري موجودة ولكنها غير مفهومة بالكامل. تم استخدام العلاجات المعتمدة على الإنكريتين بشكل متزايد في العقد الماضي للسيطرة على مرض السكري من النوع ٢ (T2DM). من المفترض وجود صلة بين مسار الإنكريتين والسرطان، لكن الجدل في اللجنة العلمية يتزايد حول ما إذا كانت العلاجات المعتمدة على الإنكريتين لها آثار مفيدة أو ضارة على المرضى الذين يعانون من أمراض خبيثة أو معرضين لخطر الإصابة بالأورام الخبيثة. تلخص هذه المراجعة الأبحاث ما قبل السريرية والسريرية المنشورة التي تناقش العلاجات القائمة على الإنكريتين والسرطان. باستثناء سرطان البنكرياس، وسرطان الغدة الدرقية، وسرطان القنوات الصفراوية، تتفق البيانات المنشورة على أن العلاجات المعتمدة على الإنكريتين لها تأثير مفيد أو صفر على خطر الإصابة بالأورام الخبيثة. فيما يتعلق بسرطان البنكرياس، هناك تقارير عن حالات الإصابة بسرطان البنكرياس بعد تلقي العلاج الدوائي القائم على الإنكريتين، ولكن تأخر تكوين الأورام أمر مشكوك فيه. حتى الآن، اتفقت التحليلات التلوية على عدم ملاحظة زيادة في الإصابة بسرطان البنكرياس بين مستخدمي العلاجات المعتمدة على الإنكريتين. ما إذا كانت العلاجات المعتمدة على الإنكريتين تزيد من خطر الإصابة بسرطان الغدة الدرقية أمر مثير للجدل، لذلك فمن المستحسن تجنب وصف منبهات مستقبلات الببتيد ١- الشبيهة بالجلوكاجون (GLP-1RAs) للمرضى الذين يعانون من ارتفاع خطر الإصابة بسرطان الغدة الدرقية. على الرغم من الدراسات العديدة المنشورة حول الإنكريتين والسرطان، إلا أنها لا تزال مجالا غنيًا لمزيد من البحث.