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REVIEW

The effect of GLP-1R agonists on the medical triad of obesity, diabetes, and cancer

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Abstract
Glucagon-like peptide-1 receptor (GLP-1R) agonists have garnered significant attention for their therapeutic potential in addressing the interconnected health challenges of diabetes, obesity, and cancer. The role of GLP-1R in type 2 diabetes mellitus (T2DM) is highlighted, emphasizing its pivotal contribution to glucose homeostasis, promoting β-cell proliferation, and facilitating insulin release. GLP-1R agonists have effectively managed obesity by reducing hunger, moderating food intake, and regulating body weight. Beyond diabetes and obesity, GLP-1R agonists exhibit a multifaceted impact on cancer progression across various malignancies. The mechanisms underlying these effects involve the modulation of signaling pathways associated with cell growth, survival, and metabolism. However, the current literature reveals a lack of *in vivo* studies on specific GLP-1R agonists such as semaglutide, necessitating further research to elucidate its precise mechanisms and effects, particularly in cancer. While other GLP-1R agonists have shown promising outcomes in mitigating cancer progression, the association between some GLP-1R agonists and an increased risk of cancer remains a topic requiring more profound investigation. This calls for more extensive research to unravel the intricate relationships between the GLP-1R agonist and different cancers, providing valuable insights for clinicians and researchers alike.

Keywords Ozempic · Semaglutide · Cancer · Diabetes · Obesity · GLP1RA

1 Introduction

Semaglutide (US brand name Ozempic or Wegovy), a Glucagon-like peptide-1 receptor (GLP-1R) agonist containing the active ingredient semaglutide, is approved by the Food and Drug Administration for its potential therapeutic role in obesity and diabetes mellitus (DM) similar to other agonists within the GLP-1R family such as liraglutide. It not only successfully regulates blood sugar levels [1] but also reduces the appetite and, thereby, the weight of patients [2], especially in individuals with obesity and type 2 diabetes mellitus (T2DM). But why is there even a need for such a medication? And are potential long-term consequences, such as promoting the development or spread of cancer, receiving sufficient attention?

The number of overweight people has been increasing rapidly in recent years due to genetic, socio-economic, lifestyle, and cultural influences. Compared to the past, this not only affects adults but also numerous children and young people. Especially in American and European regions, at least 50% of residents now weigh more than the international standardized body mass index (BMI) recommends [3]. In this relation, a BMI of 30 kg/m^2 or higher is classified as obese [4], whose causes lie in excessive calorie intake or reduced energy expenditure, and modern lifestyles promote both a lack of exercise and an unhealthy diet. Therefore, both these lifestyle factors and obesity itself represent a significant risk factor for metabolic disease T2DM [3, 5].

DM is one of the most common metabolic diseases worldwide, with around 530 million people currently affected and an estimated 1.3 billion diabetes patients in 2050. The most common disease forms are the well-known

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types 1 and 2, severe diseases with chronic hyperglycemia [6]. While type 1 often manifests as an autoimmune insulin deficiency during childhood, T2DM predominantly develops throughout life. Epigenetic modifications trigger a genetic predisposition, which leads to insulin resistance [7]. Concretely, tobacco smoking, alcohol consumption, unbalanced diet, low fitness, increased BMI as well as unhealthy environmental influences are the key risk factors for the development of T2DM, and this form accounts for 96% of all DM cases [6]. Due to the disrupted metabolic processes, numerous signaling pathways become dysregulated, resulting in epigenetically induced inflammation. This triggers the development of malignant tumors in different tissues, for example, the colorectal, liver, or breast cancer [8–10], creating a medical triad consisting of overweight, DM, and oncogenesis. Due to the close connection between this pathogenesis, it must be considered that drug manipulation of one of the diseases can also affect the other components of this interaction.

Therefore, this review presents the triangle relationship of obesity, DM as well as cancer development and elucidates the treatment of overweight-associated T2DM with semaglutide, focusing on the question of whether the development of these conditions can be combated or if any severe side effects should be considered of this therapy.

2 The medical triad

Obesity, as well as DM, are conditions associated with a heightened risk of various cancers, including pancreatic, colorectal, breast, or liver cancer, and an increased mortality risk also accompanies them [8]. The link between these health issues and cancer risk is attributed to imbalances in the interaction of complex metabolic processes.

Obesity can be prevented by regulating body weight, dieting, and exercising [9] and although obesity is preventable, the increase in body fat allows the progression of metabolic diseases. Especially interesting, these metabolic diseases are associated with approximately 20% of cancer cases [10, 11]. Obesity induces metabolic disturbances in adipose tissue, influencing the release of hormones, adipokines, inflammatory cytokines, growth factors, enzymes, and free fatty acids [12]. Notably, each 5% increase in BMI is estimated to correlate with a 10% rise in cancer-related deaths [13]. The altered physiology of adipose tissue in obesity releases metabolic substrates contributing to tumor cells' proliferation, invasion, and metastasis. Two critical factors in this association are pro-inflammatory cytokines and adipokines. Pro-inflammatory cytokines produced by adipose tissue support tumor-promoting intercellular crosstalk in the tumor microenvironment [14], thus enhancing tumor cell progression, angiogenesis, and invasion as essential requirements for metastasis [15]. For example, breast and colorectal cancer progression was attributed to obesity [16], and in liver and gallbladder cancers, 51% of the cases are caused by this overweight disease [16]. However, calorie deficit, active lifestyle, behavior therapy, and drug therapy reduce inflammatory markers and regulate insulin levels commonly associated with cancer progression [17, 18].

Adipokines such as adiponectin and leptin, derived from adipose tissue, play pivotal roles. The excessive expansion of adipose tissue in obesity disrupts adipokine secretion, fostering chronic low-grade inflammation and thereby contributing to the onset of metabolic disorders like obesity and T2DM. Adiponectin, inversely correlated with BMI, exhibits protective effects against carcinogenesis based on *in vitro* models. Leptin, implicated in inflammatory, mitogenic, and pro-angiogenic pathways, has been associated with breast cancer development, with studies indicating that inhibiting leptin signaling reduces the growth of breast cancer induced by carcinogens [12].

Moreover, high adiposity contributes to elevated serum estrogen levels, which, in excess, can promote tumor development by causing DNA damage, stimulating angiogenesis, and fostering cellular proliferation [19].

The presence of hyperglycemia and hyperinsulinemia in T2DM [20], leading to metabolic dysfunction, can also contribute to the proliferation and migration of cancer cells [21]. Cancer progression due to hyperglycemia was reported in multiple cancers, including breast, colorectal, brain, and pancreatic cancer [22–25]. Insulin is responsible for activating insulin receptors and insulin growth-like receptors. Moreover, elevated insulin levels resulting from hyperinsulinemia trigger insulin-like growth factor (IGF) signaling, activating key pathways such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) [26]. These pathways, in turn, facilitate cancer cell growth, survival, motility, and resistance to drugs. Furthermore, it has long been theorized that cancer cells exhibit heightened glucose uptake and rely on glucose as a primary fuel for proliferation because it is a substrate cancer cells use as an energy source in aerobic glycolysis, resulting in tumor progression [27]. This phenomenon, known as the Warburg effect [28, 29], is attributed to damaged mitochondria in cancer cells. Hence, anticancer therapy may include antidiabetic drugs targeting glucose metabolism and metabolic pathways that decrease the glucose uptake in cancer cells [30].

In summary, the intricate interplay of metabolic abnormalities, inflammatory responses, and hormonal influences in obesity and diabetes underscores their significant impact on cancer risk and mortality.

3 The treatment complexities

The treatment of cancer in individuals who are both obese as well as diabetic poses significant challenges due to the intricate interplay between these conditions, and addressing these challenges involves navigating a complex landscape (Fig. 1). One noteworthy obstacle is the potential need for higher chemotherapy doses in obese patients based on their body weight. However, this approach carries the inherent risk of heightened side effects and drug toxicity. In the case of obese individuals, an elevated BMI has been linked to increased interactional displacement, primarily stemming from the continuous movement of the skin and subcutaneous adiposity [31]. This displacement shift raises concerns about a potential reduction in the radiation dose reaching the target cells, leading to apprehensions about inadvertently overdosing patients with radiation and chemotherapy [31, 32].

Moreover, managing diabetes during cancer treatment is a crucial aspect often overshadowed by the primary focus on cancer therapies. Chemotherapy, in particular, can influence blood sugar levels, causing fluctuations that need careful consideration. Additionally, the use of corticosteroids alongside chemotherapy to mitigate severe nausea and vomiting introduces another layer of complexity [33]. For diabetic patients, this poses a substantial threat, as corticosteroids are known to induce hyperglycemia [34]. The combination of decreased glucose uptake by the muscle and decreased glycogenesis further contributes to hyperglycemic conditions and complicates the already challenging task of treating cancer in individuals managing diabetes.

GLP-1R plays a significant role in the triad, making it an appealing target for treatment (Fig. 1). Specifically, GLP-1R emerged as an important pharmacological target for addressing T2DM, as it actively contributes to maintaining glucose homeostasis while promoting both β cell proliferation and insulin release [35]. The impact of GLP-1R agonists such as semaglutide extends beyond diabetes control: they play a multifaceted role in regulating blood glucose levels by reducing hunger, moderating food intake, and managing body weight [36]. Notably, GLP-1R agonists inhibit cancer progression in some malignant tumors [37–40].

4 Glucagon-like peptide-1 receptor

The GLP-1R comprises seven hydrophobic transmembrane domains and a hydrophilic extracellular domain [41]. These receptors are expressed in multiple tissues, including the lung, stomach, intestine, liver, kidney, heart, pancreas, and regions in the central nervous system. Hence, it is a significant target of small-molecule drugs for signaling modulation (Fig. 2) and treating various diseases [42]. The activation of GLP-1R is associated with glucose-induced insulin secretion

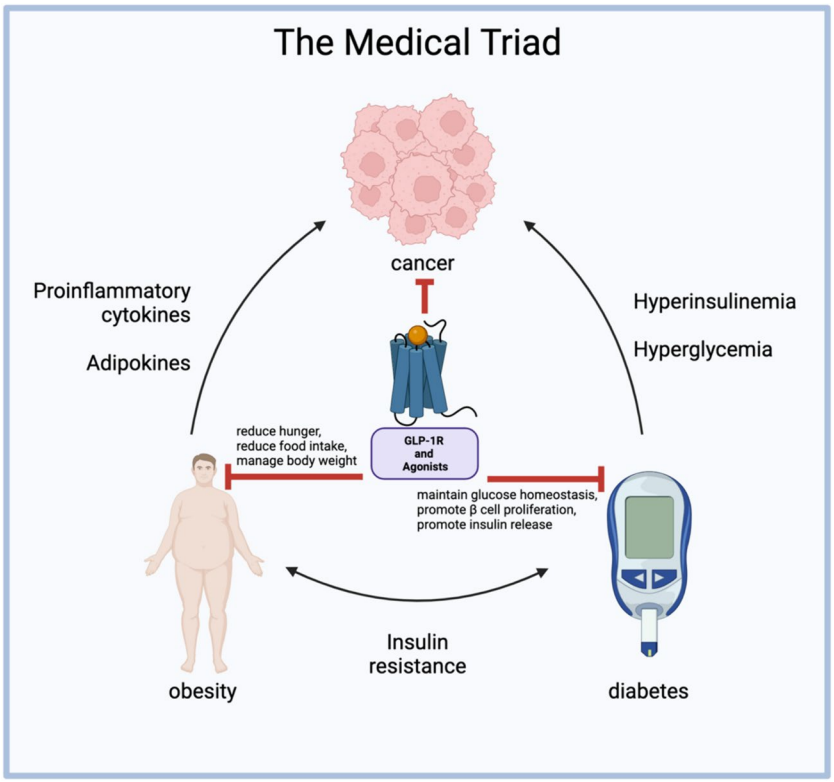

Fig. 1 The link between cancer, obesity, diabetes, and GLP-1R's effect on them. Generated using BioRender

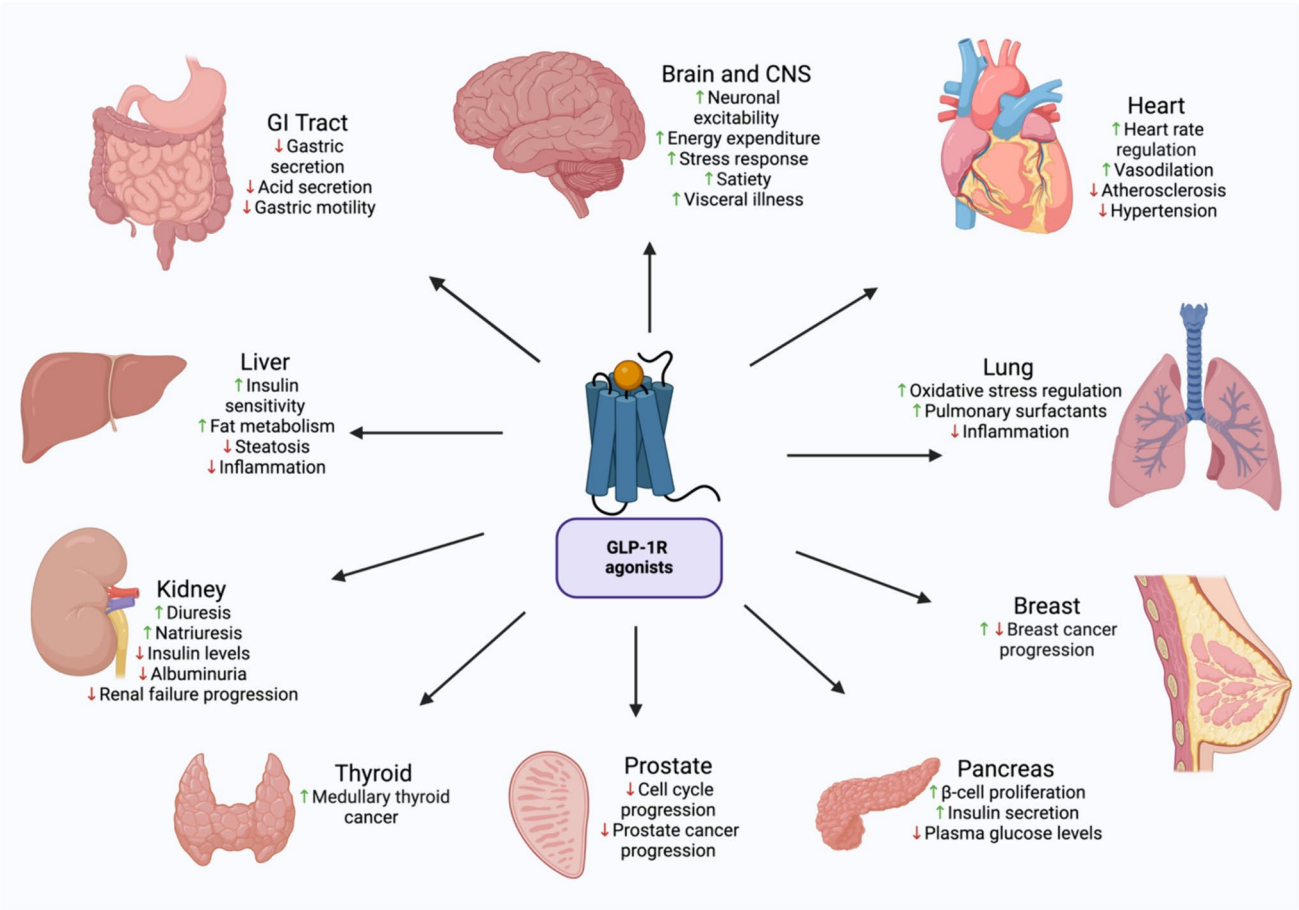

Fig. 2 Effects of GLP-1RAs on organs. GLP-1R and agonists decrease hypertension, atherosclerosis, inflammation, plasma glucose levels, prostate cancer progression, insulin levels, albuminuria, renal failure progression, steatosis, gastric and acid secretion, and gastric motility levels amongst various organs in the body. GLP-1R and agonists increase heart rate regulation, vasodilation, oxidative stress regulation, pulmonary surfactants, β cell proliferation, insulin secretion and sensitivity, medullary thyroid cancer, diuresis, natriuresis, fat metabolism, neuronal excitability, energy expenditure, stress response, satiety, and visceral illness. For breasts, GLP-1R and agonists lead to an increase or decrease in breast cancer progression. Generated using BioRender

and inhibition of α-cell glucagon release [43]. In addition, the activation of GLP-1R results in a cascade that activates adenyl cyclase via $G\alpha_s$, resulting in an increased secretion of cyclic adenosine monophosphate (cAMP) secretion and activating cAMP-dependent protein kinase (PKA). GLP-1R can also couple with adenyl cyclase using other $G\alpha_s$ subtypes such as $G\alpha_i$ and $G\alpha_q$ [44, 45]. An influx in calcium is reported upon activation of GLP-1R, and in combination with the activation of PKA, this results in insulin secretion [46].

GLP-1R reduces the inflammatory-induced response in the lungs, regulates oxidative stress and pulmonary function, and decreases excessive mucus production [47, 48]. Furthermore, GLP-1R affects the mucosal membrane in the gastric tract by decreasing gastric secretions, which restrict gastric acid secretions and motility [49–51]. GLP-1R causes a reduction in hepatic steatosis and inflammation and increases fat metabolism mediated by increasing hepatic insulin sensitivity [52–54]. The GLP-1R directly influences renal functions by enhancing diuresis and natriuresis [55]. In diabetic kidney disease patients, a reduction in insulin levels, albuminuria, and the progression of renal failure were observed as a GLP-1R effect [56, 57]. Moreover, GLP-1R is found in the heart and blood vessels and is beneficial in heart rate, vascular endothelium, atherosclerosis, and hypertension [58, 59]. Since GLP-1R is a target in diabetes mellitus, it enhances the proliferation of β-cells and insulin secretion in the pancreas and reduces plasma glucose levels [60, 61]. The significant role of GLP-1R in the brain is to regulate metabolic processes, energy expenditure, and neuronal excitability [62, 63]. It also causes stress responses, satiety, and vi0sceral illness' in the central nervous system [63]. As an alarming finding, the activation of GLP-1R has been associated with developing thyroid cancer [64, 65].

On the other hand, the activation of GLP-1R in the prostate attenuates cell proliferation and the progression of

prostate cancer [66]. Although GLP-1R's role is not fully understood or investigated in breast tissue when activated by different agonists, it may increase or decrease the progression of breast cancer [67, 68]. The extensive role of GLP-1Rs and their agonists in other organs and tissues are shown in the overview in Fig. 2.

5 Glucagon-like peptide-1 receptor agonists

GLP-1R is targeted by GLP-1R agonists, which regulate diabetes and obesity. Although diabetic patients commonly use metformin, GLP-1R agonists serve as a beneficial therapeutic option for diabetic patients with metformin intolerance. GLP-1R agonists mimic hormones that activate biological responses in GLP-1R. GLP-1R agonists fall under two groups: human GLP-1 backbone agents and exendin-4 backbone agents. Dulaglutide, albiglutide, liraglutide, and semaglutide are human GLP-1 backbone agents. Exenatide and lixisenatide are classified as Exendin-4 backbone agents. In addition, semaglutide, liraglutide, and tirzepatide are GLP-1R agonists that are FDA-approved [69]. Albiglutide was discontinued for low prescription rates rather than safety concerns [70, 71]. All GLP-1R agonists have the same mode of function but differ in half-life duration. Exenatide has a half-life of 3.3–4 h, and one dose is seen to be insufficient, so it is taken twice daily. Lixisenatide and liraglutide have half-lives of 2.6 h and 12.6–14.3 h, respectively and are taken once daily. Dulaglutide, albiglutide, and semaglutide have half-lives that range from 4.7 to 5.5, 5.7–6.8, and 5.7–6.7 days, respectively [72].

GLP-1R agonists exhibit protective and regulatory effects on blood glucose levels but have been linked to the inhibition of tumor cell proliferation in most cancer cases, as seen *in vitro* and summarized in Table 1 [51, 73]. The fact that GLP-1R agonists are sometimes introduced if the patient is intolerant to metformin or metformin is contraindicated, or when patients on metformin are not achieving their HbA1c goals [71] represents essential background information here.

The effect of GLP-1R agonists liraglutide and exendin-4 was examined *in vitro* on LOVO, CA-77, MCF-7, MDA-MB-231, KPL-1, MB-468, 4TI, BT483, ZR751, LNCap, PC3, ALVA-41, DU145, LNCap, PANC-1, MiaPaCa-2, PANC, CT26, SKOV3, OVCAR3, OVCAR4, A2780, and ES-2 cell lines that are expressed in several cancers including colorectal, pancreatic, thyroid, breast, prostate, ovarian, and colon (Table 1).

Liraglutide concentrations of 10–1000 nM implemented for 24–72 h showed an increase in apoptosis, G2/M phase arrest, Bax/Bcl-2 ratio, p38 MAPK activation, PKA expression, cAMP, caspase-3, GLP-1R expression, migration, ROS generation, NOX4 expression, VEGF, and proliferation of breast cancer in only one study. Nonetheless, a decrease in PI3K, Akt, mTOR, proliferation, migration, invasion, p-ERK1/2, growth, colony formation, and inflammation represented by nuclear factor κB (NF-κB) expression, cell viability, and an overall decrease in proliferation was noted with applying liraglutide (Table 1).

In addition, exendin-4 at 0.1–100 nM concentrations for 24–96 h increased GLP-1R activation, p53, p21, p38, cAMP, Bax/Bcl-2 ratio, and p38/MAPK activation. A reduction in proliferation, NF-κB activation, migration, invasion, migration, colony formation, Cyclin D1, p-Akt, ERK-MAPK pathway, cAMP, and GSK3 accompanied this increase (Table 1). Figure 3 shows an overview of the mentioned effects of the two GLP-1R agonists and their influence on numerous signaling pathways.

Some of the significant GLP-1R agonists studied other than semaglutide are liraglutide and exendin-4. Both agonists affect cancer *in vitro* by decreasing the proliferation and metabolic pathways at varying concentrations. Liraglutide and exendin-4 are initially antidiabetic drugs but can affect tumorigenesis, suggesting GLP-1R agonists as a potential treatment for different cancers as found *in vivo* (Table 2). Notably, an increase in calcitonin (Fig. 4), particularly observed in thyroid cancer, indicates cancer development [75], given its role as a tumor marker in medullary thyroid neoplasia [86]. More research is needed to understand the effect of other agonists, as cancer research is lacking. GLP-1R agonists are typically combined with metformin or other antidiabetic drugs. The combination of GLP-1R agonists with each other has not been studied previously, suggesting that due to their similar mode of action, there would not be an enhancement in therapy from this combination.

The effect of GLP-1R agonists liraglutide and exendin-4 was examined *in vivo* on CD-1, MCF-1, MDA-MB-468, MDA-MB-231, 4T1, LNCap, PANC-1, MIA PaCa-2, CT26, SKOV-3, and Apc(Min/+) cell lines expressed in cancers such as thyroid, breast, prostate, pancreatic, colon, ovarian, intestinal, and liver (Table 2).

Both liraglutide and exendin-4 decrease the size, weight, and proliferation of pancreatic, breast, prostate, ovarian, intestinal, liver, and colon cancer. Liraglutide slows down and sometimes even inhibits tumor growth of cancers in mice in *in vivo* studies. Moreover, it downregulates the protein levels of cell proliferation marker PCNA, decreases cell viability and number, and upregulates the protein levels of pro-apoptotic markers [91]. In addition, this GLP-1R agonist activates AMPK, inhibiting the proliferation of various cancerous cells, making it a promising cancer treatment [92].

Exendin-4 significantly inhibits different cell lines and induces apoptosis through the mechanism modification of apoptosis-related genes, which plays a role in extrinsic pathways and cell survival genes [78]. Specifically in colon cancer and prostate cancer, exendin-4 increased intracellular cAMP levels while inhibiting glycogen synthase kinase 3

Table 1 GLP-1R agonist's effect on cancer in *in vitro* studies

Cancer type	Cell line	GLP-1R agonist	Concentration and duration	Serum concentration of drug	Results	References
Colorectal cancer	LOVO	Liraglutide	10^{-5} mol/L, 10^{-8} mol/L, 10^{-11} mol/L for 24, 48, or 72 h	N/A	↓ PI3K ↓ Akt ↓ mTOR ↓ Proliferation ↓ Migration ↓ Invasion ↑ Apoptosis	[74]
Thyroid cancer	CA-77	GLP-1 (7–37) agonists	10^{-8} M from 3–48 h	N/A	↑ cAMP ↑ CGRP ↑ CT	[75]
Breast cancer	MCF-7, MDA-MB-231, KPL-1	Exendin-4	0.1–10 nM for 0–3 days	0.44 ± 0.07 ng/mL	↓ Proliferation ↓ NF-κB activation ↑ GLP-1R activation	[76]
Breast cancer	MCF-7, MDA-MB-231, KPL-1	Exendin-4 combined with metformin	10 nM for 0–3 days	N/A	↓ Proliferation ↑ GLP-1R activation	[77]
Breast cancer	MCF-7	Exendin-4	0.25, 0.5, 1, 1.5, 2, 3, 5, 7.5, or 10 μM for 72 h	5 μM	↓ Migration ↓ Invasion ↓ Colony formation ↓ Proliferation ↑ Apoptosis	[78]
Breast cancer	MCF-7, MDA-MB-231, MDA-MB-468	Exendin-4	1, 10, or 50 nM for 14 days	N/A	↓ Colony formation ↓ Cyclin D1 ↓ p-Akt ↑ p53 ↑ p21 ↑ p38 ↑ cAMP	[79]
Breast cancer	4T1, MCF-7, MDA-MB-231, MDA-MB-468, BT483, ZR751	Liraglutide	0, 10, 100, or 1000 nM for 24, 48, or 72 h	N/A	↑ GLP-1R expression ↑ Proliferation ↑ Migration ↑ ROS generation ↑ NOX4 expression ↑ VEGF	[67]
Prostate cancer	LNCap, PC3, ALVA-41, DU145	Exendin-4	0.1–10 nM for 0, 24, 48, 72, or 96 h	N/A	↓ ERK-MAPK pathway ↓ Proliferation ↑ cAMP	[80]
Prostate cancer	LNCap	Liraglutide combined with Docetaxel	10, 20, 40, or 80 μM for 48 h	N/A	↑ G2/M phase arrest ↑ Apoptosis ↓ p-ERK1/2 ↓ p-Akt	[81]
Prostate cancer	LNCap	Exenatide or liraglutide	0, 1, 10, or 100 nM for 24 h	N/A	↓ Proliferation ↓ Cell viability ↑ Apoptosis ↑ Bax/Bcl-2 ratio ↑ p38 MAPK activation	[82]
Pancreatic cancer	PANC-1, Mia-PaCa-2, PANC	Liraglutide	0, 10, 100, or 1000 nM for 48 h	N/A	↑ GLP-1R expression ↑ PKA expression ↑ cAMP ↑ Apoptosis ↑ Bax ↑ Caspase-3 ↓ Growth ↓ Colony formation ↓ NF-κB expression	[68]

Table 1 (continued)

Cancer type	Cell line	GLP-1R agonist	Concentration and duration	Serum concentration of drug	Results	References
Pancreatic cancer	MIA PaCa-2, PANC-1	Liraglutide	0, 10, 50, 100, 500, or 1000 nM for 72 h	N/A	↓ Colony formation ↓ Viability ↓ Migration ↓ Invasion ↓ Proliferation ↓ p-Akt	[83]
Colon cancer	CT26	Exendin-4	5 or 50 nM	N/A	↓ p-ERK1/2 ↓ GSK3 ↑ cAMP ↓ Proliferation ↑ Apoptosis ↓ Colony formation ↓ Viability	[84]
Ovarian cancer	SKOV3, OVCAR3, OVCAR4, A2780, ES-2	Exendin-4	0, 1, 10, or 100 nM for 96 h	N/A	↓ Proliferation ↓ Colony formation ↓ Migration ↓ Invasion ↓ p-Akt ↑ Apoptosis	[85]

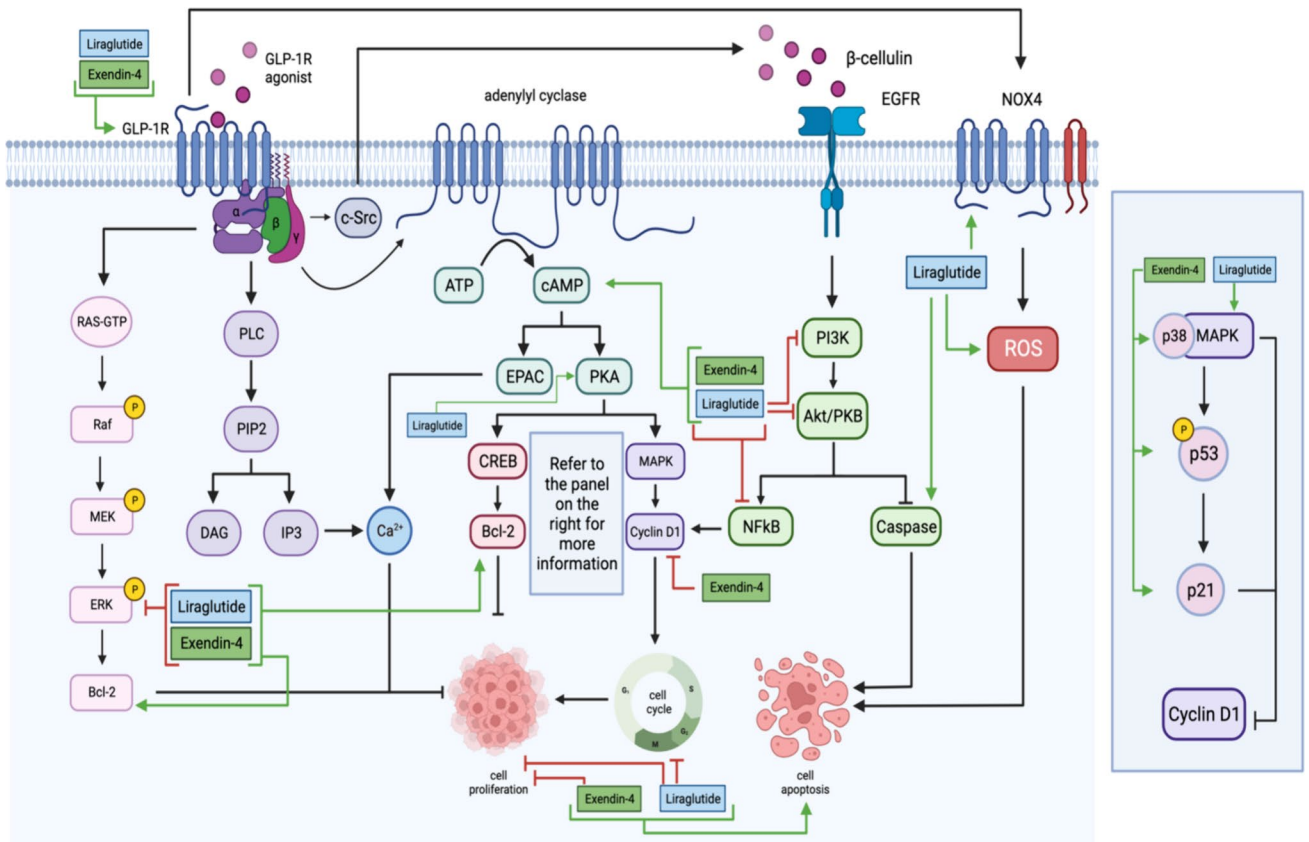

Fig. 3 Liraglutide and Exendin-4 decrease NF-κB, cell proliferation, and phosphorylated ERK in cancer. Liraglutide decreases Pl3K, Akt/PKB, and cell division while increasing GLP-1Rs, NOX4, ROS, caspase, MAPK, cAMP, Bcl-2, PKA, and cell apoptosis levels. Exendin-4 decreases Cylin D1 while increasing GLP-1Rs, MAPK, p21, p53, cAMP, Bcl-2, and cell apoptosis. Generated using BioRender

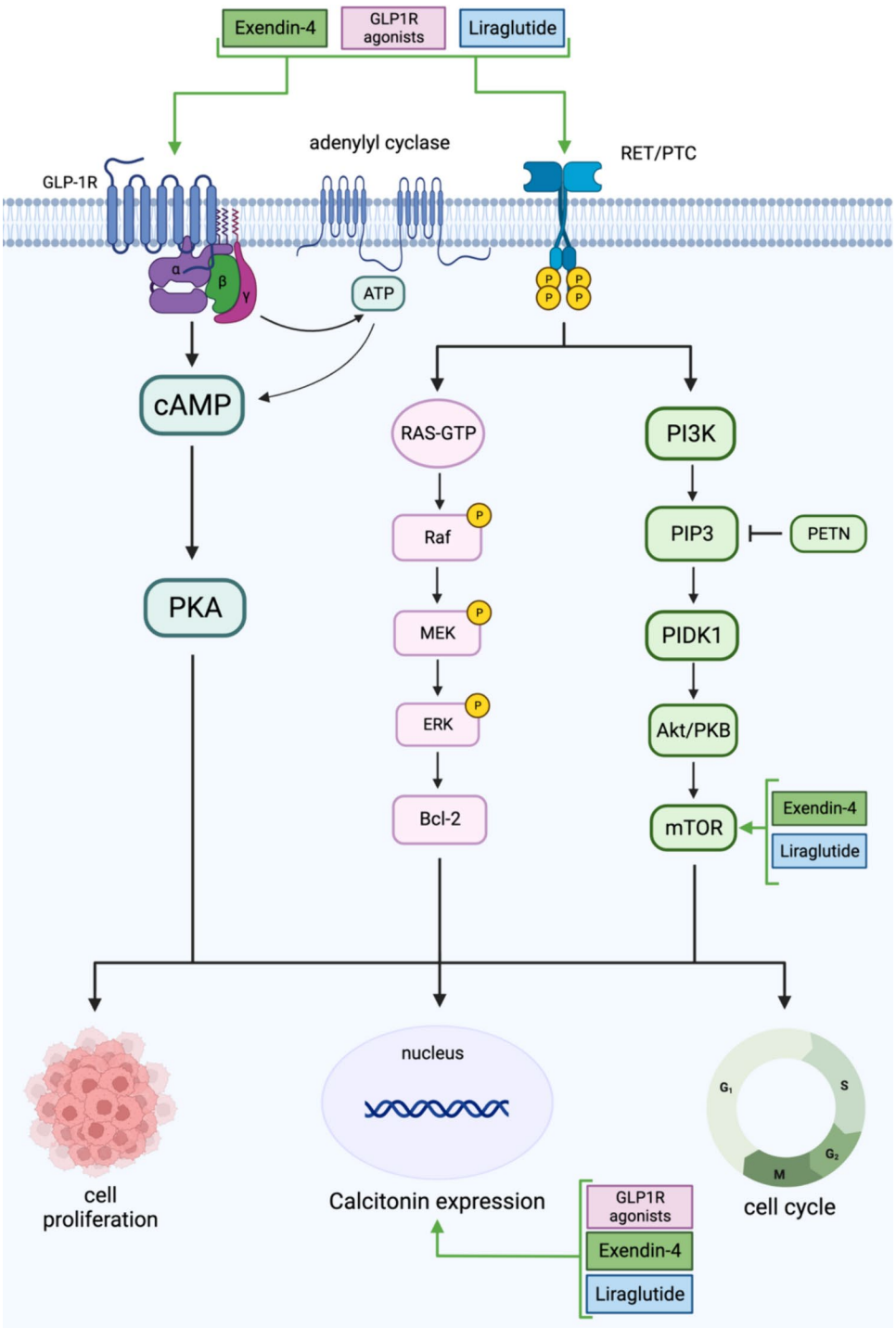

Fig. 4 GLP-1R agonists were studied in thyroid cancers. Both Liraglutide and Exendin-4 increase the levels of GLP-1R, RET/PTC, mTOR, and calcitonin expression amongst patients with thyroid cancer. Generated using BioRender

and ERK-MAPK activation, leading to an increase in apoptosis [93]. Moreover, exendin-4 inhibits migration, cell invasion, and colony formation of many cancers, making it a possible treatment for malignant cells, specifically in prostate cancer. Exendin-4 suppresses cell proliferation through the inhibition of ERK-MAPK [80]. Lastly, a combination of exendin-4 and metformin has been shown to attenuate different forms of cancer at a more noticeable rate [94, 95].

6 The popular GLP-1R agonist semaglutide

Semaglutide is a long-acting GLP-1R agonist structurally similar to GLP-1 but resistant to proteolytic cleavage [96] and is given as a subcutaneous injection to patients with T2D. This is because, in comparison to GLP-1, semaglutide has two amino acid substitutions, which makes it less vulnerable to degradation by the proteolytic enzyme

Table 2 GLP-1R agonist's effect on cancer in *in vivo* studies

Cancer type	Cell line	GLP-1R agonist	Concentration and duration	Results	References
Thyroid cancer	CD-1 wild-type mice	Liraglutide and exenatide	0.03, 0.3, or 3.0 mg/kg for 13 weeks	↑ Calcitonin ↑ C-cell hyperplasia ↑ GLP-1R ↑ mTOR activation ↑ pS6	[87]
Breast cancer	MCF-7 cells into athymic nude mice	Exendin-4 and exandin	300 pmol/kg body weight/day Ex-4 or 3 nmol/kg body weight/day exendin for 6–9 weeks	↓ Tumor size ↓ Proliferation ↓ Ki67 ↓ NF-κB activation ↑ Serum insulin	[76]
Breast cancer	MCF-7 cells into athymic mice	Exendin-4 combined with metformin	300 pmol/kg body weight/day for 8 weeks	↓ Tumor volume ↓ Tumor weight ↓ Ki67 ↑ GLP-1R	[77]
Breast cancer	MDA-MB-468 and MDA-MB-231 cells into athymic nude mice	Exendin-4	500 ng or 2 μg per day for 6 weeks	↓ Tumor weight ↓ Tumor size	[79]
Breast cancer	4T1 cells in BALB/cfC3H mice	Liraglutide	400 μg/kg for 2 weeks	↑ Tumor volume ↑ Metastasis	[67]
Prostate cancer	LNCap cells into athymic mice	Exendin-4	24 nmol/kg body weight/day or 300 pmol/kg body weight/day	↓ Tumor size ↓ P504S, prostate cancer marker ↓ Ki67 ↓ Proliferation ↓ p-ERK-MAPK	[80]
Prostate cancer	LNCap cells into athymic mice	Exendin-4 combined with metformin	300 pmol/kg body weight/day for 6 weeks	↓ Tumor volume ↓ Tumor weight ↓ Ki67 ↓ P504S ↓ Proliferation	[88]
Pancreatic cancer	PANC-1 cells into nude mice	Liraglutide	0.2 mg/kg twice daily for 4 weeks	↑ Chemosensitivity ↑ Bax ↓ Tumor volume ↓ Tumor weight ↓ Ki67	[68]
Pancreatic cancer	MIA PaCa-2 in male athymic nude mice	Liraglutide	0.2 mg/kg for 4 weeks	↓ Tumor growth	[83]
Colon cancer	CT26 cells into BALB/c mice	Exendin-4	10 nmol/kg for 2 weeks	↑ Apoptosis ↓ Proliferation	[84]
Ovarian cancer	SKOV-3 cells into female nude mice	Exendin-4	500 ng/day or 2 μg/day for 28 days	↓ Tumor size ↓ Tumor weight ↓ Tumor volume	[85, 89]
Intestinal cancer	Apc(Min/+) mice	Exendin-4	For 1 month	↑ Small bowel weight ↑ Small bowel length ↑ Large bowel weight	[89]
Liver cancer	N/A	Liraglutide	N/A	↓ Body weight ↓ Fasting blood glucose ↓ Tumor lesions ↓ Fat deposition ↑ Insulin-positive β-cells	[90]

dipeptidyl peptidase-4 (DPP-4) [97] and gives it the distinct advantage of increased albumin affinity [96]. Moreover, due to these substitutions, semaglutide has a prolonged half-life of approximately 168 h, which is impressive given the knowledge that native GLP-1 has a half-life of 2 min, in comparison [98, 99]. This progress in scientific development enables a 1-week administration of the drug, making them an efficient alternative to other antidiabetic drugs, such as metformin, which requires two daily doses, and the updated metformin, which requires daily doses [100, 101].

Furthermore, semaglutide is superior to other GLP-1R agonists, such as liraglutide, which uses similar pharmacological mechanisms but only has a half-life of 13 h and therefore has to be injected subcutaneously daily. This is underscored by the results of a clinical trial comparing the development of obese adults who received either semaglutide or liraglutide in addition to nutritional advice and physical activity, and significantly greater weight loss was achieved in the semaglutide group [102].

Semaglutide, as a GLP-1R agonist, works very similarly to GLP-1 by potentiating glucose-stimulated insulin secretion from the pancreatic β-cells while suppressing glucagon secretion by pancreatic α-cells [103]. Therefore, antidiabetic medication decreases blood sugar levels, reduces body weight through a reduction in appetite [94], and lowers glycated hemoglobin (HbA1c), all while having a low risk of causing hypoglycemia [104]. Although GLP-1R agonists exhibit protective and regulatory effects on blood glucose levels, they have been positively correlated with tumor progression in patients with diabetes [51, 73].

7 Semaglutide's role in the medical triad of diabetes, obesity, and cancer

The prevalence of T2DM has increased significantly in the past decades. It is likely to be the fifth most common cause of death, following an 8% attribution to the mortality rate in the USA, Canada, and the Middle East [105]. Patients with T2DM tend to secrete less insulin following a glucose-heavy meal possibly due to decreased levels of glucagon-like peptide-1 (GLP-1) [96]. Characterized by insulin resistance, gradual progressive loss of insulin secretion by β-cells, and being heavily driven by being overweight or obese [98], T2DM leads to hyperglycemia, excessive urine production, increased risk of cardiovascular disease, and changes in energy metabolism [106]. To lessen the effects of these symptoms, patients with T2DM are encouraged to improve their eating lifestyles and increase their physical activity [107].

Nevertheless, despite the positive outcomes of exercise and diet, recommended glycemic levels (e.g., HbA1c < 7.0%, 53.0 mmol/mol for nonpregnant adults) [108] may sometimes be challenging to achieve. Therefore, the addition of glucose-lowering agents is recommended by the American and European Diabetes Associations to control and/or minimize the risk of cardiovascular disease and microvascular complications [103]. In this regard, semaglutide is becoming increasingly important, as demonstrated in Table 3, which summarizes the previous results of phase 3 clinical trials.

Semaglutide was tested in clinical trials on individuals with obesity and diabetes. Phase three of the clinical trials was conducted using semaglutide concentrations ranging from 0.5 to 2.0 mg for 30–104 weeks. A decrease in body weight, blood pressure, HbA1c, fasting insulin, insulin resistance, plasma glucagon, total cholesterol, lipids, FPG, SMBG, cardiovascular death, nonfatal stroke, and myocardial infarction are observed with the use of semaglutide in monotherapy or in combination with other antidiabetic drugs. (Table 3). However, an increase in gastrointestinal adverse events, diarrhea, hypoglycemia, nausea, neoplasm, treatment-emergent adverse events, pancreatic enzymes, diabetic retinopathy complications, and pancreatic cancer was observed to accompany the treatment using semaglutide. Several clinical trials implemented a combination of semaglutide treatments with sulfonylurea, sitagliptin, basal insulin, metformin, or other antidiabetic drugs (Table 3).

Altogether, clinical trials in phase 3 that applied semaglutide in monotherapy and combined with other antidiabetic drugs yielded similar results. However, suppose semaglutide is reduced to $1711.03 per year. In that case, it will be considered cost-effective and preferable treatment compared to other GLP-1R agonists and antidiabetic drugs [123]. The decrease in HbA1c caused by semaglutide is accompanied by a reduction in body weight, which is unique to semaglutide as an antidiabetic medication. Therefore, injections of semaglutide can assist individuals in maintaining a healthier lifestyle with a decrease in the rate of potential cardiovascular diseases [124]. The effect of semaglutide alone is sufficient to the result in positive outcomes. Still, these positive results can be enhanced when in combination with other drugs, such as metformin, which allows for an effective treatment plan with no increase in adverse symptoms usually seen with the treatment of semaglutide alone [121, 122, 125, 126]. Furthermore, the possible promotion of cancer cell growth is increasingly being discussed with contradictory results (Table 4) that require clarification.

Semaglutide is associated with increased neoplasm and tumorigenesis, specifically in the thyroid, bladder, colorectal, and pancreas. Doses of 0.5–1.0 mg yielded 1–155 cases of cancer development in the treatment period of 30–104 weeks. Lower cases were reported in the thyroid, bladder, colorectal, and pancreas compared to a treatment period of 104 weeks with 0.5 mg of semaglutide, which yielded 155 cases of neoplasm. On the contrary, for the same treatment period but at a drug concentration of 1.0 mg, there was only 1 case of thyroid cancer (Table 4).

Semaglutide, among other antidiabetic drugs, has shown an association with cancer as it alters the rates of tumorigenesis and proliferation. This GLP-R1 agonist seems to increase oncogenesis in multiple tissues, including the thyroid, bladder, pancreatic, and colorectal [97, 110, 121].

Pharmaceutical companies have issued a warning about the use of formulations of semaglutide with those who have thyroid cancer or are at risk of developing it [128]. Despite some studies showing cases of cancer development, the numbers reported are as minimal as one case. There is no

Table 3 Semaglutide's effect on type 2 diabetes and obesity in phase 3 trials

Sustain number	Number of participants	Concentration and treatment duration	Monotherapy vs. combined therapy	Results	Reference
1	388	0.5, or 1.0 mg for 30 weeks	Monotherapy	↓ HbA1c ↓ Body weight ↑ Nausea ↑ Diarrhea	[109]
2	1231	0.5, or 1.0 mg for 56 weeks	Both, combined with 100 mg sitagliptin	Monotherapy: ↓ HbA1c ↓ Body weight Both: ↑ Hypoglycemia ↑ Nausea ↑ Diarrhea	[110]
3	813	1.0 mg for 56 weeks	Monotherapy	↓ HbA1c ↓Fasting insulin ↓Insulin resistance ↓Plasma glucagon ↓ Body weight ↑ Gastrointestinal adverse events ↑ Neoplasms	[111]
4	1089	0.5, or 1.0 mg for 30 weeks	Combined with metformin alone or with sulfonylurea	↓ HbA1c ↓ Body weight	[112]
5*	397	0.5, 1.0 mg for 30 weeks	Combined with basal insulin	↓ HbA1c ↓ Body weight ↑ Neoplasms ↑ Pancreatic cancer	[97]
6	3297	0.5, 1.0 mg for 104 weeks	Monotherapy	↓ HbA1c ↓ Body weight ↓Cardiovascular death ↓ Nonfatal stroke and myocardial infarction ↓ Mean systolic blood pressure ↑ Diabetic retinopathy complications	[113]
7	1201	0.5, 1.0 mg for 24 weeks	Monotherapy	↓ HbA1c ↓ Body weight	[114]
8	788	1.0 mg for 52 weeks	Combined with metformin	↓ HbA1c ↓ Body weight ↑ Gastrointestinal adverse events	[115]
9	302	1.0 mg for 37 weeks	Combined with sodium-glucose cotransporter-2 (SGLT-2) inhibitors and metformin or sulfonylurea	↓ HbA1c ↓ Body weight ↑ Gastrointestinal adverse events	[116]
10	577	1.0 mg for 30 weeks	Combined with oral antidiabetic drugs	↓ HbA1c ↓ Body weight ↓ FPG ↓ SMBG ↑ Gastrointestinal adverse events ↑ Improvement in total cholesterol and triglycerides	[117]
11	1748	1.0 mg for 52 weeks	Combined with metformin and insulin glargine	↓ HbA1c ↓ Body weight ↓ Systolic blood pressure ↑ Gastrointestinal adverse events	[118]
FORTE	961	1.0 or 2.0 for 40 weeks	Combined with metformin and with or without sulfonylurea	↓ HbA1c ↓ Body weight ↓ Blood pressure ↑ Gastrointestinal adverse events	[119]

Table 3 (continued)

Sustain number	Number of participants	Concentration and treatment duration	Monotherapy vs. combined therapy	Results	Reference
Japan	308	0.5 mg, or 1.0 mg for 30 weeks	Monotherapy	↓ HbA1c ↓ Body weight ↓ Blood pressure ↓ VLDL cholesterol and triglycerides ↑ Treatment of emergent adverse events	[120]
Japan	601	0.5, or 1.0 mg for 63 weeks	Both monotherapy and combined with an oral antidiabetic drug	↓ HbA1c ↓ Body weight ↓ Insulin ratios ↓ Blood pressure ↓ All lipids (except free fatty acids and HDL cholesterol) ↑ Treatment of emergent adverse events ↑ Pancreatic enzymes	[121]
China	868	0.5, or 1.0 mg for 30 weeks	Combined with metformin	↓ HbA1c ↓ Body weight ↓ Systolic blood pressure ↓ Total cholesterol ↑ Gastrointestinal adverse events ↑ Amylase and lipase	[122]

*Represents a single case

Table 4 Semaglutide's involvement with cancer as an adverse effect

Cancer type	Concentration and duration	Number of participants	Number of events in placebo	Number of events caused by semaglutide	Reference
Neoplasms	0.5 mg or 1.0 mg for 56 weeks	$n=818$	$n=0$	$n=14$	[110]
EAC-confirmed neoplasms	1.0 mg for 56 weeks	$n=813$	N/A	$n=15$	[111]
EAC-confirmed neoplasms	0.5 or 1.0 mg for 30 weeks	$n=397$	$n=1$	$n=5$	[97]
Neoplasms	0.5 or 1.0 mg for 104 weeks	$n=136$	$n=70$	$n=66$	[113]
Neoplasms	0.5 or 1.0 mg for 24 weeks	$n=601$	N/A	$n=6$	[114]
Neoplasms	1.0 mg for 52 weeks	$n=367$	N/A	$n=3$	[115]
Neoplasms	1.0 mg for 37 weeks	$n=302$	$n=5$	$n=4$	[116]
Neoplasms	1.0 mg for 30 weeks	$n=577$	N/A	$n=9$	[117]
Neoplasms	1.0 mg for 52 weeks	$n=874$	N/A	$n=11$	[118]
Neoplasms	0.5 or 1.0 mg for 63 weeks	$n=595$	N/A	$n=44$	[121]
Neoplasms	0.5 or 1.0 mg for 30 weeks	$n=578$	N/A	$n=23$	[122]
Thyroid	1.0 mg for 104 weeks	$n=1648$	$n=4$	$n=1$	[127]
Thyroid	1.0 mg for 56 weeks	$n=818$	$n=0$	$n=1$	[110]
Bladder	1.0 mg for 30 weeks	$n=205$	N/A	$n=1$	[120]
Bladder	1.0 mg for 56 weeks	$n=818$	$n=0$	$n=1$	[110]
Pancreatic	0.5 mg for 30 weeks	$n=722$	N/A	$n=1$	[112]
Pancreatic	1.0 mg for 30 weeks	$n=397$	N/A	$n=1$	[97]
Colorectal	0.5 mg for 30 weeks	$n=397$	$n=1$	$n=1$	[97]
Colorectal	0.5 or 1.0 mg for 63 weeks	$n=595$	N/A	$n=18$	[121]

conclusive evidence that semaglutide induced cancer development in tissue, which may imply that the development of cancer may pertain to other causes rather than semaglutide application [129]. On the contrary, several authors report mitigation of cancer proliferation using the same dose of 0.5–1.0 mg semaglutide ingested by diabetic patients and

for similar periods. The increase in semaglutide is gradual and can be altered to scale up every 30 days when ingested orally. This accumulation may aid semaglutide's action against cancer cells [130]. There is a pool of research on the effect of liraglutide and exendin on cancer. However, there is a lack of research data on the impact of semaglutide *in vitro* and *in vivo*, which limits its efficiency in tumor therapy. Further research must be conducted to understand the effects of semaglutide on cancer as it belongs to the GLP-1R family along with liraglutide and exendin and may provide similar results.

8 Conclusions

Semaglutide, like many other GLP-1R agonists, is used in diabetes and obesity to decrease glucose levels and manage body weight, which plays a role in tumorigenesis. The insufficient *in vivo* studies on semaglutide and limited *in vitro* research raise concerns about the imperative for more comprehensive investigations into its effects. Specifically, there is a need to elucidate a descriptive mechanism through which semaglutide reduces diabetes and obesity and potentially influences cancer. Although there is a lack of direct studies on semaglutide, the observed actions align with those of other GLP-1R agonists, indicating a potential impact on cancer. There is a notable increase in thyroid cancer with the use of GLP-1R agonists, including semaglutide. The use of GLP-1R agonists increases calcitonin gene-related peptide (CGRP) in thyroid cancer. Overexpression of pS6, mTOR activation, calcitonin, and C-cell hyperplasia reported in *in vivo* suggest the increased proliferation and tumorigenesis [75, 87]. Despite the cancer cases recorded with the use of semaglutide, other factors may have contributed to cancer development with no association with semaglutide [129]. However, whether Semaglutide's effect is mitigating or exacerbating remains unclear, emphasizing the necessity for further research on the outcome of GLP-1R agonists on cancer, specifically thyroid cancer.

Abbreviations Akt: Protein kinase B; BMI: Body mass index; cAMP: Cyclic adenosine monophosphate; CGRP: Calcitonin gene-related peptide; DM: Diabetes mellitus; DPP: 4-dipeptidyl peptidase-4; GLP: 1-glucagon-like peptide-1; GLP: 1R-glucagon-like peptide-1 receptor; HbA1c: Glycated hemoglobin; IGF: Insulin-like growth factor; MAPK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; NF: κB-nuclear factor κB; PI3K: Phosphoinositide 3-kinase; PKA: cAMP-dependent protein kinase; SGLT: 2-sodium-glucosecotransporter-2; T2DM: Type 2 diabetes mellitus

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Declarations

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