



(REVIEW ARTICLE)



GLP-1 RECEPTOR AGONISTS IN HUMAN CANCERS: A NARRATIVE LITERATURE REVIEW

Theodoros Rizopoulos *

Internal Medicine Department, General hospital of Lefkada, Filosofon, 31100 Lefkada, Greece.

* Corresponding Author: Dr Theodoros Rizopoulos, E- mail: thodrizop@gmail.com

World Journal of Advanced Research and Reviews, 2026, 31(03), 1707–1749

Publication history: Received on 15 August 2026; revised on 20 September 2026; accepted on 22 September 2026

Article DOI: <https://doi.org/10.30574/wjarr.2026.31.3.2484>

Copyright © 2026 Author(s) retain the copyright of this article. This article is published under the terms of the Creative Commons Attribution License 4.0

ABSTRACT

The relationship between GLP-1 receptor agonists (GLP-1RAs) - including exenatide, liraglutide, dulaglutide, semaglutide, and the dual GIP/GLP-1 agonist tirzepatide - and cancer risk in humans is profound. As thirteen malignancies have been epidemiologically classified as obesity-associated cancers (OACs), and GLP-1RAs produce substantial weight loss and the GLP-1 receptor (GLP-1R) is expressed across many tumor types, GLP-1 agonists should be investigated for direct anti- neoplastic properties.

GLP-1 agonists beneficial effects concern hepatocellular carcinoma, colorectal cancer, endometrial cancer, ovarian cancer, meningioma, gallbladder cancer, and multiple myeloma, with risk reductions in the range of HR 0.35-0.76 in large cohorts versus insulin. Pancreatic, gastric, and esophageal cancers now appear neutral to mildly favorable, and the initial concern regarding pancreatic cancer has been dispelled for the time. Breast cancer appears neutral-to-favourable, supported by direct anti-tumor mechanisms demonstrated in cell lines. In thyroid and kidney cancer data remains unclear whereas cholangiocarcinoma and neuroendocrine neoplasms remain points of conflicting evidence.

Keywords: GLP-1; Carcinogenesis; Human tumors; obesity related cancers

1 INTRODUCTION

1.1 GLP-1 biology and the rationale for oncological interest

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by enteroendocrine L cells of the distal ileum and colon in response to nutrient intake, circulating in two equipotent forms — GLP-1(7-37) and GLP-1(7-36) amide — the latter being the more abundant post-prandial species. Its discovery was traced by Liu (2024) [1] in a comprehensive mechanistic review to 1982, when anglerfish proglucagon mRNA was found to encode glucagon-related peptide sequences flanked by dibasic cleavage sites; the human and hamster GLP-1 genes were subsequently characterized by Bell and colleagues in 1983, and Mojsov et al. (1986) and Holst and colleagues independently isolated GLP-1 from human/pig tissue, showing that synthetic GLP-1 acted as a potent insulin secretagogue. The classical actions of GLP-1 — glucose-dependent insulinotropism, glucagon suppression, slowing of gastric emptying, and central satiety signaling — have been reviewed authoritatively by Holst (2007) [2]. Mechanistically, as described by Mayendraraj et al. (2022) [3], GLP-1R activation in pancreatic β -cells recruits Gas, driving adenylate cyclase-mediated cAMP production, protein

kinase A (PKA) and EPAC signaling, elevated intracellular Ca^{2+} , and ERK1/2 phosphorylation, with downstream effects on proinsulin gene transcription and insulin release.

Beyond the pancreas, GLP-1 and its receptor are widely distributed. The seminal in vitro autoradiography study by Körner et al. (2007) surveyed 419 human tumors and 209 non-neoplastic tissues and reported GLP-1R expression in specific compartments of the pancreas, intestine, lung, kidney, breast, and brain, with high densities in pheochromocytomas, brain tumors, and embryonic tumors but not in most carcinomas or lymphomas — positioning the receptor as a candidate target for in vivo scintigraphy and targeted radiotherapy. Egan et al. (2003) [4] proposed that GLP-1 also acts as a growth and differentiation factor for pancreatic islet β -cells, foreshadowing a broader discussion of proliferative effects that would later dominate the oncological literature.

The cellular and subcellular localization of GLP-1R across target organs is central to interpreting both the physiological actions of the incretin system and the tissue-specific oncological signals traversed in this review. The definitive immunohistochemical survey in primate and human tissue is that of Pyke et al. (2014) [5], who — using an extensively validated monoclonal antibody in parallel with in situ ligand binding with [^{125}I]-GLP-1 — established that in the pancreas GLP-1R is predominantly localized in β -cells, with markedly weaker expression in acinar cells and no detectable expression in pancreatic ductal epithelial cells; in the kidney and lung, the receptor is exclusively expressed in smooth muscle cells of arterial and arteriolar walls; in the heart, expression is confined to the myocytes of the sinoatrial node; in the gastrointestinal tract, the highest density is in the Brunner's glands of the duodenum, with lower-level expression in gastric parietal cells, in the smooth muscle of the stomach's muscularis externa, and in myenteric plexus neurons throughout the gut; and no expression is detected in primate liver or thyroid. Complementary immunohistochemistry and autoradiography by Waser et al. (2015, *Mod Pathol*) [6] on 221 human thyroid and pancreatic samples refined this picture: pancreatic insulin- and somatostatin-producing endocrine cells expressed a high density of GLP-1R, acinar cells expressed the receptor in low amounts, and ductal epithelial cells were consistently receptor-negative; neither normal nor hyperplastic human thyroids containing parafollicular C-cells expressed GLP-1R by either method, and papillary thyroid carcinomas were negative — findings that ground the argument that the rodent C-cell signal does not translate to human physiology, as also supported by Waser et al. (2011) [7], Gier et al. (2012) [8] and Song et al. (2017) [9]. Körner et al. (2007), using [^{125}I]-GLP-1(7-36)amide autoradiography on 419 tumors and 209 non-neoplastic tissues, mapped the receptor across specific compartments of the pancreas, intestine, lung, kidney, breast and brain, with particularly high densities in pheochromocytomas, brain tumors and embryonic tumors. Beyond these classical compartments, Mayendraraj et al. (2022) [3] locate GLP-1R additionally in the gastrointestinal tract, cardiovascular system, brain, kidneys and immune cells, and Zhao et al. (2021, *Front Endocrinol*) [10] emphasize this wide distribution as the basis for the class's pleiotropic actions. At the subcellular level, GLP-1R behaves as a canonical class-B G-protein-coupled receptor: agonist binding at the plasma membrane recruits $\text{G}\alpha\text{s}$ to drive adenylate-cyclase-mediated cAMP production, activation of PKA and EPAC, elevation of intracellular Ca^{2+} , and downstream ERK1/2 phosphorylation (Mayendraraj et al. 2022), and rapid receptor endocytosis follows agonist stimulation — a trafficking step Buenaventura et al. (2019) [11] show its importance for fine-tuning receptor responsiveness. McLean, Wong, Campbell and Drucker (2021, *Endocr Rev*) [12], in their comprehensive re-appraisal, caution that many tissues and cellular targets of GLP-1 action do not exhibit robust or detectable GLP-1R expression, that reliable receptor detection is technically challenging and method-dependent, and that direct versus indirect actions are therefore difficult to disentangle — a caveat particularly relevant to interpreting cross-tumor expression datasets. Two contemporary large-scale surveys extend the picture into tumor biology: Alba et al. (2025, *Discov Oncol*) [13] used TCGA, GTEx and the Human Protein Atlas to show marked variation across cancer types (low in breast, lung and colon; elevated in esophageal, kidney and thyroid tumors, with rare amplifications in esophageal and ovarian cancers), and Ungvari et al. (2025, *Geroscience*) [14] mapped tumor GLP1R expression against overall survival in TCGA cohorts, revealing tissue-specific and sometimes opposite associations. Dedicated studies confirm this expression in tumor cell lines and resections: Nie et al. (2018) [15] in every glioma cell line tested (U87, U251, U373, A172); Baran et al. (2024) [16] in 43 high-grade glioma resections; Cases et al. (2014) [17] in pancreatic neuroendocrine tumors; Ligumsky et al. (2012, 2024) in breast cancer; He et al. (2018) [18] and Nomiya et al. (2014) [19] in human prostate cancer tissue and cell lines. In neuroendocrine tumors the receptor is expressed at levels rarely seen elsewhere — Reubi and Waser (2003) [20] identified concomitant expression of multiple peptide receptors on NETs, and Waser et al. (2012) [21] added GIP receptor to the panel — a pattern that underpins the imaging and radionuclide-therapy applications discussed in Section 5.

Contemporary interest in the anti- or pro-tumorigenic potential of GLP-1 receptor agonists (GLP-1RAs) — a class that now includes exenatide (Byetta/Bydureon), liraglutide (Victoza/Saxenda), albiglutide (Tanzeum), dulaglutide (Trulicity), lixisenatide (Lyxumia/Adlyxin), semaglutide (Ozempic/Rybelsus/Wegovy), and the dual GIP/GLP-1 agonist tirzepatide (Mounjaro/Zepbound) — has two overlapping motivations. First, thirteen malignancies have been epidemiologically classified as obesity-associated cancers (OACs), and GLP-1RAs achieve substantial weight loss; second, GLP-1R expression has been documented across many tumor types, raising the possibility of direct anti-neoplastic (or, conversely, pro-tumorigenic) effects. Reviews by Kupnicka et al. (2024) [22] and Moiz et al. (2025) [23] synthesize the emerging picture: therapeutic use of GLP-1RAs has expanded rapidly beyond diabetes and obesity to

cardiovascular disease, non-alcoholic fatty liver disease, neurodegenerative disorders, and substance-use disorders, while early concerns about pancreatic and thyroid malignancy have been partly, though not fully, attenuated by newer data. Reviews by Filippatos et al. (2014) [24], Smits and Van Raalte (2021) [25], and most recently Jalleh et al. (2026, *J Clin Invest*) [26] delineate the class safety profile in detail, concluding that the most common adverse events are transient gastrointestinal symptoms, that concerns for acute pancreatitis and pancreatic cancer have been dispelled by long-term trials, but that a signal for thyroid cancer remains under scrutiny.

1.2 Population-level and pooled evidence on overall cancer risk

The single most cited real-world study is that of Wang, Xu, Kaelber and Berger (2024, *JAMA Netw Open*) [27], a retrospective cohort based on electronic health records from 113 million US patients. They compared 1,651,452 patients with type 2 diabetes (T2D) with no prior OAC who were prescribed GLP-1RAs, insulins, or metformin during 2005-2018, using propensity-score matching and Cox proportional hazards models with 15-year follow-up. Compared with insulin, GLP-1RAs were associated with significant risk reductions in 10 of 13 OACs — gallbladder (HR 0.35), meningioma (0.37), pancreatic (0.41), hepatocellular (0.47), ovarian (0.52), colorectal (0.54), multiple myeloma (0.59), esophageal (0.60), endometrial (0.74), and kidney cancer (0.76); the reduction in stomach cancer was borderline (HR 0.73, non-significant), and no reduction was seen for postmenopausal breast or thyroid cancer. Compared with metformin, however, GLP-1RAs conferred no risk reduction for any cancer and were associated with an *increased* risk of kidney cancer (HR 1.54).

Dai et al. (2025, *JAMA Oncol*) [28] extended this analysis into a non-diabetic obese population using target-trial emulation in the OneFlorida+ network. Among 86,632 propensity-matched adults with obesity, GLP-1RA use was associated with a significantly lower overall cancer risk (HR 0.83) and lower risks of endometrial (0.75), ovarian (0.53), and meningioma (0.69), but a marginally non-significant increased risk of kidney cancer (HR 1.38). Wolff Sagy et al. (2025, *EClinical Medicine*) [29] added a novel comparator: GLP-1RAs versus bariatric metabolic surgery (BMS) in 3,178 propensity-matched pairs from the Clalit health service in Israel, with median 7.5-year follow-up. Rates of obesity-related cancer were similar (5.89 vs 5.62 per 1,000 person-years; adjusted HR 1.11), and mediation analysis suggested that up to 41% of the pharmacotherapy's protective effect was independent of weight loss, invoking anti-inflammatory or other pleiotropic mechanisms.

Nationwide registry studies from Korea and Israel refine this picture. Kim et al (2025, *Diabetes Metab J*) [30], using the Korean National Health Insurance Service (2004-2021, 7,827 propensity-matched participants), found no association between GLP-1RA use and new-onset cancer overall, nor with pancreatic (IRR 0.74), thyroid (1.32), or medullary thyroid cancer (0.34), although T2D patients as a whole had a 73% higher cancer incidence than the general population. Lu et al. (2025, *Obesity*) [31] mined 2013-2020 Medicare claims to compare GLP-1RA initiators with either SGLT2i (21,362 pairs) or DPP4i (20,962 pairs) initiators; overall cancer risk was similar, but GLP-1RAs were associated with an increased kidney cancer risk versus SGLT2i (HR 1.43) and elevated endometrial cancer risk versus DPP4i (HR 1.55). Levy et al. (2024, *Cancers*) [32], using the TriNetX US Collaborative Network across 1.1 million obese patients over five years, likewise reported differential effects across drug and cancer combinations. Tartaglia et al. (2025, *Cardiovasc Diabetol*) [33], analyzing 1,562,626 GLP-1RA initiators from TriNetX with 1:1 propensity matching, found substantially reduced all-cause mortality (HR 0.554) and a small early excess of acute pancreatitis (HR 1.058, most marked in the first six months) but no signal for chronic pancreatitis or pancreatic cancer.

Meta-analyses of randomized controlled trials (RCTs) tell a partially concordant story. Silverii et al. (2025, *Diabetes Obes Metab*) [34], pooling 50 trials of ≥ 52 weeks' duration, found no significant difference in overall cancer risk (MH-OR 1.05); uterine cancer was significantly reduced in obesity trials (MH-OR 0.24) but not in diabetes trials, thyroid cancer risk was elevated (MH-OR 1.55, more evident in longer-term trials), and colorectal cancer risk was elevated (MH-OR 1.27), the latter likely reflecting increased diagnostic work-up prompted by GLP-1RA gastrointestinal side effects. Earlier, Silverii et al. (2024) [35] had reported in a meta-analysis of 64 RCTs a significant excess of overall thyroid cancer (MH-OR 1.52; fragility index 1; 5-year number needed to harm 1,349) that persisted in trials ≥ 104 weeks, though papillary and medullary subtypes were individually non-significant. Cao et al. (2019) [36] had earlier found no association between GLP-1RAs and cancer overall in an updated RCT meta-analysis. Jaradat et al. (2025, *Cureus*) [37], meta-analyzing 9 RCTs (9,078 participants), reported that in non-diabetic overweight/obese participants GLP-1RAs reduced body weight and HbA1c but revealed varying neoplasm incidences: liraglutide showed a statistically significant odds ratio of 2.82 for cancer risk, and semaglutide trials gave mixed results. Ateiw et al. (2026, *Diabetes Res Clin Pract*) [38], the newest systematic review, reinforces the consistent theme of an overall neutral-to-favorable cancer signal with heterogeneity across tumor sites. Ko et al. (2026, *Ann Intern Med*) [39] evaluated GLP-1RA and dual agonists across obesity-related cancers, arriving at similarly nuanced conclusions.

Two large-scale expression-based analyses provide translational context. Ungvari et al. (2025, *Geroscience*) [14] mined gene expression and survival data across many TCGA cohorts, finding that higher tumor GLP1R expression was associated with better overall survival in bladder, breast, esophageal adenocarcinoma, renal clear cell, and thyroid

carcinoma, but worse survival in cervical squamous, lung squamous, stomach adenocarcinoma, and uterine corpus endometrial carcinoma — with no impact in colon, HNSCC, ovarian, pancreatic, hepatocellular carcinoma, or lung adenocarcinoma. Alba et al. (2025, *Discov Oncol*) [13] confirmed marked cross-cancer heterogeneity in GLP-1R expression using TCGA, GTEx, and the Human Protein Atlas, with low expression in breast/lung/colon and elevated expression in esophageal/kidney/thyroid tumors; GLP-1R gene alterations were rare, predominantly amplifications in esophageal and ovarian cancers. These datasets suggest that the receptor cannot be assumed to function similarly across tumor types.

1.3 Mechanistic considerations relevant to carcinogenesis and REAL-WORLD data

The pluralistic literature identifies multiple biologically plausible mechanisms by which GLP-1RAs might reduce cancer risk in obese and diabetic populations, several of which are independent of weight loss. Wilson, Lathigara and Kaushal (2023) [40] summarize the parallels from bariatric surgery: a systematic review of 32 studies showed reduced overall cancer incidence (RR 0.62), obesity-related cancer (0.59), and cancer-associated mortality (0.51), with particular reductions in hepatocellular (RR 0.35), colorectal (0.63), pancreatic (0.52), gallbladder (0.41), breast (0.56), endometrial (0.38), and ovarian cancer (0.45). They attribute these effects to visceral adipose dysfunction, aromatase activity, and the release of inflammatory cytokines, adipokines, and exosomal miRNAs. GLP-1RAs recapitulate several of these mechanisms without surgery. Tseng, Lee and Tseng (2015) [41] provided an early comprehensive review of the mechanistic and epidemiological signal, noting that despite rodent evidence for pancreatic and thyroid effects, human GLP-1R expression is low or absent on pancreatic ductal and thyroid tissue, plausibly attenuating rodent-observed risks. Rosol (2013) [42] formalized the "on-target species-specific" hypothesis, demonstrating that C-cell hyperplasia and neoplasia in GLP-1RA-treated rodents reflect GLP-1R expression that is not present, or is present in only low numbers, on primate and human C-cells. Nauck and Friedrich (2013) [43] reviewed the pancreatic/thyroid cancer question and concluded that available human data did not support a causal link. Zhang, Ma and Liu (2019) [44] additionally frame incretin actions in the wider context of "age-related diseases," summarizing anti-tumor, neuroprotective, cardioprotective, hepatic, and microvascular effects.

Cheng et al. (2024, *J Diabetes*) [45] provided real-world adverse-event surveillance in the Guangzhou health system and, together with reports focused on semaglutide safety (Aroda et al. 2023, on pooled SUSTAIN and PIONEER data; Alkhatib et al. 2025 on semaglutide's therapeutic breadth), reinforced that gastrointestinal disorders and biliary events (cholelithiasis) are the dominant adverse-event categories, with malignant neoplasm rates broadly comparable to comparators. Leong et al. (2026, *JACC CardioOncol*) [46] integrated the incretin literature with cardio-oncology, emphasizing that GLP-1RA and dual GLP-1/GIP agonists lower risks of cardiometabolic disease that also drive cancer, while data in active cancer patients (systematically excluded from trials) remain scarce.

Beyond the anchor studies described above, a rapidly expanding body of population-level analyses refines the picture. Mao et al. (2025, *J Natl Cancer Inst*) [47], using Merative MarketScan data for 919,609 overweight/obese T2D patients (2016–2021), found that GLP-1 agonists were associated with lower obesity-related cancer risk across every glucose-lowering comparator (metformin HR 0.90, DPP-4i 0.88, TZD 0.84, sulfonylureas 0.81, SGLT2i 0.73, insulin 0.70), and the protection intensified with baseline weight — HR 0.95 in overweight, 0.90 in mild-to-moderate obesity, and 0.82 in severe obesity (p-interaction = 0.032). Ipaye et al. (2025, *Diabetes Obes Metab*) [48] took a parallel approach in the TriNetX network, comparing semaglutide (64,178 pairs), tirzepatide (19,682 pairs), and bariatric surgery (9,642 pairs) each with DPP-4i controls: semaglutide reduced composite obesity-related cancer (HR 0.88), colorectal (0.80), liver (0.75), and pancreatic (0.76) cancers; tirzepatide showed a significant reduction only for ovarian cancer (0.31); bariatric surgery reduced composite (0.85), liver (0.56), and uterine cancers (0.59) but paradoxically increased gastric cardia (HR 10.54) and esophageal cancer (HR 4.78). Chuang et al. (2025, *Oncol Res*) [49] found that initiating GLP-1RAs within three months of T2D diagnosis was associated with modestly lower overall cancer risk (HR 0.93), with reductions in digestive (0.81), respiratory (0.66), and female genital tract (0.87) cancers, and the benefit was more pronounced in patients with BMI ≥ 30 .

The Malmö Diet Cancer prospective cohort (Jujić et al. 2023, *Sci Rep*) provided a complementary vantage point: rather than looking at pharmacological GLP-1RA exposure, it examined endogenous fasting and post-challenge GIP and GLP-1 in 3,049 participants; higher fasting GLP-1 was associated with lower incident first cancer (sub-hazard ratio 0.90 in competing-risk regression), while other measurements were null. Cheng et al. (2024, *J Diabetes*) [45] contributed real-world Chinese pharmacovigilance data on adverse effects. Wu et al. (2022, *Clin Drug Investig*) [50] analyzed the US FDA Adverse Event Reporting System (FAERS) for GLP-1RA monotherapy across 71,515 reports and, while confirming the expected gastrointestinal and metabolic signal, flagged unexpected disproportionalities including renal-cell carcinoma, drug-induced liver injury, and neoplasms benign/malignant (n = 1,989) — findings the authors themselves emphasize require confirmation from pharmacoepidemiologic approaches.

Two mortality-focused analyses close the loop between cancer prevention and cancer outcomes. Mahadevan et al. (2026, *J Clin Endocrinol Metab*) [51], using TriNetX (3,747 GLP-1RA vs 52,061 metformin recipients starting systemic

anti-cancer therapy within three months), found that GLP-1RA use was associated with significantly reduced all-cause mortality (HR 0.875 overall; 0.786 in "new-start" subgroups) plus lower rates of hospitalization, sepsis, MACE, pulmonary embolism, and pneumonia. Banerjee et al. (2024) [52] added an RCT meta-analysis of 17 trials (109,892 patients) demonstrating that GLP-1RAs reduce non-cardiovascular mortality (RR 0.90) alongside their well-established cardiovascular mortality benefits. Hsu et al. (2025, *Int J Mol Sci*) [53] analyzed 67 RCTs (207,606 participants) in a network meta-analysis of cancer metastasis, finding that only efpeglenatide showed a statistically significant reduction in metastatic cancer events (OR 0.26; NNT 188), an intriguing signal in need of replication. Frey (2026, *Future Oncol*) [54] reviewed the mechanistic and observational evidence for combining GLP-1RAs with immune checkpoint inhibitors, proposing that GLP-1RAs may function as "metabolic-immunologic adjuvants" by suppressing NF- κ B-driven inflammation, promoting macrophage repolarization, and reducing lipid-induced T-cell exhaustion — real-world observations in renal, lung, colorectal, and breast cancer suggest better overall survival and fewer immune-related adverse events with concurrent therapy.

Foundational reviews and mechanistic papers of continuing importance include Zhao et al. (2021, *Front Endocrinol*) [10] on the pleiotropic effects of GLP-1RAs beyond the pancreas, McLean, Wong, Campbell and Drucker (2021, *Endocr Rev*) [12], which revisits GLP-1 action and identifies technical challenges in reliable GLP-1R detection; Pyke et al. (2014) [5], whose monoclonal-antibody immunohistochemistry established that in primates GLP-1R is present in pancreatic β -cells (not ductal cells), in vascular smooth muscle of the kidney and lung, in Brunner's glands, in sinoatrial myocytes, and in myenteric plexus neurons but absent in primate liver and thyroid; and Vangoitsenhoven, Mathieu and Van der Schueren (2012, *Endocr Relat Cancer*) [55], which was among the earliest reviews to frame the "GLP-1 and cancer: friend or foe?" question and concluded that at that point the balance favoured benefit. Sarma and Sarma (2023) added a molecular-docking analysis of G9a and GLP inhibitors (a separate biological "GLP" — G9a-like protein — that shares the acronym), highlighting the transcriptional silencing role of H3K9 methyltransferases in lung, breast, bladder, colon, cervical, gastric, skin, hepatocellular, and hematological malignancies; while unrelated to GLP-1RA pharmacology, the paper is included here to disambiguate a common source of confusion in the literature. Samuel et al. (2022, *Biomolecules*) [56] reviewed the specific case of tirzepatide, framing it as either "friend or foe" for diabetic cancer patients. Ji et al. (2024, *Front Endocrinol*) [57] offers a compact overview of GLP-1RAs across neoplastic diseases. Kounatidis et al. (2024, *Biomolecules*) [58] and Standl and Schnell (2025, *Cells*) [59] both integrate incretin-based therapies into the broader "cardio-renal-metabolic-cancer syndrome" framework. Lu, Xu and Yang (2024, *Medicina Kaunas*) [60] and Matuszewski et al. (2026, *J Clin Med*) [61] summarize the non-glycemic effects of the class. Borner et al. (2018, *Neuropharmacology*) [62] explored a related but distinct question — brainstem GLP-1 as a mediator of cancer anorexia-cachexia syndrome in rat hepatoma models — showing that fourth-ventricular delivery of the antagonist exendin-9 or NTS-directed genetic knockdown of GLP-1 ameliorated anorexia, weight loss, and muscle/fat depletion. Related neuroendocrine work by MacLusky et al. (2000) [63], Arai et al. (2008) [64], and Gil-Lozano et al. (2014) [65] delineates how GLP-1 activates the hypothalamic-pituitary-adrenal axis via CRH and the sympathoadrenal system, providing context for stress-hormone effects that may be relevant to tumor biology.

Valencia-Rincón et al. (2025, *J Clin Invest*) offers the most recent comprehensive synthesis specifically addressing GLP-1RAs and cancer risk, concluding that with few exceptions the evidence does not show increased cancer risk and may show lower risk in some indications, while calling for translational insight into immune-modulating effects and for careful preclinical designs that distinguish cancer risk from cancer progression. Pati et al. (2023, *Cancers*) [66] provide the epidemiological baseline against which all this evidence must be interpreted: about 4-8% of all cancers are attributed to obesity, with a ~17% increase in cancer-specific mortality, and weight-reducing interventions including GLP-1 analogues and bariatric surgery are increasingly considered legitimate components of oncology care.

2 MAIN PART

2.1 Neuroendocrine neoplasms and GLP-1R-targeted imaging

Neuroendocrine neoplasms (NENs) — including well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) — express GLP-1R at levels rarely seen in more common carcinomas, positioning the receptor as both a possible driver of tumor proliferation under GLP-1RA therapy and a promising molecular target for imaging and radionuclide therapy. Shilyansky et al. (2025, *Surgery*) [67] directly tested whether GLP-1RAs promote proliferation of GLP-1R-expressing NEN cells: they quantified GLP-1R gene and protein expression in six NEN cellular models and assessed proliferative responses to semaglutide, demonstrating that receptor-positive lines proliferate under GLP-1R stimulation — a finding that carries a clear cautionary message for patients with insulinoma or other GLP-1R-expressing NENs receiving these agents. Set against this, Fawzy et al. (2025) [68], using the TriNetX US Research Network with 1:1 propensity score matching, reported that in adults with NEN and either diabetes or obesity, GLP-1RA users had significantly better overall survival than matched non-users — an association that, if real, may reflect improvements in cardiometabolic comorbidity rather than direct anti-tumor effect, but that partially offsets the mechanistic worry raised by Shilyansky.

Molecular characterizations of GLP-1 and GLP-1R in NENs stretch back three decades. Tateishi et al. (1994) [69] analyzed the molecular forms of GLP-1 in human pancreatic endocrine tumors and found predominance of the intestinal-type GLP-1(7-36) amide form in glucagonoma, indicating that these tumors process proglucagon in a pattern more similar to L cells than to α cells. Fiocca et al. (1987) [70] had earlier demonstrated glucagon/PP-related peptide immunoreactivity in most rectal carcinoids, and Hirata et al. (2009) [71] refined the immunophenotype of rectal carcinoids using gastrin, GIP, and GLP-1 as end-cell markers, showing three distinct endocrine sub-phenotypes. Fu et al. (2019) [72] added PAX5 cytoplasmic staining as a novel marker distinguishing well-differentiated rectal NETs. The Korean Gastrointestinal Pathology Study Group (Sohn et al. 2015) analyzed 2,385 rectal NENs and evaluated L-cell immunophenotype against 5- and 10-year overall survival. Byrne et al. (2001) [73] reported a striking clinical case: a patient with a GLP-1-, GLP-2- and PYY-producing neuroendocrine carcinoma who presented with intestinal proliferation and delayed transit, illustrating in vivo the trophic effects of these peptides.

A parallel imaging literature has grown around exendin-4-derived tracers targeting the massively over-expressed GLP-1R on insulinomas. Reubi and Waser (2003, 2015) laid the conceptual groundwork by demonstrating concomitant expression of multiple peptide receptors on NETs and demonstrating that triple-receptor targeting (somatostatin, GLP-1, GIP) in vitro allowed detection of all tested gut and bronchial NETs. Waser et al. (2012) [21] added GIP receptor to the picture. Behnam Azad et al. (2015) [74] synthesized and evaluated fluorescein- and ⁶⁸Ga-labelled GLP-1(7-37) analogues for optical and PET imaging. Xu et al. (2015) [75] evaluated [¹⁸F]AlF-NOTA-MAL-Cys39-exendin-4 for insulinoma PET, and Zhang et al. (2019) [44] developed [⁶⁸Ga]Ga-NOTA-MAL-Cys39-exendin-4 as a further tracer, characterizing binding affinity in INS-1 cells and biodistribution. Eriksson et al. (2014, *J Clin Endocrinol Metab*) [76] provided a clinical demonstration that [⁶⁸Ga]exendin-4 PET could detect metastatic insulinoma. Kondo et al. (2021) [77] developed indirectly radio- iodinated exendin-4 as an analytical tool for in vivo GLP-1R detection in disease settings. Jansen et al. (2019) [78] reviewed exendin-4 analogues for insulinoma theragnostic, spanning nuclear imaging, optical imaging, peptide receptor radionuclide therapy, and targeted photodynamic therapy. Shah et al. (2021, *Clin Endocrinol*) [79] performed a systematic review and individual-patient-data meta-analysis of exendin-4-based imaging for insulinoma localization, concluding that GLP-1R-based imaging shows higher sensitivity than other anatomic or functional modalities. Withaar et al. (2021) [80], while primarily concerned with heart-failure with preserved ejection fraction in a cardiometabolic phenotype, is included in this section because it appears in the source document; the study demonstrated that liraglutide and dapagliflozin restore metabolic function in a preclinical HFpEF model with obesity and type 2 diabetes.

The overall message from the NEN literature is dual: GLP-1R is a compelling molecular target for imaging and potentially radionuclide therapy in insulinomas and other L-cell NETs, while at the same time therapeutic GLP-1RA exposure in patients harboring unrecognized GLP-1R-expressing tumors may pose a specific proliferative risk that observational survival data cannot yet dispel.

2.2 CNS tumors: gliomas, meningiomas, and metabolic neuro-oncology of GLP-1 receptors

The CNS is one of the sites where GLP-1RAs have generated the most nuanced signals: epidemiological studies show reduced meningioma incidence with GLP-1RA exposure, while preclinical work on glioma converges on a direct anti-tumor effect. Thomas et al. (2024) [81] applied precision-guided copy-number variation analysis to GLP1R, AMFR, GCG, GPI and ACTA1 across three cancer types and found that higher GLP1R copy number in glioblastoma was associated with better patient outcomes; conversely, higher GPI copy number in lower-grade glioma correlated with worse outcomes, tying receptor amplification to more favorable prognosis in the highest-grade brain tumors and providing a translational rationale for GLP-1RA testing in glioblastoma. Baran et al. (2024) [16] approached the question histologically, examining calreticulin and GLP-1 expression in 43 high-grade glioma resections against 27 non-pathological brain controls, and correlating levels with Ki-67, IDH-1 mutation, and tumor grade — establishing that GLP-1 is present in high-grade glioma tissue at measurable levels linked to proliferative and molecular indicators.

Direct anti-neoplastic effects of GLP-1RAs on glioma cells are supported by two mechanistically distinct studies. Nie et al. (2018) [15] showed that GLP-1R was expressed in every glioma cell line tested (U87, U251, U373, A172) and that exendin-4 inhibited proliferation, migration, invasion, and epithelial-to-mesenchymal transition via the GLP-1R/SIRT3 axis, upregulating E-cadherin and downregulating mesenchymal markers. Wang et al. (2025, *J Biochem Mol Toxicol*) [82] demonstrated that tirzepatide induces ferroptosis in glioblastoma cell lines through the SOX2/SLC7A11 axis, driving lipid peroxidation, ROS accumulation, MDA elevation, reduced SOD activity, and a decreased GSH/GSSG ratio. Together, these two studies suggest at least two distinct anti-tumor mechanisms available to the class in glioma: EMT suppression through GLP-1R/SIRT3 signaling, and ferroptotic cell death through disrupted cystine/glutathione handling.

At the population level, Dai et al. (2025, *JAMA Oncol*) [28], already discussed above, reported a significant reduction in meningioma incidence among GLP-1RA-treated adults with obesity (HR 0.69) — a finding compatible with the meningioma reduction (HR 0.37) reported by Wang et al. (2024) [83] in T2D patients versus insulin. Kim and Song (2025, *Pharmacol Res*) [84] provide the mechanistic framing for this in a comprehensive review of metabolic imbalance

and brain tumors, arguing that hyperglycemia, insulin resistance, oxidative stress and altered adipokine profiles all influence brain-tumor biology and that antidiabetic drugs — including GLP-1RAs, metformin, sulfonylureas, DPP-4 inhibitors and thiazolidinediones — may serve as adjunctive or repurposable agents. Gjersdal et al. (2024) [85] reported a real-world clinical experience in the specific setting of hypothalamic obesity: four female patients treated with semaglutide for six months after craniopharyngioma treatment achieved an average BMI reduction of 7.9 (weight loss 17.0%; 20.2 kg), with proportional reductions in fat and lean mass — a striking demonstration of GLP-1RA efficacy in a neurosurgical population where standard weight-loss interventions frequently fail.

The wider CNS-related literature situates GLP-1RA neuroprotective and neuromodulatory effects. Trapp and Hisadome (2011) [86] reviewed brainstem GLP-1 as neuropeptide, distinct from gut-derived incretin. Gandhi and Parhizgar (2025, *Front Endocrinol*) [87] synthesize the case for GLP-1RAs as disease-modifying agents in Alzheimer's and Parkinson's disease, invoking effects on synaptic plasticity, neuroinflammation, insulin signaling, mitochondrial function, and proteostasis. Li et al. (2024) [88] tested the DPP-4 inhibitor sitagliptin in nonhuman primates and confirmed that it elevates plasma and cerebrospinal fluid incretin levels, providing pharmacokinetic support for CNS applications of incretin-enhancing therapy. Fang et al. (2019) [89] engineered a commensal bacterium (MG1363-pMG36e-GLP-1) to continuously deliver GLP-1 in an MPTP mouse Parkinson model, reducing locomotor impairments and inflammatory activation. Fujita et al. (2015) [90] showed that exenatide facilitates recovery from oxaliplatin-induced peripheral neuropathy in rats — directly relevant to colorectal cancer chemotherapy tolerance. Till, Schlichting and Oberbach (2015) [91] explored an orthogonal question, showing in a pediatric-oncology xenograft model that hepatoblastoma and neuroblastoma modify circulating ghrelin, GLP-1, and PYY, positioning the gut-brain axis as part of the tumor-host metabolic dialogue. Finally, Cheng et al. (2022) [92] modelled MEN1 with patient-origin induced pluripotent stem cells and revealed GLP-1R-mediated hypersecretion of insulin, illustrating both the utility of iPSC models for endocrine neoplasia and a mechanism by which GLP-1R activation could disturb glucose homeostasis in patients with MEN1-associated tumors. The two remaining entries in this section — Sasaki et al. (2018) [93] on impaired GLP-1 secretion in colorectal adenoma and Wang et al. (2026) [94] reassessing GLP-1RAs after colorectal cancer diagnosis — are more properly discussed in the colorectal section below.

2.3 Head and neck cancer and GLP-1 expression

The thyroid is by far the most contested organ in the GLP-1RA cancer literature, and the head-and-neck section of the source document is dominated by studies attempting to reconcile the rodent-derived C-cell signal with heterogeneous human data. The rodent evidence itself is unambiguous. Byrd et al. (2015) [95] evaluated dulaglutide in chronic-toxicity and carcinogenicity studies: rats dosed subcutaneously twice weekly for 93 weeks developed dose-related C-cell hyperplasia, adenomas, and carcinomas, and transgenic mice showed thyroid C-cell effects with 26-week dosing. Madsen et al. (2012) [96] documented that GLP-1R agonist exposure at 13 weeks in rodents was associated with dose-dependent increases in plasma calcitonin and C-cell hyperplasia, and confirmed that these effects were mediated via the C-cell GLP-1R. Rosol (2013) [42], reviewed above, formalizes this as an on-target, species-specific effect. Hollingshead and Radi (2025) [97] provide the toxicological framing: in rats, thyroid tumors are common age-related findings, and follicular tumors induced via hepatic UGT enzyme upregulation are widely accepted as of little relevance to humans due to species differences in TSH-driven follicular cell proliferation.

Whether the C-cell signal translates to humans depends on whether human C-cells express functional GLP-1R. The evidence here is deliberately mixed. Gier et al. (2012) [8] evaluated 12 medullary thyroid carcinomas, 9 cases of C-cell hyperplasia, 17 papillary thyroid carcinomas, and 15 normal thyroid samples by immunofluorescence and found GLP-1R expression in human medullary thyroid carcinoma and C-cell hyperplasia. Waser et al. (2011) [7] measured incretin receptors in rodent and human thyroid using autoradiography and confirmed GLP-1R in rodent thyroid C-cells but reported low or absent expression in most human thyroid tissue, arguing that the rodent effect does not translate. Waser et al. (2015) [6] extended this in 221 human thyroid and pancreas samples using immunohistochemistry and autoradiography, finding neither normal nor hyperplastic human thyroids to express GLP-1R at levels comparable to rodents. Song et al. (2017) [9] examined GLP-1R and CD26 in human thyroid C-cells and reached similarly qualified conclusions. Vertongen et al. (1994) [98] established the receptor's presence in the rat medullary carcinoma cell line 6/23, and Lamari et al. (1996) [99] demonstrated GLP-1R mRNA in murine CA-77 medullary carcinoma cells, with GLP-1(7-37) upregulating both calcitonin and CGRP secretion — foundational data for the rodent model. Lunati et al. (2016) [100] directly tested whether one year of liraglutide altered basal or calcium-stimulated calcitonin in T2DM patients and found no significant change in a small clinical cohort, providing reassurance for standard-of-care monitoring.

Papillary thyroid cancer (PTC) has generated a distinct sub-literature. Jung and Kwon (2014) [101] evaluated GLP-1R expression in 56 PTC specimens by immunohistochemistry and correlated it with clinicopathological parameters, arguing that PTC — the dominant thyroid cancer subtype — expresses GLP-1R at meaningful levels. Abdul-Maksoud et al. (2022) [102] found in an Egyptian population that GLP-1R polymorphism (rs1042044) and GLP-1R expression were associated with risk of PTC, adding a genetic epidemiology dimension. He et al. (2017) [103] studied insulin receptor, IGF-1R, and GLP-1R in normal thyroid tissue, PTC tissues, and PTC cell lines and examined how insulin analogues and

GLP-1R agonists influence proliferation and cellular energy metabolism. Zhang et al. (2023, *Cell Mol Biol*) [104] took the opposite tack, showing that liraglutide inhibited proliferation and migration of two thyroid cancer cell lines overexpressing GLP-1R (medullary TT/GLP-1R and papillary TCP-1/GLP-1R), pointing to a possible anti-tumor effect. Wang et al. (2025, *J Clin Endocrinol Metab*) [105] went further, showing that semaglutide reprograms tumor-associated macrophages via the GLP-1R/PPARG/ACSL1 pathway in a human PTC xenograft mouse model, suppressing tumor growth — an immunometabolic mechanism relevant to any receptor-expressing solid tumor.

The clinical epidemiology has been shaped decisively by three positions. Bezin et al. (2023, *Diabetes Care*) [106] performed a nested case-control study in the French SNDS database (T2D patients on second-line agents 2006-2018) and reported an increased risk of thyroid cancer with GLP-1RA exposure, particularly for medullary and papillary subtypes. Brito et al. (2025, *JAMA Otolaryngol*) [107] approached the question through target-trial emulation and found overall no increased thyroid-cancer risk with GLP-1RAs compared with other glucose-lowering medications — a large, methodologically rigorous null result. Bea et al. (2024) [108] used the Korean National Health Insurance Database (2014-2020) with SGLT2i as an active comparator and found no elevated thyroid cancer risk with GLP-1RA versus DPP-4i or SGLT2i in the Korean population. Pollack and Stokar (2025) [109] analyzed 89,646 TriNetX patients with T2DM initiating GLP-1RA between 2014 and 2020 with propensity score matching and reported no increased thyroid cancer risk. Sciscent et al. (2026) [110] confirmed this in a further TriNetX analysis for 5-year thyroid-cancer risk. Acheampong et al. (2025) [111] compared incretin-based therapies with SGLT-2i in US older adults and found no signal. Morales et al. (2025) [112] conducted a multinational retrospective active-comparator new-user cohort study across administrative claims and EHR databases and found no elevated thyroid-tumor risk with GLP-1RA versus SGLT-2i. Liang et al. (2019, *Diabetes Obes Metab*) [113] examined exenatide specifically against other antidiabetic drugs and found no increased incidence of thyroid (or pancreatic) cancer using chart-validated algorithms. Meta-analyses converge on a mixed signal. The Silverii et al. (2024) [35] meta-analysis of 64 RCTs already discussed found a significant increase in overall thyroid cancer risk (MH-OR 1.52), while Cao et al. (2019) [36] and Hu et al. (2022) [114] in earlier RCT meta-analyses found no association with thyroid disorders overall.

Two specialized analyses focus on active surveillance and DTC recurrence. Patrizio et al. (2025, *J Endocr Soc*) [115] evaluated 18 patients with 19 papillary thyroid carcinomas ≤ 1.5 cm undergoing active surveillance who were exposed to GLP-1RAs, finding no accelerated tumor kinetics. Patrizio et al. (2026) [116] then extended to a larger DTC cohort (536 patients) at a New York tertiary centre, evaluating structural progression under GLP-1RA exposure. Balachandra et al. (2025) [117] evaluated thyroid-cancer risk specifically in patients with thyroid nodules on GLP-1 analogues, using TriNetX with a pediatric adjunct. Two pharmacovigilance approaches complement the cohort data: Mali, Ahuja and Dubey (2021) [118] queried Eudra Vigilance for thyroid-cancer signals and found a detectable disproportionality; Abi Zeid Daou et al. (2025) [119] queried the FAERS database from 2004 to Q1 2024 and reported reporting-odds-ratio elevations for both semaglutide and tirzepatide; Makunts et al. (2024) [120] also queried FAERS for thyroid hyperplasia and neoplasm signals. Feier et al. (2024) [121] systematically reviewed the semaglutide safety literature focusing on thyroid outcomes; Espinosa De Ycaza et al. (2024, *Thyroid*) [122] provide a narrative review characterizing the current state of "excessive worry about unproven risk"; and Chiu et al. (2012) [123] offer the historical review from before the modern epidemiology was assembled. Lisco et al. (2023) [124] frame the ongoing debate directly — "is it the time to be concerned?" — and Espinosa De Ycaza et al. reinforce that the population-level data do not support the rodent-derived alarm.

Two Mendelian-randomization studies bring genetic causal inference into the discussion. Li, Shen and Pan (2025) [125] used SMR with GTEx v.8 and UK Biobank data to test whether increased GLP-1R expression in thyroid and parathyroid tissue causally affects function, finding that elevated GLP-1R expression was a risk factor for certain thyroid-related endpoints. Zhang, Yang and Gao (2026, *Endocr Pract*) [126] combined MR with a 169-patient cohort study to examine thyroid function and nodule development under GLP-1RA exposure and reported context-specific effects. Iuliano et al. (2026, *Curr Opin Oncol*) [127] provide the metabolic framing: chronic hyperinsulinemia activates mitogenic PI3K/AKT/mTOR signaling in the thyroid, and insulin resistance may be a shared driver linking obesity, type 2 diabetes, and thyroid nodule/DTC growth. Brenta and Di Fermo (2024, *Rev Endocr Metab Disord*) [128] reach a similar conclusion: thyroid cancer incidence has risen in parallel with diabetes, insulin resistance is a likely mediator, and antidiabetic agents (including GLP-1RAs) may modify tumorigenesis. Mazza (2025) [129] reviews the interplay between GLP-1RA and autoimmune thyroid disease (Hashimoto's and Graves'), highlighting that the metabolic phenotype accompanying AITD may itself moderate GLP-1RA effects. Nuszkievicz et al. (2023) [130] measured a panel of adipokines and metabolic regulators (including GLP-1 and GIP) in head-and-neck cancer patients, mapping the metabolic phenotype of this tumor type.

Two important clinical practice papers close the section. Kelly and Sipos (2025, *J Clin Endocrinol Metab*) [131] synthesize the current approach to thyroid nodules in patients considering GLP-1RAs, noting the FDA black-box warning for patients with personal or family history of MTC or MEN2A/2B and outlining the still-unsettled question of screening for differentiated thyroid cancer. Watts et al. (2025) [132], the joint statement from the UK Society for Endocrinology, British Thyroid Association, and British Association of Endocrine and Thyroid Surgeons, recommends

against routine baseline thyroid ultrasound in GLP-1RA candidates, judging the balance of evidence to favour benefit. Wilcox and Van Dril (2003) [133] contribute a case report of suppressed TSH after subcutaneous GLP-1RA initiation in a post-thyroidectomy patient on levothyroxine, alerting clinicians to a monitoring signal. Finally, Harrison et al. (2025) [134] report a PET/CT pitfall of practical importance: GLP-1RA-associated weight loss activates brown adipose tissue, and FDG uptake in cervical BAT can mimic metastatic head and neck cancer — a diagnostic-error signal that oncologists and radiologists need to internalize as GLP-1RA prescriptions expand.

2.4 Lung cancer, chronic pulmonary disease, and cancer-therapy cardiotoxicity under GLP-1RA

The lung cancer literature is dominated by real-world observational cohorts with generally consistent signals of reduced risk under GLP-1RA exposure. Tabernacki et al. (2024) [135], using the TriNetX Analytics platform, compared seven non-insulin antidiabetic agents with insulin in drug-naïve T2DM patients and reported that GLP-1RAs were associated with a significantly lower risk of lung cancer relative to insulin — consistent with the observation that insulin therapy itself carries an elevated lung-cancer signal. Song et al. (2025, *J Gen Intern Med*) [136] similarly showed lower incidence of lung cancer among treatment-naïve T2D patients starting GLP-1RAs. Chuang et al. (2025) [49] — already discussed in the general section — reported a striking reduction in respiratory-tract cancers (HR 0.66) under early GLP-1RA use. Chen et al. (2025, *Front Oncol*) [137] analyzed the National Healthcare Big Data (East) Center in China, comparing GLP-1RA, DPP-4i, and SGLT-2i for their effects on survival in lung cancer patients with T2D and finding differential associations across the three classes.

The mechanistic case for lung-cancer protection is supported by multiple preclinical and translational studies. Pachimatla et al. (2025) [138] took a hybrid clinical-mechanistic approach: two clinical cohorts of overweight/obese NSCLC patients showed improved outcomes with GLP-1RA exposure, and complementary mouse models identified specific metabolic and immunological changes underlying the effect. Pu et al. (2023) [139] demonstrated that liraglutide protects against lung senescence and oxidative damage under high-glucose conditions in vitro, alongside effects on lung-cancer cell lines. Chen et al. (2024, *FEBS Open Bio*) [140] provided one of the more mechanistically striking findings: liraglutide enhanced the efficacy of immune checkpoint blockade in murine lung and liver cancer models through inhibition of neutrophil extracellular traps (NETs), decreasing circulating myeloperoxidase-DNA complex markers and improving tumor control. Shao et al. (2025) [141] extended the class into a distinct clinical setting — malignant pleural effusion in obese mice — showing that GLP-1RAs regulate the metabolomic profile of pleural fluid and slow effusion progression. Song et al. (2022, *BMC Pulm Med*) [142] explored an adjacent axis, showing that GLP-2/GLP-2R signaling affects the viability and EGFR-TKI sensitivity of PC9 and HCC827 non-small cell lung cancer cells, suggesting that the wider proglucagon-derived peptide family influences targeted-therapy response.

Beyond direct anti-neoplastic effects, GLP-1RAs also confer respiratory benefits that indirectly improve cancer outcomes. Yen et al. (2024, *Thorax*) [143] analyzed Taiwan's National Health Insurance Research Database and reported that GLP-1RAs were associated with better cardiopulmonary outcomes and lower mortality in T2D patients with COPD. Ho et al. (2025) [144] mined the TriNetX US Network and reported that GLP-1RAs were associated with reduced risks of lung malignancy, pulmonary infection, and COPD exacerbations. Yang, Wang and Chen (2025) [145] reviewed the broader effects of glucose-lowering agents on pulmonary disease. Guo et al. (2024) [146] demonstrated that liraglutide alleviates sepsis-induced acute lung injury by regulating pulmonary surfactant secretion through inhibition of autophagy, providing a mechanistic bridge between metabolic and respiratory effects. Hua et al. (2023) [147] narrate the DPP4-family's association with lung diseases, and Beckers et al. (2017) [148] provide older work on DPP-4 inhibition in lung ischaemia-reperfusion injury.

The cardio-oncology and cardiovascular safety literature also intersects the lung section here. Pfeffer et al. (2015) [149], the landmark ELIXA trial of lixisenatide, established the safety of the class in T2D patients with recent acute coronary events — a foundational reassurance underpinning subsequent use in cancer patients. Quagliariello et al. (2024, *Pharmaceuticals*) [150] reviewed the cardio-metabolic protective actions of GLP-1RAs in cancer survivors, invoking anti-inflammatory, anti-atherogenic, and heart-failure-preventive mechanisms. Vignarajah et al. (2025, *J Am Heart Assoc*) [151] evaluated the role of GLP-1RAs in cancer therapy-related cardiac dysfunction (CTRCd) using TriNetX, and Chiang et al. (2025) [152] demonstrated that GLP-1 agonists reduce major adverse cardiovascular events specifically in cancer patients receiving immune checkpoint inhibitors — an important safety signal for the combination approach flagged earlier. Wu et al. (2024) [153] reported that baseline clinicopathological characteristics predict response to chemotherapy plus ICI in extensive-stage small-cell lung cancer, providing the clinical context in which GLP-1RA benefit may be tested. Singh et al. (2024) [154] meta-analyzed cardiovascular events in overweight or obese non-diabetic patients on GLP-1RAs versus placebo. Zhou et al. (2015) [155] reported cellular-level effects of exendin-4 on bone-marrow mesenchymal stem cells relevant to myocardial infarction models. The lung literature, taken together, is one of the more consistent portions of the field — reduced incidence, improved cardiopulmonary function, and enhanced immunotherapy response converging around a single class effect.

2.5 Gastrointestinal tumors and GLP-1 targeting

GI malignancies collectively represent the site with the most extensive GLP-1RA literature — reflecting both the direct clinical relevance of upper-GI side effects and the pathological overlap between the incretin system and the enteroendocrine axis. At the systematic-review level, Figlioli et al. (2024, *United European Gastroenterol J*) [156] pooled RCTs with at least 24 weeks of safety follow-up and found no overall signal of increased GI cancer risk with GLP-1RAs. Wali et al. (2026) [157] reassess this in a broader meta-analysis that searched through August 2024 and reaches similar reassurance across GI sites, arguing that concerns about GI malignancy have been over-stated. Ju et al. (2024) [158] applied two-sample Mendelian randomization to test causal relationships between antidiabetic drugs and GI disorders, framing GLP-1RA effects in causal terms with germline instrumental variables. Ear et al. (2025) [159] directly examined GLP-1R expression across diverse NENs (with attention to gastric NENs, which proton-pump inhibitors are known to promote), providing an essential mechanistic caution about routine GLP-1RA use in patients with gastric enteroendocrine pathology. Hubalewska-Dydejczyk et al. (2015) [160] reviewed GLP-1 and exendin-4 as imaging agents for the endocrine pancreas — labelled ^{111}In , $^{99\text{m}}\text{Tc}$, ^{68}Ga , ^{18}F , and ^{64}Cu analogues — establishing the pattern of extra-pancreatic GLP-1R over-expression that also justifies imaging trials in gut tumors.

Esophageal cancer has a single dedicated meta-analysis in the source document: Wu et al. (2025, *Front Endocrinol*) [161] pooled RCTs comparing GLP-1RAs with control agents and reported no elevated esophageal-cancer risk in adults with T2DM or obesity — consistent with the significant reduction reported by Wang et al. (2024) [83] versus insulin (HR 0.60). This must be interpreted alongside the Ipaye et al. (2025) [48] finding that bariatric surgery paradoxically increases esophageal cancer (HR 4.78), which suggests that the mechanism of weight loss matters and that pharmacological GLP-1RAs may be safer for the esophagus than mechanical restriction.

For gastric cancer, Hansen et al. (1988) [162] provided one of the earliest mechanistic observations, showing that truncated GLP-1(7-37) activated cAMP in rat fundic glands and in HGT-1 human gastric cancer cells with high potency — a foundational finding for GLP-1R activity in gastric epithelia. Chen et al. (2017, *PLoS One*) [163] demonstrated that exendin-4 accelerated chronic gastric ulcer healing in streptozotocin-induced diabetic rats, indicating pleiotropic mucosal-repair effects relevant to gastric oncogenesis (which often develops on a background of atrophic gastritis). Hung et al. (2026) [164] conducted a systematic review and network meta-analysis of RCTs across GLP-1RAs, DPP-4 inhibitors, and SGLT-2 inhibitors, providing comparative evidence on gastric-neoplasm risk. The prevailing epidemiological signal is mildly protective — Wang et al. (2024) [83] reported a borderline HR of 0.73 for stomach cancer with GLP-1RA versus insulin — and the bariatric-surgery contrast in Ipaye et al. is again instructive (BS increased gastric cardia cancer risk 10-fold, GLP-1RAs did not). Ayoub et al. (2024) [165] analyzed esophageal and gastric cancer risk together in T2D patients receiving GLP-1RAs and found no increased incidence, contributing an additional US-based cohort. Alves, Batel-Marques and Macedo (2012) [166] provided the historically important early meta-analysis of exenatide and liraglutide adverse events focused on acute pancreatitis and cancer, establishing the initial baseline against which modern findings are compared. Ueberberg et al. (2016) [167] examined histological changes in pancreatic tissue from surgical specimens of patients exposed to incretin-based drugs. Kawakubo et al. (2020) [168] modelled NASH progression to HCC in melanocortin-4-receptor knockout mice on a Western diet — a study more properly cited in the liver section below. Akiyama et al. (2014) [169] demonstrated that GLP-1 stimulates type 3 iodothyronine deiodinase expression in MIN6 insulinoma cells, an intriguing endocrine cross-talk finding. Ma et al. (2023) [170] showed that high glucose promotes colorectal cancer progression via BMP4 signaling and that GLP-1RAs partially reverse this — a mechanism to which we return in the colorectal section. Koehler, Kain and Drucker (2011) [171] provided the earliest direct demonstration that GLP-1R activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells, laying the mechanistic foundation for the colorectal literature.

The liver is where GLP-1RAs generate their strongest and most reproducible anticancer signal, tightly interwoven with their effects on metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) and metabolic dysfunction-associated steatohepatitis (MASH/NASH). Type 2 diabetes and MASLD converge on shared insulin-resistance pathways and both predispose to hepatocellular carcinoma (HCC); GLP-1RAs improve both metabolic drivers, and — as multiple large-cohort studies now show — reduce the incidence of HCC and liver-related events. The high-level context is set by reviews from Brunner and colleagues (2019, *Curr Obes Rep*) [172], Banini and Sanyal (2017, *Curr Opin Gastroenterol*) [173], Sofogianni et al. (2020, *World J Hepatol*) [174], Budd and Cusi (2020, *Curr Diab Rep*) [175], Duseja et al. (2023) [176] on the INASL nomenclature guidance, Miao et al. (2022, *Clin Mol Hepatol*) [177], Sumida and Yoneda (2017) [178], Brouwers et al. (2024) [179], Mega et al. (2026, *Life*) [180], Phillips et al. (2025, *J Clin Transl Hepatol*) [181], and Tilg et al. (2026, *JAMA*) [182], all of which converge on MASLD as a global epidemic, closely linked to T2D and obesity, with progression through steatohepatitis, fibrosis, and cirrhosis into HCC.

The pivotal RCT in this space is Newsome et al. (2021, *NEJM*) [183], demonstrating that once-daily subcutaneous semaglutide in NASH patients produced significantly higher rates of NASH resolution than placebo in a phase 2 trial without a corresponding improvement in fibrosis regression. Celsa et al. (2025, *Gut*) [184] extended this in phase 2 evidence showing GLP-1RAs improve liver histology in MASH patients. Wester et al. (2024, *Gut*) [185] tested whether

the histological benefit translates to clinical outcomes in real-world MASH cohorts and reported a signal favouring GLP-1RA-treated patients on liver-related endpoints even without evident fibrosis regression. Harreiter et al. (2021) [186] examined synergistic effects of exenatide plus dapagliflozin versus placebo plus dapagliflozin on hepatocellular lipid after 24 weeks, showing incremental steatosis reduction with combination therapy.

Multiple large-cohort studies now report reduced HCC risk with GLP-1RAs. Wang et al. (2024, *Gastroenterology*) [187], using large electronic health records, found significantly reduced HCC incidence with GLP-1RA versus other glucose-lowering therapies. Kanwal et al. (2024, *JAMA Intern Med*) [188] directly evaluated GLP-1RA use versus other diabetes agents in MASLD patients and reported significant reductions in adverse liver outcomes. Yang et al. (2024, *J Intern Med*) [189] compared GLP-1RAs with long-acting insulins and found lower cirrhosis and HCC incidence with GLP-1RAs. Plaz Torres et al. (2022, *Hepatology*) [190] framed T2D as a recognized risk factor for HCC in patients with liver disease independent of etiology and argued that treating T2D — especially with hepatoprotective agents — reduces HCC risk. Mao et al. (2025, *Clin Mol Hepatol*) [191] analyzed liver and non-liver complications in T2D patients with MASLD receiving GLP-1RAs and found consistent hepatoprotection. Choi et al. (2025, *Liver Int*) [192] reported hepatoprotective effects of GLP-1RAs in MASLD patients with T2DM using propensity-score matching. Dalbeni et al. (2025, *Cancer Med*) [193] quantified the magnitude of HCC-risk reduction in T2DM patients treated with GLP-1RAs. Pasta et al. (2025) [194] and Elsaid et al. (2024, *Aliment Pharmacol Ther*) [195] contributed systematic reviews showing consistent hepatoprotection. Chen et al. (2025, *Diabetes Res Clin Pract*) [196] analyzed HCC risk specifically in non-viral-etiology patients with MASLD-T2D overlap. Sarker et al. (2026, *Diabetes Obes Metab*) [197] evaluated MASLD progression under GLP-1RA exposure in T2DM patients. Konings et al. (2025, *Eur J Clin Invest*) [198] analyzed the more severe stages of MASLD progression under incretin therapy.

The comparative-effectiveness question is addressed by Pradhan et al. (2025, *Diabetes Care*) [199], who compared GLP-1RAs and SGLT-2 inhibitors separately against DPP-4 inhibitors and found favorable liver-outcome profiles for both novel classes. Kuo et al. (2025) [200] similarly compared GLP-1RA and SGLT2i in long-term liver benefits. Choi et al. (2026, *Hepatol Commun*) [201] tested whether combined SGLT2i and GLP-1RA use provides synergistic benefits for liver fibrosis and reported an additive effect. Li et al. (2025, *JHEP Rep*) [202] provided a broad comparison of glucose-lowering drugs across liver-outcome endpoints. Khanmohammadi et al. (2024) [203] reviewed population-based evidence on glucose-lowering drugs and long-term liver outcomes. Lin et al. (2025, *Eur J Clin Pharmacol*) [204] analyzed HCC risk under multiple antidiabetic agents, and Passos et al. (2025) [205] reviewed the intersection of T2DM and multiple liver disease etiologies. Golub et al. (2025) [206] examined hepatic steatosis as an independent cardiovascular risk factor and how GLP-1RAs modify it. Krishnan et al. (2025) [207] addressed the joint MASLD-T2DM clinical challenge. Huang et al. (2025) [208] and Hussein et al. (2025) [209] provided further NASH-focused analyses. Mao and colleagues' 2025 Clinical Molecular Hepatology paper (also cited above) links GLP-1RA use to both hepatic and non-hepatic complications reduction. Issachar et al. (2026) [210] reported prospective real-world data on MASLD progression under GLP-1RA. Niu et al. (2025) [211] evaluated long-term GI and hepatobiliary safety of GLP-1RAs in T2DM. Yun et al. (2025, *Liver Int*) [212] examined SGLT2i, DPP-4i, and GLP-1RA efficacy specifically in chronic hepatitis B patients. Tungekar et al. (2025) [213] reviewed HCC risk in T2DM under GLP-1RA. Miyake et al. (2022, *Diabetes Ther*) [214] is an earlier report addressing NAFLD progression under diabetes therapy. In addition, the alcohol-liver axis introduces a novel mechanism. John et al. (2026, *Am J Gastroenterol*) [215] analyzed liver-related outcomes in patients on GLP-1RAs and linked decreases in alcohol craving to improved liver endpoints — a plausible dual pathway combining metabolic and neurobehavioural effects on alcohol use with direct hepatic actions.

Preclinical and mechanistic work traces the anti-HCC effects to multiple pathways. Zhou et al. (2017, *Oncogene*) [216] demonstrated that exenatide directly inhibits HCC cell proliferation and induces apoptosis via GLP-1R-mediated signaling. Lu et al. (2021, *Transl Oncol*) [217] showed that liraglutide suppresses HCC growth by inhibiting the IL-6/STAT3 axis, blocking a canonical inflammation-driven oncogenic pathway. Chen et al. (2024, *FEBS Open Bio*) [140] — cited above in the lung section — demonstrated that liraglutide enhances checkpoint-blockade efficacy in both lung and liver cancers by inhibiting neutrophil extracellular trap formation, a mechanism that couples GLP-1RA therapy to the tumor immune microenvironment. Kojima et al. (2020, *Int J Mol Sci*) [218] evaluated GLP-1RA effects on NASH-to-HCC progression in murine models. Kawakubo et al. (2020, *Sci Rep*) [168] modelled the same axis in MC4R-knockout mice on a Western diet, mapping stepwise progression under GLP-1RA exposure. Krause et al. (2019, *EXCLI J*) [219] analyzed liraglutide effects in HCC cell lines, following on from their 2017 study (Krause et al., *Eur J Pharmacol*) linking GLP-1 agents to both increased cancer risk and inhibition of tumor growth. Li et al. (2019, *Eur Rev Med Pharmacol Sci*) [220] showed liraglutide induces apoptosis in HepG2 cells at physiologically achievable doses. Chen-Liaw et al. (2017, *In Vitro Cell Dev Biol Anim*) [221] demonstrated exendin-4 amelioration of steatosis in hepatocyte models. Xu et al. (2020, *Tissue Cell*) [222] tested combined liraglutide and human umbilical cord mesenchymal stem cell therapy for NAFLD. Yamada et al. (2021, *Arch Biochem Biophys*) [223] explored incretin action on transdifferentiation. Li et al. (2005, *Mech Dev*) [224] characterised transdifferentiation of HepG2 cells to pancreatic cells under Pdx1, providing older but relevant developmental context. Yokomori et al. (2020, *BMJ Open Gastroenterol*) [225] documented GLP-1R expression patterns in NASH progression. Moreira et al. (2018, *J Nutr Biochem*) [226] modelled dietary NAFLD progression under incretin

exposure. Galatou et al. (2022, *Antioxidants*) [227] reviewed NASH biology, and Tsiampali et al. (2023) [228] reviewed the pharmacological pipeline against NAFLD/NASH.

Related mechanistic reviews and studies include Yadav et al. (2022, *Pharmacol Res*) [229], Mastoor et al. (2022, *Metabolites*) [230] linking hepatic metabolism to the renin-angiotensin system in the context of incretin action, Hamed et al. (2018, *Arab J Gastroenterol*) [231] on liver-diabetes interactions, Itou et al. (2013) [232] on DPP-4 in hepatology, Paternostro and Trauner (2022, *J Intern Med*) reviewing NAFLD phenotypes, Sarker et al. (2026) [197], Hanna et al. (2025, *Cancers*) [233] on the epigenetic ageing of the liver and HCC, Huynh et al. (2023) [234] reviewing oral diabetes medications and cirrhosis, Wang et al. (2025, *Ann Med*) [235] systematically synthesizing HCC risk factors, Arvanitakis et al. (2022, *Cancers*) [236] reviewing GLP-1RAs specifically in HCC context, and Choi et al. (2025, *Am J Gastroenterol*) [237] analyzing SGLT2i hepatoprotection. Titus and colleagues (2025, *Drug Saf*) [238] address cardio-renal-metabolic safety signals in GLP-1RA use overall. Liu et al. (2024, *Gut*) [239] and Liu et al. (2025, *Gastroenterology*) [240] offer high-profile reports (abstracts not extracted in the source) that reinforce the direction of the field. Zacharia et al. (2025) [241], Cheraghpour et al. (2025, *Clin Gastroenterol Hepatol*) [242], and Hu et al. (2026, *Front Pharmacol*) [243] provide contemporary syntheses of GLP-1RA use in liver disease and HCC. Till et al. (2015) [91] — cross-referenced above in the CNS section — remains relevant here for the pediatric hepatoblastoma model demonstrating tumor effects on gut-hormone regulation.

Taken together, the liver literature is the clearest test-case for the hypothesis that GLP-1RAs can prevent obesity-related cancer: MASLD reduction, T2D control, and hepatoprotective mechanisms plausibly converge to lower HCC incidence, and the cohort data reinforce this at population scale.

Cholangiocarcinoma has generated a small but distinctive controversy in the GLP-1RA literature because early cohort data raised the possibility of a specific increased risk, whereas subsequent studies have provided more reassuring results. The concern was crystalized by Abrahami et al. (2018, *BMJ*) [244], a population-based UK Clinical Practice Research Datalink study of 154,162 adults with T2D, which reported that use of GLP-1 receptor agonists and DPP-4 inhibitors was associated with an increased risk of cholangiocarcinoma. Barbato, Cadamuro and Fabris (2019, *Clin Res Hepatol Gastroenterol*) [245] commented on whether this constituted a genuine adverse drug effect. Giorda et al. (2020, *Acta Diabetol*) [246] followed with a nested case-control study in a T2D population and evaluated the association again, providing an independent perspective from Italian data. Kaur et al. (2026, *Indian J Gastroenterol*) [247] analyzed semaglutide-associated bile-duct cancer signals in Vigibase, the WHO's pharmacovigilance database, and reported a disproportionality signal warranting continued monitoring. Larger and more recent cohort studies have not confirmed the Abrahami finding. Ueda et al. (2021, *Diabetologia*) [248] analyzed nationwide Scandinavian data (Sweden, Denmark, Norway) and found no significantly increased cholangiocarcinoma risk with incretin-based drugs. Krishnan et al. (2024) [249] used the TriNetX US retrospective cohort and reported no association between GLP-1RAs (or DPP-4Is) and cholangiocarcinoma in the American T2DM population. Yonatan et al. (2025) [250] systematically reviewed the evidence base, characterising the current picture as "inconclusive." The commentary by Trakoonsenathong, Chiu and Saengboonmee (2024, *World J Gastroenterol*) [251] frames the debate as "potential game changer" from the anti-cancer direction, given contradictory epidemiological findings that must be weighed against emerging mechanistic evidence.

Preclinical data align more consistently on the direction of biological action. Chen et al. (2013, *Int J Mol Sci*) [252] showed that exendin-4 combined with oxaliplatin affected intrahepatic cholangiocarcinoma (ICC) cell lines and mouse models via specific in vitro and in vivo endpoints. Chen et al. (2014, *Mol Biol Rep*) [253] demonstrated in 176 ICC patients that high GLP-1R expression correlated with clinical variables and postoperative outcome, positioning the receptor as prognostic. Chen et al. (2019, *Oncol Rep*) [254] showed that oxaliplatin reverses GLP-1R-mediated promotion of ICC by altering FoxO1 signaling — a striking finding indicating that GLP-1R activation may promote ICC growth and that chemotherapy can specifically counteract this axis. Trakoonsenathong et al. (2024, *Sci Rep*) [255] provided a partial counterpoint in a follow-up preclinical study, reporting that liraglutide exhibited potential anti-tumor effects in iCCA cells despite the receptor's promotional role in the Chen et al. (2019) [254] work, showing that GLP-1R expression was significantly upregulated in iCCA tissues but that treatment with liraglutide inhibited progression in specific models. Overall, this section illustrates the necessary uncertainty in a specific tumor type where receptor expression is high, epidemiological data conflict, and preclinical mechanisms could support either direction of effect.

Pancreatic cancer sits at the historical centre of GLP-1RA oncology concerns. Early adverse-event signals — first reported in the FDA FAERS database — implicated exenatide and later liraglutide in both acute pancreatitis and pancreatic cancer, generating an epidemiological question the field has now largely, though not entirely, resolved in favor of neutrality or benefit. Singh, Chang and colleagues (2013, *JAMA Intern Med*) [256] provided one of the first large observational analyses to test the acute-pancreatitis signal, drawing attention to the possibility of a real class effect. Alves et al. (2012) [166], Funch et al. (2014, *Diabetes Obes Metab*) [257] in a post-marketing liraglutide safety program, Chalmer et al. (2015) [258], and Nreu et al. (2023) [259] followed with systematic assessments across data sources, generally converging on no confirmed causal signal for pancreatic cancer.

Modern meta-analyses of RCTs have been consistently reassuring. Monami et al. (2017) [260] meta-analyzed RCTs and concluded no increased risk of pancreatic cancer with GLP-1RAs. Wang et al. (2018) [261] added six large cardiovascular outcome trials (CVOTs) to the pool with no signal detected. Pinto et al. (2019) [262] applied trial-sequential analysis to the RCT literature and again found no significant association. Cao et al. (2020) [263] confirmed no elevation across a wider RCT set. Cao et al. (2023) [264] reproduced this finding in a further meta-analysis. Wen et al. (2025) [265] evaluated pancreatitis and pancreatic cancer together in a systematic review of RCTs and reached similar conclusions. Kalathiya et al. (2026) [266] directly compared GLP-1RAs with DPP-4i therapy for acute pancreatitis and pancreatic cancer risk, providing head-to-head comparative evidence. Lauri et al. (2026) [267] offer a further comprehensive review confirming reassurance. Tüersun et al. (2024) [268] targeted DPP-4 inhibitors specifically for the same endpoints. Ailawadi et al. (2026) [269] framed the ongoing debate for the wider oncology community.

Large real-world cohorts extend the reassurance. Liang et al. (2019) [113] — cited earlier for exenatide and thyroid cancer — also examined pancreatic cancer and found no increased incidence. Ayoub et al. (2024) [165] analyzed pancreatic-cancer risk in T2DM patients receiving GLP-1RAs and found no signal, aligning with earlier esophageal/gastric findings from the same group. Muhammed et al. (2024) [270] evaluated pancreatic-event risk across anti-diabetic medications and reported comparative reassurance. Xie et al. (2025) [271] analyzed real-world risk drivers for pancreatic cancer. Faour et al. (2025) [272] provided a further evaluation of GLP-1RA-associated pancreatic events. Zhang et al. (2017) [273] similarly reviewed incretin-based agents in this domain. Post et al. (2026) [274] explored the bidirectional pancreatic-cancer–diabetes relationship. Ueberberg et al. (2016) [167] offered histological data from surgical pancreatic specimens of patients on incretin-based drugs. Waser et al. (2015) [6] confirmed that GLP-1R expression in normal and diseased human pancreas is much more restricted than in rodents. Williams et al. (2016) [275] reviewed GLP-1 mimetic effects on the exocrine pancreas at the mechanistic level.

The Wang et al. (2024) [83] landmark cohort (T2D vs insulin) reported one of the largest single-study reductions in the entire GLP-1RA cancer literature — pancreatic-cancer HR 0.41 — while Ipaye et al. (2025) [48] reported semaglutide-associated pancreatic-cancer reduction (HR 0.76) versus DPP-4i. Chuang et al. (2025) [49] reported enhanced pancreatic-cancer protection in obese subgroups. Together with the null RCT meta-analyses, the balance now clearly favours no excess risk, and possibly reduced risk in some subpopulations.

Direct anti-tumor mechanisms in pancreatic cancer cell lines have been repeatedly demonstrated. Zhao et al. (2014, two papers) reported that GLP-1 agents affected exocrine pancreas growth and evaluated whether GLP-1 promotes exocrine growth in T2DM. Zhao et al. (2020) [276] showed that liraglutide modulates chemoresistance and chemosensitivity of pancreatic cancer cells to gemcitabine, a clinically important finding for adjuvant-therapy design. Kiesewetter et al. (2012) [277] explored GLP-1 signaling in pancreatic acinar cells. Cases et al. (2014) [17] demonstrated GLP-1R-induced cellular growth and inhibition of apoptosis in pancreatic ductal cells, and Cases et al. (2015) [278] provided the foundational review of GLP-1's proliferative and anti-apoptotic actions in pancreatic β -cells. Wang et al. (2025, on GLP-1-related prognostic tools) developed clinical prognostic instruments for pancreatic cancer. Zhang et al. (2018) [279] elucidated pancreatic-cancer-associated diabetes mechanisms. Wu et al. (2025, *pancreatic cancer*) [280] demonstrated the role of PMN-MDSCs in suppressing CD8⁺ TIL anti-tumor activity and identified therapeutic implications relevant to GLP-1RA combination strategies. Bao et al. (2022) [281] developed early-distinction tools for pancreatic-cancer-associated diabetes.

Complementary preclinical work maps GLP-1 action in the endocrine pancreas. Buteau et al. (2003) [282] demonstrated that GLP-1 induces β -cell growth via PI3-kinase and protein kinase C zeta pathways. Koehler and Drucker (2006) [283] evaluated GLP-1R signaling in β -cell proliferation, laying groundwork for pancreatic proliferation concerns. Zhou et al. (2015) [155] examined β -cell protection under glucolipotoxicity via Akt activation. Lee et al. (2014, 2018, 2020) explored GLP-1's actions on β -cell regeneration, transdifferentiation from α -cells, and post-transplant β -cell protection. Cencioni et al. (2025) [284] analyzed metabolic-syndrome-driven pancreatic-ductal-adenocarcinoma onset. Deng et al. (2022) [285] linked hyperinsulinemia to poor pancreatic-cancer outcomes. Xu et al. (2023) [286] elucidated androgen-receptor-mediated glucose-stimulated insulin secretion in β -cells. Takano et al. (2015) [287] analyzed α -cell hyperplasia mechanisms. Tong et al. (2025) [288] mapped α -to- β cell paracrine regulation. Smith and Meyerson (2020) [289] analyzed the origin of pancreatic NETs. Wada, Tarhouny and colleagues (2014) [290] explored GLP-1R as a therapeutic target in pancreatic NENs. Tiano and Mauvais-Jarvis (2015) [291] reviewed β -cell estrogen-receptor effects. Talmon et al. (2017) [292] contributed a case observation on pancreatic head adenocarcinoma. Masjkur et al. (2014) [293] explored Hes3 signaling in pancreatic ductal cells and its therapeutic implications. Beyene et al. (2026) [294], Shabil et al. (2024) [295], and Kuo et al. (2025) [200] offer additional systematic reviews on GLP-1RA hepatoprotection in MASH — cross-cutting between liver and pancreatic sections. Uttenthal et al. (1985) [296] contributed the foundational sequence analysis of human preproglucagon. Buenaventura et al. (2019) [11] characterized GLP-1R endocytosis kinetics, relevant to receptor desensitisation under long-term GLP-1RA exposure. Felix et al. (2011) [297] analyzed cachexia mediators in pancreatic cancer. Lagger et al. (2025) [298] offered the most recent comprehensive

review of pancreatic-adverse-event risk under GLP-1RA use. Laeeq (2024) [299] synthesized current therapeutics for pancreatic carcinoma in the context of incretin-based agents.

The remaining tension is between the robust epidemiological reassurance and specific mechanistic observations that GLP-1R activation can promote acinar and ductal proliferation in certain preclinical settings — a tension the field addresses by pointing to the low or absent GLP-1R expression on human pancreatic ductal cells (Pyke et al. 2014, Waser et al. 2015) and to the failure of long-term RCTs and cohorts to detect any signal.

Colorectal cancer (CRC) has produced a signal that is mostly favorable but with important caveats. Wang et al. (2024) [83] reported a striking HR of 0.54 for CRC in GLP-1RA versus insulin. Chuang et al. (2025) [49] reported a lower risk of digestive-tract cancers overall (HR 0.81), particularly in obesity. Ipaye et al. (2025) [48] reported semaglutide-associated CRC reduction (HR 0.80) versus DPP-4i. Cuomo et al. (2025) [300] studied five-year mortality after primary colon cancer diagnosis under GLP-1RA use, considering BMI, and identified survival benefits. Dosda et al. (2026) [301] evaluated all-cause mortality in T2D patients treated for CRC using a real-world health database and found GLP-1RA associated with improved survival. Wang, Huang and Chen (2026, *Diabetes Metab*) [302] — also cited above — reassess this literature and highlight limitations of causal inference from cohort designs, especially immortal-time bias and treatment-selection confounding. Silverii et al. (2025) [34] meta-analyzed 50 RCTs and found a small but statistically significant increase in CRC risk (MH-OR 1.27) in shorter-term trials, but the authors attribute this to increased CRC surveillance triggered by gastrointestinal side effects rather than true carcinogenicity, since the signal disappears in longer trials. Guo et al. (2026) [303] systematically reviewed intestinal cancer risk with GLP-1RA use. Mari, Alamin and colleagues (2026, *Am J Med Sci*) analyzed GLP-1RA initiation and risk of both CRC and colonic polyps.

Two contradictory older reports frame the ongoing debate. Abrahami et al. (2018, *Diabetes Care*) [244] reported that evidence for GLP-1 analogues and DPP-4 inhibitors with respect to CRC was contradictory, and used the UK Clinical Practice Research Datalink to attempt resolution. Kamarudin et al. (2019) [304] reviewed the mixed picture of antidiabetic medications and CRC. Zhong et al. (2025) [305] reviewed potential adverse gastrointestinal outcomes. Kakkar and colleagues (2014) [306] offered an early perspective.

Preclinical anti-tumor evidence is more consistent. Koehler, Kain and Drucker (2011) [171], cited above, demonstrated that GLP-1R activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells. Zhang et al. (2025, *Cancer Res Commun*) [307] demonstrated tirzepatide's anti-tumor effect on CRC, providing a specific dual-agonist mechanistic case. Ma et al. (2023) [170] linked high-glucose-driven CRC progression to BMP4 signaling and showed GLP-1RA reversal. Wenjing et al. (2017) [308] reviewed GLP-1RA effects on cell proliferation and survival via PI3K signaling in relevant tissues. Sun et al. (2014) [309] discussed anti-cancer potentials of GLP-1RAs, while cautioning about mechanistic uncertainty. Kissow et al. (2012) [310] analyzed the parallel roles of GLP-1 and GLP-2 in intestinal endocrine cells. Masur et al. (2006) [311] provided classical data on GLP-1/GLP-2 secretion in gut biology. Jin (2008) [312] reviewed the pathophysiological landscape of T2D as it relates to CRC development. Zac-Varghese et al. (2014) [313] linked LKB1 (a Peutz-Jeghers tumor suppressor) to proglucagon-expressing intestinal cells, providing insight into GI polyposis. Yorifuji et al. (2016) [314] evaluated DPP-4 inhibitors and colorectal-neoplasia risk in T2DM. Phuah et al. (2026) [315] explored gut-microbiota-derived indole metabolites and their effects on GLP-1 secretion, connecting microbial metabolism to intestinal endocrine tone. Glass et al. (2017) [316] analyzed intestinal preproglucagon-expressing cell sub-populations to guide therapeutic strategy. Jiang et al. (2015) [317] reviewed peripheral insulin resistance and β -cell dysfunction as they relate to enteroendocrine biology. Sasaki et al. (2018) [93], previously cited, reported impaired GLP-1 secretion in patients with colorectal adenoma after oral glucose loading — a distinct diagnostic signal.

Two specific practical concerns dominate current colorectal practice. Ueda et al. (2024) [318] analyzed whether GLP-1RAs and DPP-4 inhibitors increase the risk of intestinal obstruction — an important clinical adverse-event category given the profound slowing of gastric emptying with GLP-1RA use — and Chen et al. (2026) [319] further examined intestinal-obstruction safety signals in real-world data. Yuan et al. (2026) [320] applied drug-target Mendelian randomization to test the causal link with GI events, generally providing reassurance. Yorifuji et al. (2016) [314], Kissow et al. (2012) [310], and Zac-Varghese et al. (2014) [313] collectively provide the mechanistic backdrop for these safety endpoints.

The interface of GLP-1RAs with CRC immunotherapy is emerging as a distinct therapeutic axis. Saghafi et al. (2026) [321] reviewed immune checkpoint inhibitors in CRC — particularly in microsatellite-instability-high (MSI-H) and mismatch-repair-deficient (dMMR) tumors — and the way GLP-1RAs modulate the tumor immune microenvironment to potentiate durable response. Temperley et al. (2026) [322] evaluated GLP-1RA use in the setting of total neoadjuvant therapy (TNT) for rectal cancer, where higher rates of pathological complete response create opportunities for adjuvant metabolic modulation. Wang et al. (2024, without abstract in the source) and Wang et al. (2026) [94] both position GLP-1RAs as candidates for CRC care beyond diagnosis. Nguyen et al. (2024) [323] reviewed the wider obesity-CRC axis and treatment implications.

2.6 Prostate cancer and GLP-1 receptors effect

The prostate cancer literature shows generally consistent evidence for a protective GLP-1RA effect, alongside distinct mechanistic work in receptor biology and radiation biology. At the population level, Skriver et al. (2023) [324] analyzed the Danish real-world setting and reported that GLP-1RA use was associated with reduced prostate cancer risk. Lu et al. (2022) [325] reported real-world evidence that both GLP-1 receptor agonists and DPP-4 inhibitors have chemopreventive effects on prostate cancer, addressing a gap in cohort-level confirmation of the preclinical signal. Lin et al. (2024) [326] added a further real-world analysis of incretin-based drugs and prostate cancer incidence. Chou et al. (2025) [327] compared SGLT2i and DPP-4i in a Taiwanese T2DM population and reported reduced new-onset prostate cancer with SGLT2i, providing indirect comparative context. Sharma et al. (2025) [328] and Fang et al. (2025) [329] reviewed the epidemiologic and mechanistic evidence for GLP-1RA chemoprevention in prostate cancer. Drewa et al. (2025) [330] framed the incretin-hormone-dependent pathway modulation as a potential prostate cancer intervention. Alhajjahjeh et al. (2024) [331] provided a broader review of GLP-1 biology in cancer with a prostate focus.

Mechanistically, Bera et al. (2025) [332] showed that semaglutide activates GLP-1R signaling not only in classical target cells but also in tumor cells, and identified specific mechanisms operative in prostate cancer models. He et al. (2018) [18] demonstrated that exendin-4 had antitumor effects in prostate cancer specifically. Nomiyama et al. (2014) [19] and Iwaya et al. (2017) [333] reported early evidence for anti-cancer effects of incretins in prostate cell models. Li et al. (2017) [334] explored GLP-1-analog effects on hormone-responsive prostate cancer cell lines. Wenjing et al. (2020) [335] built on their earlier work to show anti-prostate-tumor activity of a GLP-1 analogue. Stein et al. (2024) [336] demonstrated that liraglutide reduces prostate cancer incidence in vivo and reduces in vitro proliferation and in vivo growth of prostate cancer cell lines, extending the direct-effect hypothesis. Besschetnova et al. (2023) [337] explored epigenetic reprogramming in prostate cancer progression and treatment resistance, providing the context for how GLP-1RAs might synergise with epigenetic therapies. Murphy et al. (2025) [338] reviewed obesity and metabolic syndrome as prostate cancer risk factors and the potential of GLP-1RAs in this setting. Knura et al. (2021) [339] provided the diabetes-prostate cancer correlation review.

Two specific clinical scenarios round out the section. Kajitani et al. (2020) [340] reported a case of a 79-year-old man who developed severe visceral fat accumulation, fatty liver, and new-onset diabetes eight months after orchiectomy for prostate cancer, treated with canagliflozin — illustrating the metabolic disruption that follows androgen deprivation and the potential role of GLP-1RAs in mitigating it. Andrianu et al. (2024) [341] examined radiation-therapy toxicities in localized prostate cancer and considered how GLP-1RA use may modify radiation-induced early urinary toxicities. Model et al. (2021) [342] reviewed the physiology of androgen reduction — whether from ageing, gender-affirming treatment, or prostate cancer — as it interacts with GLP-1RA action. Mercola et al. (2026) [343] analyzed the genomic mechanisms of increased prostate cancer risk in migrating Asian and Hispanic populations to countries with higher affluence, providing epidemiologic context for how metabolic changes drive cancer risk.

2.7 Breast, endometrial and ovarian cancer under GLP-1 activity

Breast cancer is the most common malignancy among women and — like prostate cancer — is closely linked to obesity, insulin resistance, and metabolic syndrome, particularly in the hormone-receptor-positive postmenopausal setting. Piccoli et al. (2021) [344] analyzed liraglutide's clinical development program and reported no increased breast cancer risk. Hicks et al. (2016, *BMJ*) [345], using the Clinical Practice Research Datalink, reported no increased incident breast cancer risk with GLP-1 analogues compared with DPP-4 inhibitors — an important early result from a well-conducted UK cohort. Sarti et al. (2025) [346] reviewed the pharmacological prevention of hormone-receptor-positive breast cancer in high-risk women, situating GLP-1RAs alongside SERMs and aromatase inhibitors in the prevention toolkit. Xande et al. (2025) [347], Parsons et al. (2025) [348], and Naaman et al. (2022) [349] provided epidemiological and mechanistic reviews on the obesity-breast cancer axis and the potential of GLP-1RAs to modify it, particularly in postmenopausal women where aromatase-driven estrogen from adipose tissue drives HR+ disease.

Preclinical evidence for direct anti-tumor action in breast cancer is extensive. Ligumsky et al. (2012) [350] provided one of the earliest demonstrations that GLP-1 has effects on breast cancer cell biology, and Ligumsky et al. (2024) [351] synthesized the accumulated evidence linking GLP-1RAs to breast cancer prevention in T2DM and obesity. Hashimoto et al. (2021) [352] analyzed diabetes as a breast cancer risk factor and the therapeutic potential of GLP-1RAs. Tanaka et al. (2021) [353] reported anti-breast-cancer effects of exendin-4 and characterized the associated tissue-protective mechanisms. Iwaya et al. (2017) [333] — cited above for prostate cancer — extended their incretin-cancer work to breast cancer. Liu et al. (2022) [354] analyzed the role of GLP-1R signaling in breast cancer cells, characterizing direct receptor-mediated effects. Shadboorestan et al. (2021) [355] demonstrated that liraglutide inhibits breast cancer cell growth. Stanisavljevic et al. (2024) [356] showed that semaglutide exhibits immunomodulatory and antitumor effects in breast cancer models. Atasoy et al. (2025) [357] demonstrated synergistic effects between GLP-1RAs and radiotherapy in preclinical breast cancer models, an important translational finding for combination oncology. Santos et al. (2026) [358] provided a comprehensive assessment of GLP-1R expression and activity across human tumors, with particular relevance to breast cancer.

Two mortality-oriented studies from the diabetic breast cancer intersection are particularly informative. Lemon et al. (2022) [359] evaluated metformin and survival in women with T2DM and hormonally-mediated cancers (breast, endometrial, ovarian), providing comparative context for GLP-1RA effects. Sukumar et al. (2026) [360] reported treatment patterns, weight loss, and outcomes in breast cancer survivors using GLP-1RAs — an important real-world safety-and-efficacy signal for the survivor population where use is growing rapidly. De and colleagues (2025) analyzed HR+/HER2- early-stage breast cancer outcomes with adjuvant endocrine therapy and considered how obesity modification via GLP-1RAs might improve recurrence-free survival. Fujiwara et al. (2017) [361] provided the intestinal-neoplasia-diabetes mechanistic link relevant to hormonally-mediated cancers.

Two direct clinical scenarios complete the section. Cornelio et al. (2026) [362] analyzed cardiovascular benefits of GLP-1RA therapies in women with breast cancer and T2D, addressing the cardio-oncology intersection. Brown et al. (2024) [363] examined GLP-1RA use in axillary lymph node dissection patients with high BMI and insulin resistance, addressing lymphedema prevention. Santella et al. (2020) [364] tested the intriguing hypothesis that weight loss on GLP-1RA therapy improves breast-cancer detection sensitivity — a diagnostic-imaging consideration. Hung et al. (2026) [164] provided the systematic review addressing concerns about pro-oncogenic effects of GLP-1RA and SGLT2i therapies, arriving at a generally reassuring conclusion.

Endometrial and ovarian cancers are among the sites where GLP-1RA benefit is most consistently reported, reflecting their strong association with obesity, insulin resistance, unopposed estrogen, and polycystic ovary syndrome. Wang et al. (2024) [83] reported HR 0.52 for ovarian cancer and 0.74 for endometrial cancer with GLP-1RA versus insulin. Dai et al. (2025) [28] reported HR 0.53 for ovarian and 0.75 for endometrial. Ipaye et al. (2025) [48] reported ovarian-cancer reduction (HR 0.31) with tirzepatide versus DPP-4i. Bourou et al. (2024) [365] reviewed the endometrial cancer landscape and its drivers, including unopposed estrogen, obesity, and insulin resistance. Riedinger et al. (2024) [366] reviewed the expanding scope of GLP-1RA use amid the obesity epidemic and its gynecological implications. Kong and Kadan-Lottick (2024) [367] evaluated tirzepatide and other pharmacotherapeutic interventions for endometrial-cancer prevention, arguing that combating obesity may reduce EC incidence and improve outcomes. Hagemann et al. (2025) [368] evaluated the combination of progestin therapy with semaglutide in conservative endometrial cancer treatment, exploring GLP-1RA-assisted weight loss in fertility-sparing management. Hsieh et al. (2026) [369] tested whether the addition of GLP-1RA to progestin therapy reduces hysterectomy rates in patients with endometrial intraepithelial neoplasia and endometrial cancer under fertility-sparing management. Podder et al. (2026) [370] reviewed treatment options for obesity-associated, hormone-resistant, and fertility-preserving endometrial cancer, highlighting GLP-1RAs as a rising modality.

Real-world observational cohorts extend the epidemiology. Rothman et al. (2025) [371] used the UK Clinical Practice Research Datalink to test whether incretin-based drugs are associated with decreased endometrial cancer risk in women with T2D. Tseng et al. (2025) [372] analyzed GLP-1RA and SGLT2i oncogenic potential in gynecological malignancies and reported reassurance. Yen et al. (2026) [373] evaluated endometrial cancer risk in patients with obesity and metabolic disorders under GLP-1RA exposure. Moshayedi et al. (2025) [374] reviewed the obesity-endometrial cancer axis and the role of effective weight management. Violette et al. (2023) [375] analyzed the interplay of obesity, PCOS, and T2DM in driving malignant endometrial transformation. Karkia et al. (2025) [376] evaluated plasma adipokines as endometrial-cancer biomarkers. Wang et al. (2025) [82] analyzed all-cause mortality in women with ovarian cancer under GLP-1RA use, providing evidence for survival benefit. Kosowska et al. (2017) [377] reviewed diabetes-ovarian-cancer interactions.

Preclinical work characterizes GLP-1R action directly on gynecological cancer cells. He et al. (2016) [378] tested whether GLP-1 receptor agonists promote growth of human ovarian cancer cells; contrary to the pro-proliferative concern, the study demonstrated cell-line-specific effects that are largely inhibitory. Liu et al. (2026) [379] analyzed subtype-specific ovarian cancer biology under GLP-1R activation, showing heterogeneous effects across ovarian cancer subtypes and pointing to the need for individualised approaches. Tang et al. (2026) [380] explored anti-diabetic drug repurposing in ovarian cancer therapy. Khan et al. (2025) [381] analyzed GLP-1R and NPY receptor expression in reproductive tissues under gonadal regulation, providing endocrine context. Zhu et al. (2021) [382] contributed to the ovarian-cancer literature (no abstract in source). Li et al. (2022) [383] explored the role and mechanism of GLP-1R in endometrial carcinoma via receptor overexpression and knockdown experiments. Li et al. (2024) [88] further investigated GLP-1R properties in endometrial cancer in vitro. Zhang et al. (2016) [384] demonstrated anti-cancer effects of exenatide on endometrial cancer cells; Zhang et al. (2021) [385] built on this by showing that exendin-4 modulates the response of endometrial cancer cells to chemotherapy under high-glucose conditions. Kanda (2018) [386] provided background on GLP-1RA effects. Devis-Jauregui et al. (2021) [387] reviewed autophagy in endometrial cancer, providing a mechanistic axis relevant to GLP-1RA effects.

2.8 Hematologic malignancies and other tumor types under the GLP-1 prism

The hematologic-cancer literature is dominated by a small set of observational cohorts and mechanistic reviews, given that active hematologic malignancy patients were largely excluded from GLP-1RA trials. Irons et al. (2026) [388] analyzed patients with T2DM taking multiple metabolic-pathway-targeting agents and evaluated the incidence of hematologic malignancies under GLP-1RA exposure. Lin et al. (2025) [389] and Lin et al. (2026) [390] reviewed and analyzed the effects of GLP-1RAs, SGLT2i, and DPP-4i on hematologic malignancy risk, providing a comparative-drug context for this understudied endpoint. The Wang et al. (2024) [83] landmark cohort reported HR 0.59 for multiple myeloma with GLP-1RA versus insulin — one of the more striking risk reductions in the OAC panel. Grandhi et al. (2024) [391] directly examined the impact of GLP-1RAs on the natural history of monoclonal gammopathy of uncertain significance (MGUS) in T2D patients, finding that GLP-1RA exposure was associated with reduced progression to multiple myeloma. Tentolouris et al. (2026) [392] reinforced this in a similar analysis of MGUS progression under GLP-1RA exposure. Lopez and colleagues (2026) [393] contributed further evidence (no abstract in source). Ebbesen et al. (2019) [394] evaluated GLP-1RA effects in autologous stem cell transplantation, showing potential mitigation of chemotherapy-induced mucositis and its downstream bacterial translocation and systemic inflammation — a supportive-care mechanism relevant to intensive hematology.

Two additional cancer sites feature in this section. Pradhan et al. (2024) [395] analyzed GLP-1RA use and both melanoma and non-melanoma skin cancer risk versus sulfonylurea comparators. Feng et al. (2024) [396] and Haq et al. (2024) [397] reviewed metformin's protective effects against skin cancer, providing indirect comparative context. Pimenta et al. (2026) [398] analyzed sarcomas, particularly liposarcoma, as a model of dysfunctional mesenchymal-stem-cell differentiation and the potential of GLP-1RAs to modulate this axis. Honors and Kinzig (2014) [399] reviewed cancer cachexia and available treatment strategies, providing the clinical context for GLP-1RA's paradoxical potential in both wasting and metabolic modulation.

Table 1: Results table

Cancer type	Risk direction	Key findings / evidence
Hepatocellular carcinoma (HCC)	Reduced risk	Consistent reduction across multiple large cohorts (Wang 2024, Kanwal 2024, Yang 2024), mainly via MASLD/MASH reduction
Colorectal cancer	Reduced risk	HR 0.54 vs insulin (Wang 2024); mild increase in surveillance detection in RCT meta-analysis (MH-OR 1.27) attributed to increased screening from GI side effects, not true carcinogenesis
Endometrial cancer	Reduced risk	HR 0.74 (Wang 2024), 0.75 (Dai 2025); strong link to obesity/insulin resistance
Ovarian cancer	Reduced risk	HR 0.52 (Wang 2024), 0.53 (Dai 2025), 0.31 with tirzepatide (Ipaye 2025)
Meningioma	Reduced risk	HR 0.37 (Wang 2024), 0.69 (Dai 2025)
Gallbladder cancer	Reduced risk	HR 0.35 vs insulin (Wang 2024)
Multiple myeloma	Reduced risk	HR 0.59 (Wang 2024); reduced progression from MGUS to myeloma (Grandhi 2024, Tentolouris 2026)
Prostate cancer	Reduced risk (preliminary)	Danish/Taiwanese cohorts plus mechanistic data in cell lines
Breast cancer	Neutral to favourable	No increased risk (Hicks 2016 BMJ, Piccoli 2021); direct antitumor mechanisms in vitro
Pancreatic cancer	Neutral / reassuring	Multiple RCT meta-analyses show no signal; HR 0.41 in one large cohort (Wang 2024)
Gastric cancer	Mild favourable trend	HR 0.73 (borderline, non-significant) vs insulin (Wang 2024)
Esophageal cancer	Neutral / favourable	HR 0.60 (Wang 2024); no increase in meta-analysis (Wu 2025)
Thyroid cancer	Conflicting findings	RCT meta-analysis shows MH-OR 1.52 (Silverii 2024); many large cohorts are null (Brito 2025, Bea 2024, Pollack 2025); rodent C-cell signal not fully confirmed in humans

Kidney (renal) cancer	Increased risk (vs certain comparators)	HR 1.54 vs metformin, 1.43 vs SGLT2i, 1.38 in non-diabetic obese patients (Dai 2025)
Cholangiocarcinoma	Conflicting findings	Initial concern (Abrahami 2018, BMJ); not confirmed in Scandinavian data (Ueda 2021) or TriNetX (Krishnan 2024)
Neuroendocrine neoplasms (NENs)	Theoretical concern	Proliferation shown in GLP-1R-positive cell lines (Shilyansky 2025); conversely, better survival in observational data (Fawzy 2025)
Lung cancer	Reduced risk	Lower incidence vs insulin across multiple cohorts (Tabernacki 2024, Song 2025)
Glioma / CNS tumors	Reduced risk (preclinical)	Exendin-4 inhibits glioma proliferation (Nie 2018); better glioblastoma outcomes with higher GLP1R copy number

3 CONCLUSION

GLP-1 receptor agonists show a consistent pattern of reduced risk for many obesity-associated cancers. The strongest and most reproducible signals of benefit concern hepatocellular carcinoma (via MASLD reduction), colorectal cancer, endometrial cancer, ovarian cancer, meningioma, gallbladder cancer, and multiple myeloma. The picture for pancreatic cancer, once a source of significant concern, is now dominated by neutrality-to-benefit; the picture for prostate cancer is favorable but preliminary; the picture for breast cancer is neutral-to-favorable and mechanistically supported by direct anti-tumor effects on cell lines. Two areas of continuing concern warrant closer surveillance: thyroid cancer, where a modest but statistically significant signal exists in some (but not all) meta-analyses and where rodent evidence is unambiguous even though human relevance is disputed on receptor-expression grounds; and kidney cancer, where multiple studies report modestly increased risk versus specific comparators (metformin, SGLT2i, DPP-4i).

Three orthogonal lines of evidence support a coherent biological story. First, the class produces substantial weight loss and improves the metabolic drivers (hyperinsulinaemia, chronic inflammation, adipose dysfunction, elevated free IGF-1) that link obesity to cancer. Second, direct anti-tumor actions have been demonstrated in cell lines and animal models across many cancer types, operating through GLP-1R/SIRT3-mediated EMT suppression (glioma), IL-6/STAT3 axis inhibition (HCC), ferroptosis induction via SLC7A11 (glioblastoma), tumor-associated macrophage reprogramming (PTC), and NET inhibition (lung, liver). Third, immunomodulatory effects — cAMP-PKA-AMPK signaling suppression of NF- κ B-driven inflammation, macrophage repolarisation, improved CD8 T-cell metabolic fitness, and reduced lipid-induced T-cell exhaustion — position the class as a possible metabolic-immunologic adjuvant to immune checkpoint inhibitor therapy, with real-world observational data across renal, lung, colorectal, and breast cancers already suggesting improved survival and fewer immune-related adverse events.

The tensions in the literature — the residual signal for thyroid and kidney cancer, the mechanistic proliferation of NEN cells expressing GLP-1R, the diagnostic-imaging pitfalls introduced by rapid weight loss and BAT activation, the excess acute-pancreatitis risk in the first six months of therapy, the paradoxical increases in esophageal and gastric cardia cancers after bariatric surgery (but not GLP-1RAs) — do not overturn the overall picture but do delineate the boundaries within which the class should be prescribed with caution. The next generation of randomized trials, ideally including patients with active cancer, may be required to convert the current observational reassurance into firm therapeutic guidance.

REFERENCES

- [1] Liu QK. Mechanisms of action and therapeutic applications of GLP-1 and dual GIP/GLP-1 receptor agonists. *Front Endocrinol (Lausanne)*. 2024 Jul 24;15:1431292. doi: 10.3389/fendo.2024.1431292. PMID: 39114288; PMCID: PMC11304055
- [2] Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev*. 2007 Oct;87(4):1409-39. doi: 10.1152/physrev.00034.2006. PMID: 17928588.
- [3] Mayendraraj A, Rosenkilde MM, Gasbjerg LS. GLP-1 and GIP receptor signaling in beta cells - A review of receptor interactions and co-stimulation. *Peptides*. 2022 May;151:170749. doi: 10.1016/j.peptides.2022.170749. Epub 2022 Jan 19. PMID: 35065096.
- [4] Egan JM, Bulotta A, Hui H, Perfetti R. GLP-1 receptor agonists are growth and differentiation factors for pancreatic islet beta cells. *Diabetes Metab Res Rev*. 2003 Mar-Apr;19(2):115-23. doi: 10.1002/dmrr.357. PMID: 12673779.

- [5] Pyke C, Heller RS, Kirk RK, Ørskov C, Reedtz-Runge S, Kastrup P, Hvelplund A, Bardram L, Calatayud D, Knudsen LB. GLP-1 receptor localization in monkey and human tissue: novel distribution revealed with extensively validated monoclonal antibody. *Endocrinology*. 2014 Apr;155(4):1280-90. doi: 10.1210/en.2013-1934. Epub 2014 Jan 27. PMID: 24467746.
- [6] Waser B, Blank A, Karamitopoulou E, Perren A, Reubi JC. Glucagon-like-peptide-1 receptor expression in normal and diseased human thyroid and pancreas. *Mod Pathol*. 2015 Mar;28(3):391-402. doi: 10.1038/modpathol.2014.113. Epub 2014 Sep 12. PMID: 25216224.
- [7] Waser B, Beetschen K, Pellegata NS, Reubi JC. Incretin receptors in non-neoplastic and neoplastic thyroid C cells in rodents and humans: relevance for incretin-based diabetes therapy. *Neuroendocrinology*. 2011;94(4):291-301. doi: 10.1159/000330447. Epub 2011 Sep 2. PMID: 21893952.
- [8] Gier B, Butler PC, Lai CK, Kirakossian D, DeNicola MM, Yeh MW. Glucagon like peptide-1 receptor expression in the human thyroid gland. *J Clin Endocrinol Metab*. 2012 Jan;97(1):121-31. doi: 10.1210/jc.2011-2407. Epub 2011 Oct 26. PMID: 22031513; PMCID: PMC3412261.
- [9] Song Y, Zhou M, Cao Y, Qi J, Geng J, Liu X. Expression of GLP-1 receptor and CD26 in human thyroid C-cells: The association of thyroid C-cell tumorigenesis with incretin-based medicine. *Oncol Lett*. 2017 Apr;13(4):2684-2690. doi: 10.3892/ol.2017.5752. Epub 2017 Feb 20. PMID: 28454451; PMCID: PMC5403711.
- [10] Zhao X, Wang M, Wen Z, Lu Z, Cui L, Fu C, Xue H, Liu Y, Zhang Y. GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects. *Front Endocrinol (Lausanne)*. 2021 Aug 23;12:721135. doi: 10.3389/fendo.2021.721135. PMID: 34497589; PMCID: PMC8419463.
- [11] Buenaventura T, Bitsi S, Laughlin WE, Burgoyne T, Lyu Z, Oqua AI, Norman H, McGlone ER, Klymchenko AS, Corrêa IR Jr, Walker A, Inoue A, Hanyaloglu A, Grimes J, Koszegi Z, Calebiro D, Rutter GA, Bloom SR, Jones B, Tomas A. Agonist-induced membrane nanodomain clustering drives GLP-1 receptor responses in pancreatic beta cells. *PLoS Biol*. 2019 Aug 20;17(8):e3000097. doi: 10.1371/journal.pbio.3000097. PMID: 31430273; PMCID: PMC6716783.
- [12] McLean BA, Wong CK, Campbell JE, Hodson DJ, Trapp S, Drucker DJ. Revisiting the Complexity of GLP-1 Action from Sites of Synthesis to Receptor Activation. *Endocr Rev*. 2021 Mar 15;42(2):101-132. doi: 10.1210/edrev/bnaa032. PMID: 33320179; PMCID: PMC7958144.
- [13] Alba MM, Lee WH, Lee JSH, Lu Z, Stiles B, Ligumsky H. Expression and functional diversity of the glucagon-like peptide-1 receptor across tumor types. *Discov Oncol*. 2025 Dec 3;17(1):36. doi: 10.1007/s12672-025-04097-4. PMID: 41331220; PMCID: PMC12779865.
- [14] Ungvari Z, Barthá Á, Ungvari A, Fekete M, Bianchini G, Györfy B. Prognostic impact of glucagon-like peptide-1 receptor (GLP1R) expression on cancer survival and its implications for GLP-1R agonist therapy: an integrative analysis across multiple tumor types. *Geroscience*. 2025 Jun;47(3):4413-4427. doi: 10.1007/s11357-024-01494-5. Epub 2025 Jan 8. PMID: 39777709; PMCID: PMC12181560.
- [15] Nie ZJ, Zhang YG, Chang YH, Li QY, Zhang YL. Exendin-4 inhibits glioma cell migration, invasion and epithelial-to-mesenchymal transition through GLP-1R/sirt3 pathway. *Biomed Pharmacother*. 2018 Oct;106:1364-1369. doi: 10.1016/j.biopha.2018.07.092. Epub 2018 Jul 23. PMID: 30119208.
- [16] Baran O, Akgun MY, Kayhan A, Evran S, Ozbek A, Akyoldas G, Samanci MY, Demirel N, Sonmez D, Serin H, Kocak A, Kemerdere R, Tanriverdi T. The association between calreticulin and glucagon-like peptide-1 expressions with prognostic factors in high-grade gliomas. *J Cancer Res Ther*. 2024 Jan 1;20(1):25-32. doi: 10.4103/jcrt.jcrt_1519_22. Epub 2023 Apr 8. PMID: 38554294.
- [17] Cases AI, Ohtsuka T, Fujino M, Ideno N, Kozono S, Zhao M, Ohuchida K, Aishima S, Nomura M, Oda Y, Mizumoto K, Tanaka M. Expression of glucagon-like Peptide 1 receptor and its effects on biologic behavior in pancreatic neuroendocrine tumors. *Pancreas*. 2014 Jan;43(1):1-6. doi: 10.1097/MPA.0b013e3182a71537. PMID: 24326362.
- [18] He W, Li J. Exendin-4 enhances radiation response of prostate cancer. *Prostate*. 2018 Nov;78(15):1125-1133. doi: 10.1002/pros.23687. Epub 2018 Jul 15. PMID: 30009503.
- [19] Nomiya T, Kawanami T, Irie S, Hamaguchi Y, Terawaki Y, Murase K, Tsutsumi Y, Nagaishi R, Tanabe M, Morinaga H, Tanaka T, Mizoguchi M, Nabeshima K, Tanaka M, Yanase T. Exendin-4, a GLP-1 receptor agonist, attenuates prostate cancer growth. *Diabetes*. 2014 Nov;63(11):3891-905. doi: 10.2337/db13-1169. Epub 2014 May 30. PMID: 24879833.
- [20] Reubi JC, Waser B. Concomitant expression of several peptide receptors in neuroendocrine tumors: molecular basis for in vivo multireceptor tumor targeting. *Eur J Nucl Med Mol Imaging*. 2003 May;30(5):781-93. doi: 10.1007/s00259-003-1184-3. Epub 2003 Apr 18. PMID: 12707737.

- [21] Waser B, Rehmann R, Sanchez C, Fourmy D, Reubi JC. Glucose-dependent insulinotropic polypeptide receptors in most gastroenteropancreatic and bronchial neuroendocrine tumors. *J Clin Endocrinol Metab*. 2012 Feb;97(2):482-8. doi: 10.1210/jc.2011-2454. Epub 2011 Nov 23. PMID: 22112810.
- [22] Kupnicka P, Król M, Żychowska J, Łagowski R, Prajwos E, Surówka A, Chlubek D. GLP-1 Receptor Agonists: A Promising Therapy for Modern Lifestyle Diseases with Unforeseen Challenges. *Pharmaceuticals (Basel)*. 2024 Nov 1;17(11):1470. doi: 10.3390/ph17111470. PMID: 39598383; PMCID: PMC11597758.
- [23] Moiz A, Filion KB, Tsoukas MA, Yu OHY, Peters TM, Eisenberg MJ. The expanding role of GLP-1 receptor agonists: a narrative review of current evidence and future directions. *EClinicalMedicine*. 2025 Jul 17;86:103363. doi: 10.1016/j.eclinm.2025.103363. PMID: 40727007; PMCID: PMC12303005.
- [24] Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse Effects of GLP-1 Receptor Agonists. *Rev Diabet Stud*. 2014 Fall-Winter;11(3-4):202-30. doi: 10.1900/RDS.2014.11.202. Epub 2015 Feb 10. PMID: 26177483; PMCID: PMC5397288.
- [25] Smits MM, Van Raalte DH. Safety of Semaglutide. *Front Endocrinol (Lausanne)*. 2021 Jul 7;12:645563. doi: 10.3389/fendo.2021.645563. Erratum in: *Front Endocrinol (Lausanne)*. 2021 Nov 10;12:786732. doi: 10.3389/fendo.2021.786732. PMID: 34305810; PMCID: PMC8294388.
- [26] Jalleh RJ, Talley NJ, Horowitz M, Nauck MA. The science of safety: adverse effects of GLP-1 receptor agonists as glucose-lowering and obesity medications. *J Clin Invest*. 2026 Feb 16;136(4):e194740. doi: 10.1172/JCI194740. PMID: 41697736; PMCID: PMC12904723.
- [27] Wang L, Xu R, Kaelber DC, Berger NA. Glucagon-Like Peptide 1 Receptor Agonists and 13 Obesity-Associated Cancers in Patients With Type 2 Diabetes. *JAMA Netw Open*. 2024 Jul 1;7(7):e2421305. doi: 10.1001/jamanetworkopen.2024.21305. Erratum in: *JAMA Netw Open*. 2025 Jun 2;8(6):e2519224. doi: 10.1001/jamanetworkopen.2025.19224. PMID: 38967919; PMCID: PMC11227080.
- [28] Dai H, Li Y, Lee YA, Lu Y, George TJ, Donahoo WT, Lee KP, Nakshatri H, Allen J, Guo Y, Sun RC, Guo J, Bian J. GLP-1 Receptor Agonists and Cancer Risk in Adults With Obesity. *JAMA Oncol*. 2025 Oct 1;11(10):1186-1193. doi: 10.1001/jamaoncol.2025.2681. PMID: 40839273; PMCID: PMC12371547.
- [29] Wolff Sagy Y, Ramot N, Battat E, Arbel R, Reges O, Dicker D, Lavie G. Glucagon-like peptide-1 receptor agonists compared with bariatric metabolic surgery and the risk of obesity-related cancer: an observational, retrospective cohort study. *EClinicalMedicine*. 2025 May 11;83:103213. doi: 10.1016/j.eclinm.2025.103213. PMID: 40599584; PMCID: PMC12208935.
- [30] Kim M, Kim SC, Kim J, Kim BH. Use of Glucagon-Like Peptide-1 Receptor Agonists Does Not Increase the Risk of Cancer in Patients with Type 2 Diabetes Mellitus. *Diabetes Metab J*. 2025 Jan;49(1):49-59. doi: 10.4093/dmj.2024.0105. Epub 2024 Oct 24. PMID: 39443282; PMCID: PMC11788542.
- [31] Lu Y, Dai H, Tang H, Donahoo WT, George TJ, Sun RC, Jiang S, Tan AC, Guo Y, Licht JD, Allen JM, Lee KP, Guo J, Bian J. Association of Glucagon-Like Peptide-1 Receptor Agonists With Cancer Risk in Older Adults With Type 2 Diabetes. *Obesity (Silver Spring)*. 2025 Aug 21;10.1002/oby.24366. doi: 10.1002/oby.24366. Epub ahead of print. PMID: 40841345; PMCID: PMC12906048.
- [32] Levy S, Attia A, Elshazli RM, Abdelmaksoud A, Tatum D, Aiash H, Toraih EA. Differential Effects of GLP-1 Receptor Agonists on Cancer Risk in Obesity: A Nationwide Analysis of 1.1 Million Patients. *Cancers (Basel)*. 2024 Dec 30;17(1):78. doi: 10.3390/cancers17010078. PMID: 39796706; PMCID: PMC11720624.
- [33] Tartaglia E, Bucci T, Rossi M, Rigutini AG, Askarinejad A, Alam U, Nabrdalik K, Boriani G, Lip GYH. Risk of all-cause death and pancreatic events following GLP-1 RA initiation in people with obesity or type 2 diabetes: observations from a federated research network. *Cardiovasc Diabetol*. 2025 Nov 19;24(1):438. doi: 10.1186/s12933-025-02986-0. PMID: 41257737; PMCID: PMC12628983.
- [34] Silverii GA, Marinelli C, Bettarini C, Del Vescovo GG, Monami M, Mannucci E. GLP-1 receptor agonists and the risk for cancer: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2025 Aug;27(8):4454-4468. doi: 10.1111/dom.16489. Epub 2025 May 29. PMID: 40437949; PMCID: PMC12232360.
- [35] Silverii GA, Monami M, Gallo M, Ragni A, Prattichizzo F, Renzelli V, Ceriello A, Mannucci E. Glucagon-like peptide-1 receptor agonists and risk of thyroid cancer: A systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2024 Mar;26(3):891-900. doi: 10.1111/dom.15382. Epub 2023 Nov 29. PMID: 38018310.
- [36] Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and risk of cancer in type 2 diabetes: an updated meta-analysis of randomized controlled trials. *Endocrine*. 2019 Nov;66(2):157-165. doi: 10.1007/s12020-019-02055-z. Epub 2019 Aug 16. PMID: 31420784.

- [37] Jaradat JH, Al-Ahmad RI, Al Jaghbeer M, Abdelaziz AA, Abu Afifeh NM, Abu Afifeh G, Rao A, Alzoubi A, Nashwan AJ. Assessing the Oncological Safety of Glucagon-Like Peptide-1 Receptor Agonists: A Systematic Review and Meta-Analysis. *Cureus*. 2025 Nov 4;17(11):e96071. doi: 10.7759/cureus.96071. PMID: 41356998; PMCID: PMC12676983.
- [38] Ateiwi YA, Mahmood R, Wong HJ, Low CE, Yau CE, Lee ARYB, Eng PC, Lee M, Chan MY, Sia CH. Glucagon-like peptide-1 receptor agonists and the risk of obesity-related cancers: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2026 Apr;234:113158. doi: 10.1016/j.diabres.2026.113158. Epub 2026 Feb 19. PMID: 41722869.
- [39] Ko A, Chang YC, Bahar F, Wang TH, Xanthavanij N, Yu CC, Hsieh RJ, See XY, Lo SW, Song J, Hsia YP, Chiang CH, Xu X, Lin S, Chiang CH. Risk for Cancer With Glucagon-Like Peptide-1 Receptor Agonists and Dual Agonists : A Systematic Review and Meta-analysis. *Ann Intern Med*. 2026 Feb;179(2):216-229. doi: 10.7326/ANNALS-25-02237. Epub 2025 Dec 9. PMID: 41359966.
- [40] Wilson RB, Lathigara D, Kaushal D. Systematic Review and Meta-Analysis of the Impact of Bariatric Surgery on Future Cancer Risk. *Int J Mol Sci*. 2023 Mar 24;24(7):6192. doi: 10.3390/ijms24076192. PMID: 37047163; PMCID: PMC10094585.
- [41] Tseng CH, Lee KY, Tseng FH. An updated review on cancer risk associated with incretin mimetics and enhancers. *J Environ Sci Health C Environ Carcinog Ecotoicol Rev*. 2015;33(1):67-124. doi: 10.1080/10590501.2015.1003496. PMID: 25803196.
- [42] Rosol TJ. On-target effects of GLP-1 receptor agonists on thyroid C-cells in rats and mice. *Toxicol Pathol*. 2013 Feb;41(2):303-9. doi: 10.1177/0192623312472402. PMID: 23471186.
- [43] Nauck MA, Friedrich N. Do GLP-1-based therapies increase cancer risk? *Diabetes Care*. 2013 Aug;36 Suppl 2(Suppl 2):S245-52. doi: 10.2337/dcS13-2004. PMID: 23882053; PMCID: PMC3920789.
- [44] Zhang P, Zhao Z, Zhang L, Wu W, Xu Y, Pan D, Wang F, Yang M. [⁶⁸Ga]Ga-NOTA-MAL-Cys³⁹-exendin-4, a potential GLP-1R targeted PET tracer for the detection of insulinoma. *Nucl Med Biol*. 2019 Jul-Aug;74-75:19-24. doi: 10.1016/j.nucmedbio.2019.08.002. Epub 2019 Aug 16. PMID: 31450071.
- [45] Cheng Z, Wang S, Li FR, Jin C, Mo C, Zheng J, Li X, Liang F, Yang J, Gu D. The potential adverse effects of hypodermic glucagon-like peptide -1 receptor agonist on patients with type 2 diabetes: A population-based study. *J Diabetes*. 2024 Oct;16(10):e70013. doi: 10.1111/1753-0407.70013. PMID: 39435881; PMCID: PMC11494487.
- [46] Leong D, Gong S, Sattar N, Narayan V, Reizine NM, Gerstein H, Vellky J. Incretin Mimetics in Cancer and Cardiovascular Disease: JACC: CardioOncology State-of-the-Art Review. *JACC CardioOncol*. 2026 Feb;8(1):1-16. doi: 10.1016/j.jaccao.2025.12.003. PMID: 41705747; PMCID: PMC12922619.
- [47] Mao X, Zhang X, Henry L, Cheung KS, Yuen MF, Cheung R, Seto WK, Nguyen MH. Association between glucagon-like peptidase 1 receptor agonist and obesity-related cancer in overweight or obese patients with type 2 diabetes: a nationwide cohort study. *J Natl Cancer Inst*. 2025 Oct 1;117(10):2053-2061. doi: 10.1093/jnci/djaf163. PMID: 40632592; PMCID: PMC12593220.
- [48] Ipaye T, Goldney J, Wilkinson TJ, Zaccardi F, Yates T, Davies MJ, Brown K, Papamargaritis D. Weight loss interventions and obesity-associated cancers in people with type 2 diabetes and overweight/obesity: A real-world observational study. *Diabetes Obes Metab*. 2025 Dec;27(12):6914-6926. doi: 10.1111/dom.70090. Epub 2025 Sep 3. PMID: 40903861; PMCID: PMC12587238.
- [49] Chuang CH, Tsai PK, Kao SW, Wang YH, Yeh CB. Early GLP-1 Agonist Use and Cancer Risk in Type 2 Diabetes: A Real-World Data Cohort Study. *Oncol Res*. 2025 Dec 30;34(1):12. doi: 10.32604/or.2025.072875. PMID: 41502515; PMCID: PMC12774574.
- [50] [50] Wu T, Zhang Y, Shi Y, Yu K, Zhao M, Liu S, Zhao Z. Safety of Glucagon-Like Peptide-1 Receptor Agonists: A Real-World Study Based on the US FDA Adverse Event Reporting System Database. *Clin Drug Investig*. 2022 Nov;42(11):965-975. doi: 10.1007/s40261-022-01202-1. Epub 2022 Sep 30. PMID: 36175609.
- [51] Mahadevan A, Vosooghi A, Arora JS, Kumar RS, Singh G, Tsai KK, Quandt Z. GLP- 1 Receptor Agonists in Patients with Cancer are Associated with Reduced All-Cause Mortality and Hospitalization. *J Clin Endocrinol Metab*. 2026 Jan 2;dgaf703. doi: 10.1210/clinem/dgaf703. Epub ahead of print. PMID: 41482652.
- [52] Banerjee M, Pal R, Maisnam I, Mukhopadhyay S. GLP-1 receptor agonists, SGLT2 inhibitors and noncardiovascular mortality in type 2 diabetes: Insights from a meta-analysis. *Diabetes Metab Syndr*. 2024 Jan;18(1):102943. doi: 10.1016/j.dsx.2024.102943. Epub 2024 Jan 5. PMID: 38211482.
- [53] Hsu CW, Zeng BS, Liang CS, Zeng BY, Hung CM, Stubbs B, Chen YW, Lei WT, Chen JJ, Chen PH, Su KP, Chen TY, Tseng PT. The Preventive Effects of GLP-1 Receptor Agonists and SGLT2 Inhibitors on Cancer Metastasis: A

Network Meta-Analysis of 67 Randomized Controlled Trials. *Int J Mol Sci.* 2025 Aug 23;26(17):8202. doi: 10.3390/ijms26178202. PMID: 40943127; PMCID: PMC12428495.

- [54] Frey C. GLP-1 receptor agonists and immune checkpoint inhibitor therapy: a narrative review on mechanistic and clinical evidence. *Future Oncol.* 2026 Apr;22(10):1221-1231. doi: 10.1080/14796694.2026.2654735. Epub 2026 Apr 3. PMID: 41930781; PMCID: PMC13089914.
- [55] Vangoitsenhoven R, Mathieu C, Van der Schueren B. GLP1 and cancer: friend or foe? *Endocr Relat Cancer.* 2012 Sep 5;19(5):F77-88. doi: 10.1530/ERC-12-0111. PMID: 22691625.
- [56] Samuel SM, Varghese E, Kubatka P, Büsselberg D. Tirzepatide-Friend or Foe in Diabetic Cancer Patients? *Biomolecules.* 2022 Oct 28;12(11):1580. doi: 10.3390/biom12111580. PMID: 36358930; PMCID: PMC9687454.
- [57] Ji L, He X, Min X, Yang H, Wu W, Xu H, Chen J, Mei A. Glucagon-like peptide-1 receptor agonists in neoplastic diseases. *Front Endocrinol (Lausanne).* 2024 Sep 20;15:1465881. doi: 10.3389/fendo.2024.1465881. PMID: 39371922; PMCID: PMC11449759.
- [58] Kounatidis D, Vallianou NG, Karampela I, Rebelos E, Kouveletsou M, Dalopoulos V, Koufopoulos P, Diakoumopoulou E, Tentolouris N, Dalamaga M. Anti-Diabetic Therapies and Cancer: From Bench to Bedside. *Biomolecules.* 2024 Nov 20;14(11):1479. doi: 10.3390/biom14111479. PMID: 39595655; PMCID: PMC11591849.
- [59] Standl E, Schnell O. Increased Risk of Cancer-An Integral Component of the Cardio-Renal-Metabolic Disease Cluster and Its Management. *Cells.* 2025 Apr 9;14(8):564. doi: 10.3390/cells14080564. PMID: 40277890; PMCID: PMC12025391.
- [60] Lu C, Xu C, Yang J. The Beneficial Effects of GLP-1 Receptor Agonists Other than Their Anti-Diabetic and Anti-Obesity Properties. *Medicina (Kaunas).* 2024 Dec 26;61(1):17. doi: 10.3390/medicina61010017. PMID: 39858999; PMCID: PMC11767243.
- [61] Matuszewski W, Wołos-Kłosowicz K, Włodarczyk P, Waśniewska P, Modzelewski R, Górny JM, Szklarz M, Madeksha M, Juranek J. Beyond Glycemic Control: GLP-1RA-Based Therapies and Emerging Targets Beyond the Metabolic Axis. *J Clin Med.* 2026 Apr 7;15(7):2786. doi: 10.3390/jcm15072786. PMID: 41977086; PMCID: PMC13073043.
- [62] Borner T, Liberini CG, Lutz TA, Riediger T. Brainstem GLP-1 signaling contributes to cancer anorexia-cachexia syndrome in the rat. *Neuropharmacology.* 2018 Mar 15;131:282-290. doi: 10.1016/j.neuropharm.2017.12.024. Epub 2017 Dec 13. PMID: 29247677.
- [63] MacLusky NJ, Cook S, Scrocchi L, Shin J, Kim J, Vaccarino F, Asa SL, Drucker DJ. Neuroendocrine function and response to stress in mice with complete disruption of glucagon-like peptide-1 receptor signaling. *Endocrinology.* 2000 Feb;141(2):752-62. doi: 10.1210/endo.141.2.7326. PMID: 10650957.
- [64] Arai J, Okada S, Yamaguchi-Shima N, Shimizu T, Sasaki T, Yorimitsu M, Wakiguchi H, Yokotani K. Role of brain prostanoids in glucagon-like peptide-1-induced central activation of sympatho-adrenomedullary outflow in rats. *Clin Exp Pharmacol Physiol.* 2008 Aug;35(8):965-70. doi: 10.1111/j.1440-1681.2008.04957.x. Epub 2008 May 25. PMID: 18505450.
- [65] Gil-Lozano M, Romaní-Pérez M, Outeiriño-Iglesias V, Vigo E, González-Matías LC, Brubaker PL, Mallo F. Corticotropin-releasing hormone and the sympathoadrenal system are major mediators in the effects of peripherally administered exendin-4 on the hypothalamic-pituitary-adrenal axis of male rats. *Endocrinology.* 2014 Jul;155(7):2511-23. doi: 10.1210/en.2013-1718. Epub 2014 Apr 14. PMID: 24731096.
- [66] Pati S, Irfan W, Jameel A, Ahmed S, Shahid RK. Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. *Cancers (Basel).* 2023 Jan 12;15(2):485. doi: 10.3390/cancers15020485. PMID: 36672434; PMCID: PMC9857053.
- [67] Shilyansky JS, Chan CJ, Xiao S, Gribovskaja-Rupp I, Quelle DE, Howe JR, Dillon JS, Ear PH. GLP-1R agonist promotes proliferation of neuroendocrine neoplasm cells expressing GLP-1 receptors. *Surgery.* 2025 Mar;179:108943. doi: 10.1016/j.surg.2024.09.052. Epub 2024 Dec 10. PMID: 39665969.
- [68] Fawzy MS, Alenezzy A, Jishu JA, Khan I, Dessouky A, Abdelmaksoud A, Limbach KE, Toraih EA. Survival Benefits of GLP-1 Receptor Agonists in Patients with Neuroendocrine Neoplasms: A Large-Scale Propensity-Matched Cohort Study. *Cancers (Basel).* 2025 May 7;17(9):1593. doi: 10.3390/cancers17091593. PMID: 40361517; PMCID: PMC12072167.
- [69] Tateishi K, Shima K, Funakoshi A, Yasunami Y, Iwamoto N, Matsuoka Y. Glucagon-like peptide-1 (GLP-1) molecular forms in human pancreatic endocrine tumors resemble those in intestine rather than pancreas. *Diabetes Res Clin Pract.* 1994 Aug;25(1):43-9. doi: 10.1016/0168-8227(94)90160-0. PMID: 7835211.

- [70] Fiocca R, Rindi G, Capella C, Grimelius L, Polak JM, Schwartz TW, Yanaihara N, Solcia E. Glucagon, glicentin, proglucagon, PYY, PP and proPP-icosapeptide immunoreactivities of rectal carcinoid tumors and related non-tumor cells. *Regul Pept.* 1987 Jan;17(1):9-29. doi: 10.1016/0167-0115(87)90029-2. PMID: 2882565.
- [71] Hirata Y, Mizoshita T, Mizushima T, Shimura T, Mori Y, Kubota E, Wada T, Ogasawara N, Tanida S, Kataoka H, Sasaki M, Kamiya T, Tsukamoto T, Tatematsu M, Joh T. Gastric-and-intestinal mixed endocrine cell phenotypic expression of carcinoid tumors in the rectum. *Oncol Rep.* 2009 Jan;21(1):107-12. PMID: 19082450.
- [72] Fu Z, Zuo C, Sheehan CE, Patil DT, Lin J, Yang Z, Lee H. Novel Finding of Paired Box 5 (PAX5) Cytoplasmic Staining in Well-differentiated Rectal Neuroendocrine Tumors (Carcinoids) and Its Diagnostic and Potentially Prognostic Utility. *Appl Immunohistochem Mol Morphol.* 2019 Jul;27(6):454-460. doi: 10.1097/PAL.0000000000000635. PMID: 29561272.
- [73] Byrne MM, McGregor GP, Barth P, Rothmund M, Göke B, Arnold R. Intestinal proliferation and delayed intestinal transit in a patient with a GLP-1-, GLP-2- and PYY-producing neuroendocrine carcinoma. *Digestion.* 2001;63(1):61-8. doi: 10.1159/000051874. PMID: 11173902.
- [74] Behnam Azad B, Rota V, Yu L, McGirr R, St Amant AH, Lee TY, Dhanvantari S, Luyt LG. Synthesis and evaluation of optical and PET GLP-1 peptide analogues for GLP-1R imaging. *Mol Imaging.* 2015;14. doi: 10.2310/7290.2014.00057. PMID: 25762192.
- [75] Xu Q, Zhu C, Xu Y, Pan D, Liu P, Yang R, Wang L, Chen F, Sun X, Luo S, Yang M. Preliminary evaluation of [18F]AlF-NOTA-MAL-Cys39-exendin-4 in insulinoma with PET. *J Drug Target.* 2015;23(9):813-20. doi: 10.3109/1061186X.2015.1020808. Epub 2015 Mar 11. PMID: 25758750.
- [76] Eriksson O, Velikyan I, Selvaraju RK, Kandeel F, Johansson L, Antoni G, Eriksson B, Sörensen J, Korsgren O. Detection of metastatic insulinoma by positron emission tomography with [(68)ga]exendin-4-a case report. *J Clin Endocrinol Metab.* 2014 May;99(5):1519-24. doi: 10.1210/jc.2013-3541. Epub 2014 Feb 10. PMID: 24512490; PMCID: PMC4010711.
- [77] Kondo N, Oishi A, Hirata M, Temma T. Indirectly radioiodinated exendin-4 as an analytical tool for in vivo detection of glucagon-like peptide-1 receptor in a disease setting. *Ann Nucl Med.* 2021 Jan;35(1):83-91. doi: 10.1007/s12149-020-01540-0. Epub 2020 Oct 16. PMID: 33067731.
- [78] Jansen TJP, van Lith SAM, Boss M, Brom M, Joosten L, Béhé M, Buitinga M, Gotthardt M. Exendin-4 analogs in insulinoma theranostics. *J Labelled Comp Radiopharm.* 2019 Aug;62(10):656-672. doi: 10.1002/jlcr.3750. PMID: 31070270; PMCID: PMC6771680.
- [79] Shah R, Garg R, Majmundar M, Purandare N, Malhotra G, Patil V, Ramteke-Jadhav S, Lila A, Shah N, Bandgar T. Exendin-4-based imaging in insulinoma localization: Systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2021 Aug;95(2):354-364. doi: 10.1111/cen.14406. Epub 2021 Jan 21. PMID: 33386617.
- [80] Withaar C, Meems LMG, Markousis-Mavrogenis G, Boogerd CJ, Silljé HHW, Schouten EM, Dokter MM, Voors AA, Westenbrink BD, Lam CSP, de Boer RA. The effects of liraglutide and dapagliflozin on cardiac function and structure in a multi-hit mouse model of heart failure with preserved ejection fraction. *Cardiovasc Res.* 2021 Jul 27;117(9):2108-2124. doi: 10.1093/cvr/cvaa256. PMID: 32871009; PMCID: PMC8318109.
- [81] Thomas TM, Aboujaoude MT, Barker VR, Varkhedi M, Jain R, Blanck G. High GLP1R gene copy numbers associated with microsatellite instability for multiple cancers and with better survival probabilities for glioblastoma. *Cell Cycle.* 2024 Sep-Oct;23(17-20):913-921. doi: 10.1080/15384101.2025.2485873. Epub 2025 Apr 10. PMID: 40207977; PMCID: PMC12269650.
- [82] Wang J, Chen H, Wang X. Tirzepatide Induces Ferroptosis in Glioblastoma Cell Lines via the SOX2/SLC7A11 Axis: A Potential Therapeutic Strategy for Glioma Treatment. *J Biochem Mol Toxicol.* 2025 Aug;39(8):e70392. doi: 10.1002/jbt.70392. PMID: 40678831.
- [83] Wang L, Wang W, Kaelber DC, Xu R, Berger NA. GLP-1 Receptor Agonists and Colorectal Cancer Risk in Drug-Naive Patients With Type 2 Diabetes, With and Without Overweight/Obesity. *JAMA Oncol.* 2024 Feb 1;10(2):256-258. doi: 10.1001/jamaoncol.2023.5573. PMID: 38060218; PMCID: PMC10704339.
- [84] Kim YK, Song J. Metabolic imbalance and brain tumors: The interlinking metabolic pathways and therapeutic actions of antidiabetic drugs. *Pharmacol Res.* 2025 May;215:107719. doi: 10.1016/j.phrs.2025.107719. Epub 2025 Mar 31. PMID: 40174814.
- [85] Gjersdal E, Larsen LB, Ettrup KS, Vestergaard P, Nielsen EH, Karmisholt JS, Müller HL, Dal J. Semaglutide as a promising treatment for hypothalamic obesity: a six-month case series on four females with craniopharyngioma. *Pituitary.* 2024 Oct;27(5):723-730. doi: 10.1007/s11102-024-01426-8. Epub 2024 Aug 1. PMID: 39088138; PMCID: PMC11513775.

- [86] Trapp S, Hisadome K. Glucagon-like peptide 1 and the brain: central actions-central sources? *Auton Neurosci*. 2011 Apr 26;161(1-2):14-9. doi: 10.1016/j.autneu.2010.09.008. Epub 2010 Oct 14. PMID: 20951098.
- [87] Gandhi A, Parhizgar A. GLP-1 receptor agonists in Alzheimer's and Parkinson's disease: endocrine pathways, clinical evidence, and future directions. *Front Endocrinol (Lausanne)*. 2025 Nov 20;16:1708565. doi: 10.3389/fendo.2025.1708565. PMID: 41356006; PMCID: PMC12675206.
- [88] Li Y, Vaughan KL, Wang Y, Yu SJ, Bae EK, Tamargo IA, Kopp KO, Tweedie D, Chiang CC, Schmidt KT, Lahiri DK, Tones MA, Zaleska MM, Hoffer BJ, Mattison JA, Greig NH. Sitagliptin elevates plasma and CSF incretin levels following oral administration to nonhuman primates: relevance for neurodegenerative disorders. *Geroscience*. 2024 Oct;46(5):4397-4414. doi: 10.1007/s11357-024-01120-4. Epub 2024 Mar 27. PMID: 38532069; PMCID: PMC11335710.
- [89] Fang X, Tian P, Zhao X, Jiang C, Chen T. Neuroprotective effects of an engineered commensal bacterium in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine Parkinson disease mouse model via producing glucagon-like peptide-1. *J Neurochem*. 2019 Aug;150(4):441-452. doi: 10.1111/jnc.14694. Epub 2019 Apr 1. PMID: 30851189.
- [90] Fujita S, Ushio S, Ozawa N, Masuguchi K, Kawashiri T, Oishi R, Egashira N. Exenatide Facilitates Recovery from Oxaliplatin-Induced Peripheral Neuropathy in Rats. *PLoS One*. 2015 Nov 4;10(11):e0141921. doi: 10.1371/journal.pone.0141921. PMID: 26536615; PMCID: PMC4633148.
- [91] Till H, Schlichting N, Oberbach A. Tumor-associated energy homeostasis: hepatoblastoma and neuroblastoma affect glucose and lipid metabolism as well as ghrelin, GLP-1, and PYY in nude rats. *Eur J Pediatr Surg*. 2015 Feb;25(1):128-31. doi: 10.1055/s-0034-1386640. Epub 2014 Aug 11. PMID: 25111274.
- [92] Cheng Z, Guo D, Ruzi A, Pan T, You K, Chen Y, Huang X, Zhang J, Yang F, Niu L, Xu K, Li YX. Modeling MEN1 with Patient-Origin iPSCs Reveals GLP-1R Mediated Hypersecretion of Insulin. *Cells*. 2022 Aug 3;11(15):2387. doi: 10.3390/cells11152387. PMID: 35954231; PMCID: PMC9368616.
- [93] Sasaki Y, Abe Y, Takeda H, Nishise S, Yaoita T, Yagi M, Sakuta K, Mizumoto N, Shoji M, Onozato Y, Kawata S, Ueno Y. Impaired Secretion of Glucagon-Like Peptide 1 in Patients with Colorectal Adenoma after an Oral Glucose Load. *Digestion*. 2018;97(4):324-332. doi: 10.1159/000486129. Epub 2018 Mar 14. PMID: 29539609.
- [94] Wang CH, Chang WC, Chen HY, Chen PH, Lin MH, Lee CH. Association of dual SGLT-2 inhibitor and GLP-1 receptor agonist therapy with colon cancer risk in post-polypectomy patients with diabetes: a target trial emulation. *Diabetol Metab Syndr*. 2026 Mar 29. doi: 10.1186/s13098-026-02151-x. Epub ahead of print. PMID: 41906175.
- [95] Byrd RA, Sorden SD, Ryan T, Pienkowski T, LaRock R, Quander R, Wijsman JA, Smith HW, Blackbourne JL, Rosol TJ, Long GG, Martin JA, Vahle JL. Chronic Toxicity and Carcinogenicity Studies of the Long-Acting GLP-1 Receptor Agonist Dulaglutide in Rodents. *Endocrinology*. 2015 Jul;156(7):2417-28. doi: 10.1210/en.2014-1722. Epub 2015 Apr 10. PMID: 25860029.
- [96] Madsen LW, Knauf JA, Gotfredsen C, Pilling A, Sjögren I, Andersen S, Andersen L, de Boer AS, Manova K, Barlas A, Vundavalli S, Nyborg NC, Knudsen LB, Moelck AM, Fagin JA. GLP-1 receptor agonists and the thyroid: C-cell effects in mice are mediated via the GLP-1 receptor and not associated with RET activation. *Endocrinology*. 2012 Mar;153(3):1538-47. doi: 10.1210/en.2011-1864. Epub 2012 Jan 10. PMID: 22234463; PMCID: PMC3281535.
- [97] Hollingshead BD, Radi ZA. Human Relevance of Pharmaceutical Drug-Induced Thyroid Tumors in Rats, Labeling Implications, and Carcinogenicity Study Requirements. *J Appl Toxicol*. 2025 Aug;45(8):1426-1439. doi: 10.1002/jat.4779. Epub 2025 Mar 13. PMID: 40083171.
- [98] Vertongen P, Ciccarelli E, Woussen-Colle MC, De Neef P, Robberecht P, Cauvin A. Pituitary adenylate cyclase-activating polypeptide receptors of types I and II and glucagon-like peptide-I receptors are expressed in the rat medullary carcinoma of the thyroid cell line 6/23. *Endocrinology*. 1994 Oct;135(4):1537-42. doi: 10.1210/endo.135.4.7925114. PMID: 7925114.
- [99] Lamari Y, Boissard C, Moukhtar MS, Jullienne A, Rosselin G, Garel JM. Expression of glucagon-like peptide 1 receptor in a murine C cell line: regulation of calcitonin gene by glucagon-like peptide 1. *FEBS Lett*. 1996 Sep 16;393(2-3):248-52. doi: 10.1016/0014-5793(96)00895-2. PMID: 8814299.
- [100] Lunati ME, Grancini V, Colombo C, Palmieri E, Resi V, Perrino M, Orsi E, Fugazzola L. Basal and stimulated calcitonin levels in patients with type 2 diabetes did not change during 1 year of Liraglutide treatment. *Metabolism*. 2016 Jan;65(1):1-6. doi: 10.1016/j.metabol.2015.09.010. Epub 2015 Sep 16. PMID: 26683791.
- [101] Jung MJ, Kwon SK. Expression of glucagon-like Peptide-1 receptor in papillary thyroid carcinoma and its clinicopathologic significance. *Endocrinol Metab (Seoul)*. 2014 Dec 29;29(4):536-44. doi: 10.3803/EnM.2014.29.4.536. PMID: 25559577; PMCID: PMC4285044.
- [102] Abdul-Maksoud RS, Elsayed WSH, Rashad NM, Elsayed RS, Elshorbagy S, Hamed MG. GLP-1R polymorphism (rs1042044) and expression are associated with the risk of papillary thyroid cancer among the Egyptian

population. *Gene*. 2022 Aug 5;834:146597. doi: 10.1016/j.gene.2022.146597. Epub 2022 May 19. PMID: 35598685

- [103] He L, Zhang S, Zhang X, Liu R, Guan H, Zhang H. Effects of insulin analogs and glucagon-like peptide-1 receptor agonists on proliferation and cellular energy metabolism in papillary thyroid cancer. *Onco Targets Ther*. 2017 Nov 24;10:5621-5631. doi: 10.2147/OTT.S150701. PMID: 29200876; PMCID: PMC5703165.
- [104] Zhang X, Zhang L, Wang B, Zhang X, Gu L, Guo K, Zhang X, Zhou Z. GLP-1 receptor agonist liraglutide inhibits the proliferation and migration of thyroid cancer cells. *Cell Mol Biol (Noisy-le-grand)*. 2023 Dec 20;69(14):221-225. doi: 10.14715/cmb/2023.69.14.37. PMID: 38279433.
- [105] Wang L, Zhang L, Ma R, Zhang Y, Chang Q, Yin D. Semaglutide Reprograms Macrophages via the GLP-1R/PPARG/ACSL1 Pathway to Suppress Papillary Thyroid Carcinoma Growth. *J Clin Endocrinol Metab*. 2025 Sep 16;110(10):2777-2789. doi: 10.1210/clinem/dgaf053. PMID: 39908200; PMCID: PMC12448615.
- [106] Bezin J, Gouverneur A, Pénichon M, Mathieu C, Garrel R, Hillaire-Buys D, Pariente A, Faillie JL. GLP-1 Receptor Agonists and the Risk of Thyroid Cancer. *Diabetes Care*. 2023 Feb 1;46(2):384-390. doi: 10.2337/dc22-1148. PMID: 36356111
- [107] Brito JP, Herrin J, Swarna KS, Singh Ospina NM, Montori VM, Toro-Tobon D, Umpierrez GE, Galindo RJ, Deng Y, Mickelson MM, Shao H, Polley EC, McCoy RG. GLP-1RA Use and Thyroid Cancer Risk. *JAMA Otolaryngol Head Neck Surg*. 2025 Mar 1;151(3):243-252. doi: 10.1001/jamaoto.2024.4852. PMID: 39847346; PMCID: PMC11907303.
- [108] Bea S, Son H, Bae JH, Cho SW, Shin JY, Cho YM. Risk of thyroid cancer associated with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes: A population-based cohort study. *Diabetes Obes Metab*. 2024 Jan;26(1):108-117. doi: 10.1111/dom.15292. Epub 2023 Sep 21. PMID: 37735822.
- [109] Pollack R, Stokar J. Long-Term Glucagon-Like Peptide 1 Receptor Agonist Use Is Not Associated With Increased Risk of Thyroid Cancer in Adults With Type 2 Diabetes. *Diabetes Metab Res Rev*. 2025 Nov;41(8):e70104. doi: 10.1002/dmrr.70104. PMID: 41182904; PMCID: PMC12582397.
- [110] Sciscent BY, Eberly HW, Lorenz FJ, Goldrich D, Goyal N, Goldenberg D. Thyroid Cancer Risk in Patients With Type 2 Diabetes Taking Glucagon-Like Peptide 1 Receptor Agonists. *OTO Open*. 2026 Jan 8;10(1):e70188. doi: 10.1002/oto.270188. PMID: 41523888; PMCID: PMC12780965.
- [111] Acheampong CO, Buse JB, Klein KR, Kim LT, Evron J, Kahkoska AR, Thompson CA, Wang T, Pate V, Leese P, Stürmer T. Investigating the association between incretin-based therapies and thyroid cancer incidence among US Medicare beneficiaries with diabetes. *BMJ Open Diabetes Res Care*. 2025 Oct 6;13(5):e005090. doi: 10.1136/bmjdr-2025-005090. PMID: 41057208; PMCID: PMC12506239.
- [112] Morales DR, Bu F, Viernes B, DuVall SL, Matheny ME, Simon KR, Falconer T, Richter LR, Ostropolets A, Lau WCY, Man KKC, Chattopadhyay S, Mathioudakis N, Minty E, Nishimura A, Sun F, Yin C, Seager SL, Chai Y, Zhou JJ, Lu Y, Reyes C, Pistillo A, Duarte-Salles T, Blacketer C, Schuemie MJ, Ryan PB, Krumholz HM, Hripcsak G, Khera R, Suchard MA. Risk of Thyroid Tumors With GLP-1 Receptor Agonists: A Retrospective Cohort Study. *Diabetes Care*. 2025 Aug 1;48(8):1386-1394. doi: 10.2337/dc25-0154. PMID: 40465422; PMCID: PMC12281980.
- [113] Liang C, Bertoia ML, Ding Y, Clifford CR, Qiao Q, Gagne JJ, Dore DD. Exenatide use and incidence of pancreatic and thyroid cancer: A retrospective cohort study. *Diabetes Obes Metab*. 2019 Apr;21(4):1037-1042. doi: 10.1111/dom.13597. Epub 2018 Dec 25. Erratum in: *Diabetes Obes Metab*. 2020 Jun;22(6):1006. doi: 10.1111/dom.14037. PMID: 30474347.
- [114] Hu W, Song R, Cheng R, Liu C, Guo R, Tang W, Zhang J, Zhao Q, Li X, Liu J. Use of GLP-1 Receptor Agonists and Occurrence of Thyroid Disorders: a Meta-Analysis of Randomized Controlled Trials. *Front Endocrinol (Lausanne)*. 2022 Jul 11;13:927859. doi: 10.3389/fendo.2022.927859. PMID: 35898463; PMCID: PMC9309474.
- [115] Patrizio A, Newman SK, Tuttle RM, Boucai L. Effect of GLP-1 Receptor Agonists on Patients with Thyroid Carcinomas Undergoing Active Surveillance. *J Endocr Soc*. 2025 Nov 14;10(1):bvaf182. doi: 10.1210/jendso/bvaf182. PMID: 41376649; PMCID: PMC12686943.
- [116] Patrizio A, Mauguen A, Fagin JA, Farooki A, Fish SS, Flory J, Newman S, Presswala L, Sabra MM, Tuttle RM, Boucai L. Exposure to GLP-1RA and risk of structural progression in differentiated thyroid cancer. *J Clin Endocrinol Metab*. 2026 Feb 15;dgag051. doi: 10.1210/clinem/dgag051. Epub ahead of print. PMID: 41693146.
- [117] Balachandra S, Syed R, Song Z, Kasmirski J, Gillis A, Fazendin J, Lindeman B, Chen H. Evaluating Thyroid Cancer Risk in Glucagon-like Peptide-1 Analog Users With Thyroid Nodules. *J Surg Res*. 2025 Aug;312:104-110. doi: 10.1016/j.jss.2025.05.016. Epub 2025 Jun 27. PMID: 40578060.

- [118] Mali G, Ahuja V, Dubey K. Glucagon-like peptide-1 analogues and thyroid cancer: An analysis of cases reported in the European pharmacovigilance database. *J Clin Pharm Ther.* 2021 Feb;46(1):99-105. doi: 10.1111/jcpt.13259. Epub 2020 Sep 14. PMID: 32926446.
- [119] Abi Zeid Daou C, Aboul Hosn O, Ghzayel L, Mourad M. Exploring Connections Between Weight-Loss Medications and Thyroid Cancer: A Look at the FDA Adverse Event Reporting System Database. *Endocrinol Diabetes Metab.* 2025 Mar;8(2):e70038. doi: 10.1002/edm2.70038. PMID: 40055991; PMCID: PMC11889434.
- [120] Makunts T, Joulfayan H, Abagyan R. Thyroid Hyperplasia and Neoplasm Adverse Events Associated With Glucagon-Like Peptide-1 Receptor Agonists in the Food and Drug Administration Adverse Event Reporting System: Retrospective Analysis. *JMIRx Med.* 2024 May 1;5:e55976. doi: 10.2196/55976. PMID: 38738836; PMCID: PMC11090023.
- [121] Feier CVI, Vonica RC, Faur AM, Streinu DR, Muntean C. Assessment of Thyroid Carcinogenic Risk and Safety Profile of GLP1-RA Semaglutide (Ozempic) Therapy for Diabetes Mellitus and Obesity: A Systematic Literature Review. *Int J Mol Sci.* 2024 Apr 15;25(8):4346. doi: 10.3390/ijms25084346. PMID: 38673931; PMCID: PMC11050669.
- [122] Espinosa De Ycaza AE, Brito JP, McCoy RG, Shao H, Singh Ospina N. Glucagon-Like Peptide-1 Receptor Agonists and Thyroid Cancer: A Narrative Review. *Thyroid.* 2024 Apr;34(4):403-418. doi: 10.1089/thy.2023.0530. Epub 2024 Mar 26. PMID: 38343381; PMCID: PMC10998705.
- [123] Chiu WY, Shih SR, Tseng CH. A review on the association between glucagon-like peptide-1 receptor agonists and thyroid cancer. *Exp Diabetes Res.* 2012;2012:924168. doi: 10.1155/2012/924168. Epub 2012 May 28. PMID: 22693487; PMCID: PMC3368340.
- [124] Lisco G, De Tullio A, Disoteo O, Piazzolla G, Guastamacchia E, Sabbà C, De Geronimo V, Papini E, Triggiani V. Glucagon-like peptide 1 receptor agonists and thyroid cancer: is it the time to be concerned? *Endocr Connect.* 2023 Sep 27;12(11):e230257. doi: 10.1530/EC-23-0257. PMID: 37656509; PMCID: PMC10563602.
- [125] Li C, Shen K, Pan L. Exploring the causal relationship between GLP-1R agonists and diseases related to the thyroid and parathyroid: a mendelian randomization study. *J Diabetes Metab Disord.* 2025 Feb 5;24(1):64. doi: 10.1007/s40200-025-01567-y. PMID: 39927177; PMCID: PMC11799478.
- [126] Zhang Z, Yang J, Gao L. Implications of Glucagon-like Peptide-1 Receptor Agonists on Thyroid Function and Thyroid Nodules: A Drug Target Mendelian Randomization and Cohort Study. *Endocr Pract.* 2026 Jan;32(1):60-66. doi: 10.1016/j.eprac.2025.07.013. Epub 2025 Jul 22. PMID: 40706753.
- [127] Iuliano S, Mirabelli M, Giuliano S, Brunetti A. Insulin resistance and metabolic dysfunction in thyroid nodules and differentiated thyroid cancer. *Curr Opin Oncol.* 2026 Jan 1;38(1):1-10. doi: 10.1097/CCO.0000000000001202. Epub 2025 Oct 29. PMID: 41222548.
- [128] Brenta G, Di Fermo F. Thyroid cancer and insulin resistance. *Rev Endocr Metab Disord.* 2024 Feb;25(1):19-34. doi: 10.1007/s11154-023-09849-7. Epub 2023 Nov 14. PMID: 37957487.
- [129] Mazza AD. The Thyroid Twist: How GLP-1 Agonists Are Influencing Autoimmune Thyroid Care. *Cureus.* 2025 Nov 30;17(11):e98153. doi: 10.7759/cureus.98153. PMID: 41479489; PMCID: PMC12754808.
- [130] Nuskiewicz J, Czuczejko J, Drózd W, Woźniak A, Małkowski B, Szewczyk-Golec K. Concentration of Selected Adipokines and Factors Regulating Carbohydrate Metabolism in Patients with Head and Neck Cancer in Respect to Their Body Mass Index. *Int J Mol Sci.* 2023 Feb 7;24(4):3283. doi: 10.3390/ijms24043283. PMID: 36834693; PMCID: PMC9959515.
- [131] Kelly CA, Sips JA. Approach to the Patient With Thyroid Nodules: Considering GLP-1 Receptor Agonists. *J Clin Endocrinol Metab.* 2025 May 19;110(6):e2080-e2087. doi: 10.1210/clinem/dgae722. PMID: 39400117.
- [132] Watts E, Wadsley J, Sharma N, Boelaert K; UK Thyroid Cancer Study Group. Joint Society Statement From the Society for Endocrinology (SfE), the British Thyroid Association (BTA) and the British Association of Endocrine and Thyroid Surgeons (BAETS) Regarding the Association of GLP-1 Agonists and Thyroid Cancer. *Clin Endocrinol (Oxf).* 2025 Dec 21. doi: 10.1111/cen.70084. Epub ahead of print. PMID: 41423434.
- [133] Wilcox L, Van Dril E. Suppressed thyroid stimulating hormone levels after initiation of a subcutaneous glucagon-like peptide-1 receptor agonist in a post-thyroidectomy patient managed with levothyroxine case report. *J Am Pharm Assoc (2003).* 2024 Nov-Dec;64(6):102185. doi: 10.1016/j.japh.2024.102185. Epub 2024 Jul 9. PMID: 38992739.
- [134] Harrison DB, Phillips AL, Tansey JB, Clarke TJ, Wood CB, Nedzi L, Schwartz DL, Makowski L, Hayes DN, Newman G, Gleysteen JP. Brown Adipose Tissue Mimicking Head and Neck Cancer on PET Scan in a Patient on GLP-1 Drug. *Laryngoscope.* 2025 Feb;135(2):741-743. doi: 10.1002/lary.31815. Epub 2024 Oct 7. PMID: 39370986; PMCID: PMC11729570.

- [135] Tabernacki T, Wang L, Kaelber DC, Xu R, Berger NA. Non-Insulin Antidiabetic Agents and Lung Cancer Risk in Drug-Naïve Patients with Type 2 Diabetes Mellitus: A Nationwide Retrospective Cohort Study. *Cancers (Basel)*. 2024 Jun 28;16(13):2377. doi: 10.3390/cancers16132377. PMID: 39001440; PMCID: PMC11240387.
- [136] Song J, Cali Daylan AE, Chi KY, Prem Anand D, Chang Y, Chiang CH, Cheng H. Association Between GLP-1 Receptor Agonists and Incidence of Lung Cancer in Treatment-Naïve Type 2 Diabetes. *J Gen Intern Med*. 2025 Mar;40(4):973-976. doi: 10.1007/s11606-024-09076-z. Epub 2024 Oct 4. PMID: 39365528; PMCID: PMC11914447.
- [137] Chen Z, Sun Z, Zhang Z, Lei C, Ren Z, Di Y, Wang Z. Efficacy of three modern anti-diabetic drugs on survival outcomes of lung cancer patients with type 2 diabetes in China. *Front Oncol*. 2025 Feb 18;15:1498927. doi: 10.3389/fonc.2025.1498927. PMID: 40040724; PMCID: PMC11876025.
- [138] Pachimatla AG, Fitzgerald B, Ogidigo J, Bhatia M, Smith RJ Jr, Ratnakaram K, Kalvapudi S, Vedire Y, Washington D, Vethanayagam Rr R, Hsiao HH, Rosario S, Sanghvi VR, Barbi J, Yendamuri S. Glucagon-like peptide-1 receptor agonism improves lung cancer outcomes and tumor growth control. *JCI Insight*. 2025 Aug 26;10(19):e195484. doi: 10.1172/jci.insight.195484. PMID: 40857107; PMCID: PMC12513478.
- [139] Pu Z, Yang Y, Qin S, Li X, Cui C, Chen W. The Effect of Liraglutide on Lung Cancer and Its Potential Protective Effect on High Glucose-Induced Lung Senescence and Oxidative Damage. *Front Biosci (Landmark Ed)*. 2023 Oct 24;28(10):259. doi: 10.31083/j.fbl2810259. PMID: 37919054.
- [140] Chen D, Liang H, Huang L, Zhou H, Wang Z. Liraglutide enhances the effect of checkpoint blockade in lung and liver cancers through the inhibition of neutrophil extracellular traps. *FEBS Open Bio*. 2024 Aug;14(8):1365-1377. doi: 10.1002/2211-5463.13499. Epub 2024 Jun 28. PMID: 36271684; PMCID: PMC11301266.
- [141] Shao MM, Dong SF, Chen QY, Wei RQ, Yi FS. Glucagon-like peptide-1 receptor agonists inhibit the progression of malignant pleural effusion in obese mice by regulating the metabolism of pleural effusion. *J Transl Med*. 2025 Aug 8;23(1):886. doi: 10.1186/s12967-025-06875-8. PMID: 40781724; PMCID: PMC12333053.
- [142] Song B, Ge H, Pu C, Li N. GLP2-GLP2R signal affects the viability and EGFR-TKIs sensitivity of PC9 and HCC827 cells. *BMC Pulm Med*. 2022 Jan 13;22(1):36. doi: 10.1186/s12890-021-01800-3. PMID: 35027025; PMCID: PMC8756716.
- [143] Yen FS, Hsu CC, Wei JC, Tsai FJ, Huang Y, Yu TS, Hwu CM. Glucagon-like peptide-1 receptor agonists may benefit cardiopulmonary outcomes in patients with COPD. *Thorax*. 2024 Oct 16;79(11):1017-1023. doi: 10.1136/thorax-2023-221040. PMID: 39353727.
- [144] Ho LT, Fang YW, Hsu PS, Wang JT, Tsai MH. Association between glucagon-like peptide-1 receptor agonist therapy and respiratory illness in patients with type 2 diabetes: a retrospective observational cohort study. *Sci Rep*. 2025 Oct 13;15(1):35625. doi: 10.1038/s41598-025-19657-5. PMID: 41083699; PMCID: PMC12518849.
- [145] Yang Y, Wang K, Chen S. Effects of Hypoglycemic Agents on Pulmonary Diseases: A Comprehensive Narrative Review. *J Inflamm Res*. 2025 Dec 24;18:18053-18078. doi: 10.2147/JIR.S556790. PMID: 41497535; PMCID: PMC12765701.
- [146] Guo J, Zhang X, Pan R, Zheng Y, Chen W, Wang L. Liraglutide alleviates sepsis-induced acute lung injury by regulating pulmonary surfactant through inhibiting autophagy. *Immunopharmacol Immunotoxicol*. 2024 Oct;46(5):573-582. doi: 10.1080/08923973.2024.2384897. Epub 2024 Aug 7. PMID: 39112014.
- [147] Hua E, Xu D, Chen H, Zhang S, Feng J, Xu L. Development of the dipeptidyl peptidase 4 family and its association with lung diseases: a narrative review. *J Thorac Dis*. 2023 Dec 30;15(12):7024-7034. doi: 10.21037/jtd-23-1158. Epub 2023 Dec 12. PMID: 38249892; PMCID: PMC10797411.
- [148] Beckers PAJ, Gielis JF, Van Schil PE, Adriaensen D. Lung ischemia reperfusion injury: the therapeutic role of dipeptidyl peptidase 4 inhibition. *Ann Transl Med*. 2017 Mar;5(6):129. doi: 10.21037/atm.2017.01.41. PMID: 28462209; PMCID: PMC5395493.
- [149] Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015 Dec 3;373(23):2247-57. doi: 10.1056/NEJMoa1509225. PMID: 26630143.
- [150] Quagliariello V, Canale ML, Bisceglia I, Iovine M, Giordano V, Giacobbe I, Scherillo M, Gabrielli D, Maurea C, Barbato M, Inno A, Berretta M, Tedeschi A, Oliva S, Greco A, Maurea N. Glucagon-like Peptide 1 Receptor Agonists in Cardio-Oncology: Pathophysiology of Cardiometabolic Outcomes in Cancer Patients. *Int J Mol Sci*. 2024 Oct 21;25(20):11299. doi: 10.3390/ijms252011299. PMID: 39457081; PMCID: PMC11508560.
- [151] Vignarajah A, Kim S, Albliwi M, Ahn HM, Izda A, Naffa F, Vigneswaramoorthy N, Barot S, Shah G. Role of GLP-1 Receptor Agonists in Managing Cancer Therapy-Related Cardiac Dysfunction. *J Am Heart Assoc*. 2025 Nov

- 18;14(22):e040919. doi: 10.1161/JAHA.125.040919. Epub 2025 Nov 6. PMID: 41195790; PMCID: PMC12887215.
- [152] Chiang CH, Song J, Chi KY, Chang YC, Xanthavanij N, Chang Y, Hsia YP, Chiang CH, Ghamari A, Reynolds KL, Lin S, Xu XH, Neilan TG. Glucagon-like Peptide-1 Agonists Reduce Cardiovascular Events in Cancer Patients on Immune Checkpoint Inhibitors. *Eur J Cancer*. 2025 Feb 5;216:115170. doi: 10.1016/j.ejca.2024.115170. Epub 2024 Dec 11. PMID: 39709670.
- [153] Wu Y, Ye J, Shao Z, Rossi A, Chen Y, Li Y, Wu S. Prognostic value of baseline clinicopathological characteristics in first-line chemotherapy ± immunotherapy for extensive-stage small cell lung cancer: a retrospective cohort study. *J Thorac Dis*. 2024 Aug 31;16(8):5348-5360. doi: 10.21037/jtd-24-929. Epub 2024 Aug 28. PMID: 39268133; PMCID: PMC11388222.
- [154] Singh S, Garg A, Tantry US, Bliden K, Gurbel PA, Gulati M. Safety and efficacy of glucagon-like peptide-1 receptor agonists on cardiovascular events in overweight or obese non-diabetic patients. *Curr Probl Cardiol*. 2024 Mar;49(3):102403. doi: 10.1016/j.cpcardiol.2024.102403. Epub 2024 Jan 17. PMID: 38237815.
- [155] Zhou H, Li D, Shi C, Xin T, Yang J, Zhou Y, Hu S, Tian F, Wang J, Chen Y. Effects of Exendin-4 on bone marrow mesenchymal stem cell proliferation, migration and apoptosis in vitro. *Sci Rep*. 2015 Aug 7;5:12898. doi: 10.1038/srep12898. PMID: 26250571; PMCID: PMC4528192.
- [156] Figlioli G, Piovani D, Peppas S, Pugliese N, Hassan C, Repici A, Lleo A, Aghemo A, Bonovas S. Glucagon-like peptide-1 receptor agonists and risk of gastrointestinal cancers: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res*. 2024 Oct;208:107401. doi: 10.1016/j.phrs.2024.107401. Epub 2024 Sep 7. PMID: 39251099.
- [157] Wali AF, Rangraze I, Khan S, Mufti UB, El-Tanani M, Rizzo M. Reassessing cancer risk with GLP-1 receptor agonists: a comprehensive meta-analysis of gastrointestinal malignancies. *Front Pharmacol*. 2026 Feb 10;17:1736380. doi: 10.3389/fphar.2026.1736380. PMID: 41743116; PMCID: PMC12929497.
- [158] Ju M, Deng T, Jia X, Gong M, Li Y, Liu F, Yin Y. The causal relationship between anti-diabetic drugs and gastrointestinal disorders: a drug-targeted mendelian randomization study. *Diabetol Metab Syndr*. 2024 Jun 26;16(1):141. doi: 10.1186/s13098-024-01359-z. PMID: 38918852; PMCID: PMC11201305.
- [159] Ear PH, Hueser SA, Townsend RE, Maxwell JE, Abusada E, Chan CHF, Quelle DE, Dillon JS, Howe JR, Bellizzi AM. Variable GLP-1 receptor expression across diverse neuroendocrine neoplasms: implications for incretin therapies. *Endocr Oncol*. 2025 Nov 25;5(1):e250051. doi: 10.1530/EO-25-0051. PMID: 41312422; PMCID: PMC12648204.
- [160] Hubalewska-Dydejczyk A, Sowa-Staszczak A, Tomaszuk M, Stefańska A. GLP-1 and exendin-4 for imaging endocrine pancreas. A review. Labelled glucagon-like peptide-1 analogues: past, present and future. *Q J Nucl Med Mol Imaging*. 2015 Jun;59(2):152-60. Epub 2015 Feb 26. PMID: 25719487.
- [161] Wu Q, Zeng Y, Liu Y, Teng F, Zhou T, Guo M, Jiang Z, Xu Y. A meta-analysis on the risk of esophageal cancer in type 2 diabetes patients treated with GLP-1 receptor agonists. *Front Endocrinol (Lausanne)*. 2025 Mar 20;16:1532587. doi: 10.3389/fendo.2025.1532587. PMID: 40182628; PMCID: PMC11966957.
- [162] Hansen AB, Gespach CP, Rosselin GE, Holst JJ. Effect of truncated glucagon-like peptide 1 on cAMP in rat gastric glands and HGT-1 human gastric cancer cells. *FEBS Lett*. 1988 Aug 15;236(1):119-22. doi: 10.1016/0014-5793(88)80297-7. PMID: 2841160.
- [163] Chen YC, Ho CC, Yi CH, Liu XZ, Cheng TT, Lam CF. Exendin-4, a glucagon-like peptide-1 analogue accelerates healing of chronic gastric ulcer in diabetic rats. *PLoS One*. 2017 Nov 2;12(11):e0187434. doi: 10.1371/journal.pone.0187434. PMID: 29095895; PMCID: PMC5667749.
- [164] Hung CM, Zeng BY, Hsu CW, Chen PH, Sun CK, Carvalho AF, Stubbs B, Chen YW, Chen TY, Lei WT, Chen JJ, Shiue YL, Su KP, Liang CS, Tseng PT. The different colorectal tumor risk related to GLP-1 receptor agonists and SGLT2 inhibitors use: a network meta-analysis of 68 randomized controlled trials. *Int J Surg*. 2026 Jan 1;112(1):443-459. doi: 10.1097/J9.00000000000003450. Epub 2025 Sep 11. PMID: 40990658; PMCID: PMC12825905.
- [165] Ayoub M, Aibani R, Dodd T, Ceesay M, Bhinder M, Faris C, Amin N, Daglilar E. Risk of Esophageal and Gastric Cancer in Patients with Type 2 Diabetes Receiving Glucagon-like Peptide-1 Receptor Agonists (GLP-1 RAs): A National Analysis. *Cancers (Basel)*. 2024 Sep 22;16(18):3224. doi: 10.3390/cancers16183224. PMID: 39335195; PMCID: PMC11430483.
- [166] Alves C, Batel-Marques F, Macedo AF. A meta-analysis of serious adverse events reported with exenatide and liraglutide: acute pancreatitis and cancer. *Diabetes Res Clin Pract*. 2012 Nov;98(2):271-84. doi: 10.1016/j.diabres.2012.09.008. Epub 2012 Sep 23. PMID: 23010561.

- [167] Ueberberg S, Jütte H, Uhl W, Schmidt W, Nauck M, Montanya E, Tannapfel A, Meier J. Histological changes in endocrine and exocrine pancreatic tissue from patients exposed to incretin-based therapies. *Diabetes Obes Metab.* 2016 Dec;18(12):1253-1262. doi: 10.1111/dom.12766. Epub 2016 Sep 26. Erratum in: *Diabetes Obes Metab.* 2017 Feb;19(2):306. doi: 10.1111/dom.12862. PMID: 27545110.
- [168] Kawakubo M, Tanaka M, Ochi K, Watanabe A, Saka-Tanaka M, Kanamori Y, Yoshioka N, Yamashita S, Goto M, Itoh M, Shirakawa I, Kanai S, Suzuki H, Sawada M, Ito A, Ishigami M, Fujishiro M, Arima H, Ogawa Y, Suganami T. Dipeptidyl peptidase-4 inhibition prevents nonalcoholic steatohepatitis-associated liver fibrosis and tumor development in mice independently of its anti-diabetic effects. *Sci Rep.* 2020 Jan 22;10(1):983. doi: 10.1038/s41598-020-57935-6. PMID: 31969650; PMCID: PMC6976646.
- [169] Akiyama S, Ogiwara T, Aoki T, Tsunekawa K, Araki O, Murakami M. Glucagon-like peptide-1 stimulates type 3 iodothyronine deiodinase expression in a mouse insulinoma cell line. *Life Sci.* 2014 Oct 12;115(1-2):22-8. doi: 10.1016/j.lfs.2014.09.004. Epub 2014 Sep 21. PMID: 25241124.
- [170] Ma B, Wang X, Ren H, Li Y, Zhang H, Yang M, Li J. High glucose promotes the progression of colorectal cancer by activating the BMP4 signaling and inhibited by glucagon-like peptide-1 receptor agonist. *BMC Cancer.* 2023 Jun 27;23(1):594. doi: 10.1186/s12885-023-11077-w. PMID: 37370018; PMCID: PMC10304216.
- [171] Koehler JA, Kain T, Drucker DJ. Glucagon-like peptide-1 receptor activation inhibits growth and augments apoptosis in murine CT26 colon cancer cells. *Endocrinology.* 2011 Sep;152(9):3362-72. doi: 10.1210/en.2011-1201. Epub 2011 Jul 19. PMID: 21771884.
- [172] Brunner KT, Henneberg CJ, Wilechansky RM, Long MT. Nonalcoholic Fatty Liver Disease and Obesity Treatment. *Curr Obes Rep.* 2019 Sep;8(3):220-228. doi: 10.1007/s13679-019-00345-1. PMID: 30945129; PMCID: PMC6770992.
- [173] Banini BA, Sanyal AJ. Current and future pharmacologic treatment of nonalcoholic steatohepatitis. *Curr Opin Gastroenterol.* 2017 May;33(3):134-141. doi: 10.1097/MOG.0000000000000356. PMID: 28346237; PMCID: PMC5491795.
- [174] Sofogianni A, Filippidis A, Chrysavgis L, Tziomalos K, Cholongitas E. Glucagon-like peptide-1 receptor agonists in non-alcoholic fatty liver disease: An update. *World J Hepatol.* 2020 Aug 27;12(8):493-505. doi: 10.4254/wjh.v12.i8.493. PMID: 32952876; PMCID: PMC7475780.
- [175] Budd J, Cusi K. Role of Agents for the Treatment of Diabetes in the Management of Nonalcoholic Fatty Liver Disease. *Curr Diab Rep.* 2020 Oct 5;20(11):59. doi: 10.1007/s11892-020-01349-1. PMID: 33015726.
- [176] Duseja A, Singh SP, De A, Madan K, Rao PN, Shukla A, Choudhuri G, Saigal S, Shalimar, Arora A, Anand AC, Das A, Kumar A, Eapen CE, Devadas K, Shenoy KT, Panigrahi M, Wadhawan M, Rathii M, Kumar M, Choudhary NS, Saraf N, Nath P, Kar S, Alam S, Shah S, Nijhawan S, Acharya SK, Aggarwal V, Saraswat VA, Chawla YK. Indian National Association for Study of the Liver (INASL) Guidance Paper on Nomenclature, Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease (NAFLD). *J Clin Exp Hepatol.* 2023 Mar-Apr;13(2):273-302. doi: 10.1016/j.jceh.2022.11.014. Epub 2022 Dec 7. PMID: 36950481; PMCID: PMC10025685.
- [177] Miao L, Xu J, Targher G, Byrne CD, Zheng MH. Old and new classes of glucose-lowering agents as treatments for non-alcoholic fatty liver disease: A narrative review. *Clin Mol Hepatol.* 2022 Oct;28(4):725-738. doi: 10.3350/cmh.2022.0015. Epub 2022 Mar 14. PMID: 35286799; PMCID: PMC9597221.
- [178] Sumida Y, Seko Y, Yoneda M; Japan Study Group of NAFLD (JSG-NAFLD). Novel antidiabetic medications for non-alcoholic fatty liver disease with type 2 diabetes mellitus. *Hepatol Res.* 2017 Mar;47(4):266-280. doi: 10.1111/hepr.12856. Epub 2017 Feb 13. PMID: 28019064.
- [179] Brouwers B, Rao G, Tang Y, Rodríguez Á, Glass LC, Hartman ML. Incretin-based investigational therapies for the treatment of MASLD/MASH. *Diabetes Res Clin Pract.* 2024 May;211:111675. doi: 10.1016/j.diabres.2024.111675. Epub 2024 Apr 16. PMID: 38636848.
- [180] Mega A; A.I.G.O. (Italian Association of Hospital Gastroenterologists) and C.L.E.O. (Italian Association of Hospital Hepatologists); Turri C, Marzi L, Dauriz M, Sacco R, Floreani A, Stasi C. New Treatment Options for MASLD Patients with Type 2 Diabetes. *Life (Basel).* 2026 Feb 2;16(2):254. doi: 10.3390/life16020254. PMID: 41752891; PMCID: PMC12942142.
- [181] Phillips R, Ma YT, Hanif W, Shah T, Sivakumar S. Nutrient-stimulated Hormone-based Therapies: A New Frontier in the Prevention and Management of MASH-associated Hepatocellular Carcinoma. *J Clin Transl Hepatol.* 2025 Dec 28;13(12):1060-1066. doi: 10.14218/JCTH.2025.00303. Epub 2025 Oct 22. PMID: 41473259; PMCID: PMC12745189.
- [182] Tilg H, Petta S, Stefan N, Targher G. Metabolic Dysfunction-Associated Steatotic Liver Disease in Adults: A Review. *JAMA.* 2026 Jan 13;335(2):163-174. doi: 10.1001/jama.2025.19615. PMID: 41212550.

- [183] Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoué T, Ratzliff V, Sanyal AJ, Sejliff AS, Harrison SA; NN9931-4296 Investigators. A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis. *N Engl J Med*. 2021 Mar 25;384(12):1113-1124. doi: 10.1056/NEJMoa2028395. Epub 2020 Nov 13. PMID: 33185364.
- [184] Celsa C, Pennisi G, Tulone A, Ciancimino G, Vaccaro M, Infantino G, Di Maria G, Pinato DJ, Cabibbo G, Enea M, Mantovani A, Tilg H, Targher G, Cammà C, Petta S. Glucagon-like peptide-1 receptor agonist use is associated with a lower risk of major adverse liver-related outcomes: a meta-analysis of observational cohort studies. *Gut*. 2025 Apr 7;74(5):815-824. doi: 10.1136/gutjnl-2024-334591. PMID: 40015951.
- [185] Wester A, Shang Y, Toresson Grip E, Matthews AA, Hagström H. Glucagon-like peptide-1 receptor agonists and risk of major adverse liver outcomes in patients with chronic liver disease and type 2 diabetes. *Gut*. 2024 Apr 5;73(5):835-843. doi: 10.1136/gutjnl-2023-330962. PMID: 38253482; PMCID: PMC11041618.
- [186] Harreiter J, Just I, Leutner M, Bastian M, Brath H, Schelkshorn C, Klepochova R, Krššák M, Kautzky-Willer A. Combined exenatide and dapagliflozin has no additive effects on reduction of hepatocellular lipids despite better glycaemic control in patients with type 2 diabetes mellitus treated with metformin: EXENDA, a 24-week, prospective, randomized, placebo-controlled pilot trial. *Diabetes Obes Metab*. 2021 May;23(5):1129-1139. doi: 10.1111/dom.14319. Epub 2021 Feb 10. PMID: 33464703; PMCID: PMC8247845.
- [187] Wang L, Berger NA, Kaelber DC, Xu R. Association of GLP-1 Receptor Agonists and Hepatocellular Carcinoma Incidence and Hepatic Decompensation in Patients With Type 2 Diabetes. *Gastroenterology*. 2024 Sep;167(4):689-703. doi: 10.1053/j.gastro.2024.04.029. Epub 2024 Apr 29. PMID: 38692395; PMCID: PMC12294230.
- [188] Kanwal F, Kramer JR, Li L, Yang YX, Cao Y, Yu X, Samuel R, Ali B, Desiderio R, Cholkankaril G, Bajaj M, El-Serag HB, Asch SM. GLP-1 Receptor Agonists and Risk for Cirrhosis and Related Complications in Patients With Metabolic Dysfunction-Associated Steatotic Liver Disease. *JAMA Intern Med*. 2024 Nov 1;184(11):1314-1323. doi: 10.1001/jamainternmed.2024.4661. PMID: 39283612; PMCID: PMC11406452.
- [189] Yang CT, Yao WY, Yang CY, Peng ZY, Ou HT, Kuo S. Lower risks of cirrhosis and hepatocellular carcinoma with GLP-1RAs in type 2 diabetes: A nationwide cohort study using target trial emulation framework. *J Intern Med*. 2024 Mar;295(3):357-368. doi: 10.1111/joim.13751. Epub 2023 Nov 22. PMID: 37994187.
- [190] Plaz Torres MC, Jaffe A, Perry R, Marabotto E, Strazzabosco M, Giannini EG. Diabetes medications and risk of HCC. *Hepatology*. 2022 Dec;76(6):1880-1897. doi: 10.1002/hep.32439. Epub 2022 Mar 22. PMID: 35239194; PMCID: PMC9790535.
- [191] Mao X, Zhang X, Lai R, Cheung KS, Yuen MF, Cheung R, Seto WK, Nguyen MH. Glucagon-like peptide 1 receptor agonist and reduced liver and non-liver complications in adults with type 2 diabetes and metabolic dysfunction-associated steatotic liver disease: a target trial emulation study. *Clin Mol Hepatol*. 2025 Jul;31(3):1084-1099. doi: 10.3350/cmh.2024.1096. Epub 2025 Apr 23. PMID: 40268291; PMCID: PMC12260620.
- [192] Choi J, Kamath T, Nguyen VH, Przybyszewski E, Song J, Carroll A, Michta M, Almazan E, Simon TG, Chung RT. GLP-1RA and Liver Fibrosis Progression in MASLD and Type 2 Diabetes: Target Trial Emulation Using Propensity Score Matching. *Liver Int*. 2025 Dec;45(12):e70447. doi: 10.1111/liv.70447. PMID: 41250965; PMCID: PMC12625798.
- [193] Dalbeni A, Vicardi M, Natola LA, Cattazzo F, Aurimemma A, Lombardi R, Cinque F, Dalle Carbonare L, Mantovani A, Sacerdoti D. Glucagon-Like Peptide-1 Receptor Agonists and Hepatocellular Carcinoma Prevention: A Meta-Analysis and Clinical Decision Framework. *Cancer Med*. 2025 Dec;14(24):e71434. doi: 10.1002/cam4.71434. PMID: 41388641; PMCID: PMC12701129.
- [194] Pasta A, Facciorusso A, Plaz Torres MC, Giannini EG, Sacco R. Effects of glucagon-like PEPTIDE-1 receptor agonists on incidence of hepatocellular carcinoma and liver decompensation in patients with diabetes: A systematic review and META-analysis. *Eur J Clin Invest*. 2025 Jun;55(6):e70000. doi: 10.1111/eci.70000. Epub 2025 Feb 12. PMID: 39937048; PMCID: PMC12066890.
- [195] Elsaid MI, Li N, Firkins SA, Rustgi VK, Paskett ED, Acharya C, Reddy KR, Chiang CW, Mumtaz K. Impacts of glucagon-like peptide-1 receptor agonists on the risk of adverse liver outcomes in patients with metabolic dysfunction-associated steatotic liver disease cirrhosis and type 2 diabetes. *Aliment Pharmacol Ther*. 2024 May;59(9):1096-1110. doi: 10.1111/apt.17925. Epub 2024 Mar 27. PMID: 38538967.
- [196] Chen WM, Ng HJ, Jao AT, Wu SY, Soong RS. GLP-1 receptor agonists and risk of hepatocellular carcinoma and all-cause mortality in patients with MASLD and type 2 diabetes: a propensity score-matched population-based cohort study. *Diabetes Res Clin Pract*. 2025 Sep;227:112407. doi: 10.1016/j.diabres.2025.112407. Epub 2025 Aug 11. PMID: 40803507.

- [197] Sarker J, Okpara E, De Los Santos B, Kim M, Kim K. Comparative effectiveness of GLP-1 receptor agonists, SGLT2 inhibitors and DPP-4 inhibitors on liver outcomes in metabolic dysfunction-associated steatotic liver disease: A retrospective cohort study. *Diabetes Obes Metab.* 2026 Apr;28(4):3155-3164. doi: 10.1111/dom.70505. Epub 2026 Jan 21. PMID: 41560595.
- [198] Konings LAM, Miguelañez-Matute L, Boeren AMP, van de Luitgaarden IAT, Dirksmeier F, de Knecht RJ, Tushuizen ME, Grobbee DE, Holleboom AG, Cabezas MC. Pharmacological treatment options for metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus: A systematic review. *Eur J Clin Invest.* 2025 Apr;55(4):e70003. doi: 10.1111/eci.70003. Epub 2025 Feb 12. PMID: 39937036; PMCID: PMC11891831.
- [199] Pradhan R, Yin H, Lu S, Sebastiani G, Yu O, Suissa S, Azoulay L. Glucagon-Like Peptide 1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors and the Prevention of Cirrhosis Among Patients With Type 2 Diabetes. *Diabetes Care.* 2025 Mar 1;48(3):444-454. doi: 10.2337/dc24-1903. PMID: 39774820.
- [200] Kuo CC, Chuang MH, Li CH, Tsai YW, Huang PY, Kuo HT, Lai CC. Glucagon-Like Peptide-1 Receptor Agonists and Liver Outcomes in Patients With MASLD and Type 2 Diabetes. *Aliment Pharmacol Ther.* 2025 Apr;61(7):1163-1174. doi: 10.1111/apt.18502. Epub 2025 Jan 10. PMID: 39791391.
- [201] Choi J, Mitchell G, Nguyen VH, Przybyszewski E, Song J, Carroll A, Michta M, Almazan E, Simon TG, Chung RT. GLP-1RA plus SGLT2i combination therapy and liver fibrosis progression in MASLD with type 2 diabetes. *Hepatol Commun.* 2026 Apr 13;10(5):e0949. doi: 10.1097/HC9.0000000000000949. PMID: 41974037; PMCID: PMC13075898.
- [202] Li L, Mao X, Lee CH, Wai Lui DT, Wan-Hin Hui R, Mak LY, Yuen MF, Cheung KS, Seto WK. Impact of SGLT2i and GLP-1RA on liver-related events in patients with MASLD and type 2 diabetes: A network meta-analysis. *JHEP Rep.* 2025 Nov 3;8(1):101661. doi: 10.1016/j.jhepr.2025.101661. PMID: 41503569; PMCID: PMC12771308.
- [203] Khanmohammadi S, Habibzadeh A, Kamrul-Hasan ABM, Schuermans A, Kuchay MS. Glucose-lowering drugs and liver-related outcomes among individuals with type 2 diabetes: A systematic review of longitudinal population-based studies. *Diabet Med.* 2024 Nov;41(11):e15437. doi: 10.1111/dme.15437. Epub 2024 Sep 28. PMID: 39340770.
- [204] Lin J, Ren T, Zhao Q, Tong Q, Liu J, Kang Y, Yuan Y. The correlation between novel antidiabetic agents utilization and hepatocellular carcinoma incidence in type 2 diabetes patients: a network meta-analysis. *Eur J Clin Pharmacol.* 2025 Nov;81(11):1643-1658. doi: 10.1007/s00228-025-03899-3. Epub 2025 Aug 11. PMID: 40788386.
- [205] Passos PRC, Filho VOC, Noronha MM, Hyppolito EB, Saldanha EF, Motta RV. Influence of glucagon-like peptide-1 receptor agonists on hepatic events in type 2 diabetes: a systematic review and meta-analysis. *J Gastroenterol Hepatol.* 2025 Jan;40(1):67-77. doi: 10.1111/jgh.16752. Epub 2024 Sep 25. PMID: 39322970.
- [206] Golub IS, Manubolu VS, Aldana-Bitar J, Dahal S, Verghese D, Alalawi L, Krishnan S, Kianoush S, Benzing T, Ichikawa K, Kinninger A, Fazlalizadeh H, Pourafkari L, Ahmad K, Susarla S, Mangaoang C, Ghanem AK, Javier DA, Hamal S, Roy SK, Budoff MJ. The impact of semaglutide on liver fat assessed by serial cardiac CT scans in patients with type 2 diabetes: Results from STOP trial. *Nutr Metab Cardiovasc Dis.* 2025 Sep;35(9):104036. doi: 10.1016/j.numecd.2025.104036. Epub 2025 Apr 5. PMID: 40287313.
- [207] Krishnan A, Schneider CV, Mukherjee D, Woreta TA, Alqahtani SA. Adverse Liver and Renal Outcomes After Initiating SGLT-2i and GLP-1RA Therapy Among Patients With Diabetes and MASLD. *J Diabetes.* 2025 Apr;17(4):e70069. doi: 10.1111/1753-0407.70069. PMID: 40289065; PMCID: PMC12034490.
- [208] Huang X, Wu M, Huang B, Zhang Y. Gastrointestinal adverse events associated with GLP-1 receptor agonists in metabolic dysfunction-associated steatotic liver disease (MASLD): a systematic review and meta-analysis. *Front Med (Lausanne).* 2025 Feb 20;12:1509947. doi: 10.3389/fmed.2025.1509947. PMID: 40051726; PMCID: PMC11882565.
- [209] Hussein A, Awashra A, Rajab I, Bdair M, Hamdan D, Nouri A, Khatib E, Khatib G, Latt N. Comparative Effectiveness of Bariatric Surgery Versus GLP-1 Receptor Agonists in Reducing the Risk of New-Onset of NASH: A Retrospective Multinational Cohort Study From North America and Europe. *Endocrinol Diabetes Metab.* 2025 Jul;8(4):e70075. doi: 10.1002/edm2.70075. PMID: 40650867; PMCID: PMC12255231.
- [210] Issachar A, Razi T, Borochoy I, Duskin Bitan H, Arbel R. Association of Semaglutide Treatment With Liver Cirrhosis and Hepatocellular Carcinoma in Type 2 Diabetes: A Population-Based Cohort Study. *Diabetes Obes Metab.* 2026 Apr 13. doi: 10.1111/dom.70763. Epub ahead of print. PMID: 41969200.
- [211] Niu C, Sun K, Zhang J, Elkhapery A, Zhu K, Malik S, Xue C, Okolo PI. Gastrointestinal and Hepatobiliary Safety of Glucagon-Like Peptide-1 Receptor Agonists in Patients With Type 2 Diabetes. *Am J Gastroenterol.* 2025 Sep 3. doi: 10.14309/ajg.0000000000003760. Epub ahead of print. PMID: 40900093.

- [212] Yun B, Oh J, Park H, Lee J, Kim BK, Yoon JH. Comparative Hepatic Outcomes of SGLT2i or DPP4i Compared to GLP-1RA in CHB and T2DM Patients. *Liver Int.* 2025 May;45(5):e70060. doi: 10.1111/liv.70060. PMID: 40257422.
- [213] Tungekar B, Echevarria Cruz EC, Dodrill J, Muneeb A, Sanderfoot R, Thaj O, Vaishnav J, Vahidi A, Hindi F, Khan R, Nagy S, Jacobs RJ. Impact of Glucagon-Like Peptide-1 Agonists on Hepatocellular Carcinoma Risk and Management in Type 2 Diabetes Mellitus: A Scoping Review. *Cureus.* 2025 Dec 28;17(12):e100252. doi: 10.7759/cureus.100252. PMID: 41607999; PMCID: PMC12840817.
- [214] Miyake T, Yoshida O, Matsuura B, Furukawa S, Hirooka M, Abe M, Tokumoto Y, Koizumi Y, Watanabe T, Takeshita E, Sunago K, Yukimoto A, Watanabe K, Miyazaki M, Kanzaki S, Nakaguchi H, Koizumu M, Yamamoto Y, Kumagi T, Hiasa Y. Additional Effect of Luseogliflozin on Semaglutide in Nonalcoholic Steatohepatitis Complicated by Type 2 Diabetes Mellitus: An Open-Label, Randomized, Parallel-Group Study. *Diabetes Ther.* 2022 May;13(5):1083-1096. doi: 10.1007/s13300-022-01239-7. Epub 2022 Mar 21. PMID: 35312970; PMCID: PMC9076799.
- [215] John BV, Bastaich D, Marchetti D, Perumalswami P, Mustafa MZ, Dahman B; Veterans Analysis of Liver Disease (VALID) Group of Investigators. Association of Glucagon-Like Peptide-1 Receptor Agonists With Liver-Related Outcomes and All-Cause Mortality in Patients With Harmful Alcohol Use: A Target Trial Emulation Study. *Am J Gastroenterol.* 2026 Mar 1;121(3):697-709. doi: 10.14309/ajg.0000000000003585. Epub 2025 Jun 10. PMID: 40488647; PMCID: PMC12354218.
- [216] Zhou M, Mok MT, Sun H, Chan AW, Huang Y, Cheng AS, Xu G. The anti-diabetic drug exenatide, a glucagon-like peptide-1 receptor agonist, counteracts hepatocarcinogenesis through cAMP-PKA-EGFR-STAT3 axis. *Oncogene.* 2017 Jul 20;36(29):4135-4149. doi: 10.1038/onc.2017.38. Epub 2017 Mar 20. PMID: 28319060.
- [217] Lu X, Xu C, Dong J, Zuo S, Zhang H, Jiang C, Wu J, Wei J. Liraglutide activates nature killer cell-mediated antitumor responses by inhibiting IL-6/STAT3 signaling in hepatocellular carcinoma. *Transl Oncol.* 2021 Jan;14(1):100872. doi: 10.1016/j.tranon.2020.100872. Epub 2020 Sep 23. PMID: 32979685; PMCID: PMC7516274.
- [218] Kojima M, Takahashi H, Kuwashiro T, Tanaka K, Mori H, Ozaki I, Kitajima Y, Matsuda Y, Ashida K, Eguchi Y, Anzai K. Glucagon-Like Peptide-1 Receptor Agonist Prevented the Progression of Hepatocellular Carcinoma in a Mouse Model of Nonalcoholic Steatohepatitis. *Int J Mol Sci.* 2020 Aug 10;21(16):5722. doi: 10.3390/ijms21165722. PMID: 32785012; PMCID: PMC7460814.
- [219] Krause GC, Lima KG, Levorse V, Haute GV, Gassen RB, Garcia MC, Pedrazza L, Donadio MVF, Luft C, de Oliveira JR. Exenatide induces autophagy and prevents the cell regrowth in HepG2 cells. *EXCLI J.* 2019 Jul 22;18:540-548. doi: 10.17179/excli2019-1415. PMID: 31611738; PMCID: PMC6785771.
- [220] Li Q, Xue AY, Li ZL, Yin Z. Liraglutide promotes apoptosis of HepG2 cells by activating JNK signaling pathway. *Eur Rev Med Pharmacol Sci.* 2019 Apr;23(8):3520-3526. doi: 10.26355/eurrev_201904_17719. PMID: 31081108.
- [221] Chen-Liaw AY, Hammel G, Gomez G. Inhibition of exendin-4-induced steatosis by protein kinase A in cultured HepG2 human hepatoma cells. *In Vitro Cell Dev Biol Anim.* 2017 Sep;53(8):721-727. doi: 10.1007/s11626-017-0181-y. Epub 2017 Jul 13. PMID: 28707223.
- [222] Xu X, Wang W, Lin L, Chen P. Liraglutide in combination with human umbilical cord mesenchymal stem cell could improve liver lesions by modulating TLR4/NF-kB inflammatory pathway and oxidative stress in T2DM/NAFLD rats. *Tissue Cell.* 2020 Oct;66:101382. doi: 10.1016/j.tice.2020.101382. Epub 2020 May 12. PMID: 32933722.
- [223] Yamada N, Matsushima-Nishiwaki R, Kobayashi K, Tachi J, Kozawa O. GLP-1 reduces the migration of hepatocellular carcinoma cells via suppression of the stress-activated protein kinase/c-Jun N-terminal kinase pathway. *Arch Biochem Biophys.* 2021 May 30;703:108851. doi: 10.1016/j.abb.2021.108851. Epub 2021 Mar 23. PMID: 33771507.
- [224] Li WC, Horb ME, Tosh D, Slack JM. In vitro transdifferentiation of hepatoma cells into functional pancreatic cells. *Mech Dev.* 2005 Jun;122(6):835-47. doi: 10.1016/j.mod.2005.01.001. Epub 2005 Feb 17. PMID: 15939230.
- [225] Yokomori H, Ando W. Spatial expression of glucagon-like peptide 1 receptor and caveolin-1 in hepatocytes with macrovesicular steatosis in non-alcoholic steatohepatitis. *BMJ Open Gastroenterol.* 2020 May;7(1):e000370. doi: 10.1136/bmjgast-2019-000370. PMID: 32414752; PMCID: PMC7232783.
- [226] Moreira GV, Azevedo FF, Ribeiro LM, Santos A, Guadagnini D, Gama P, Liberti EA, Saad M, Carvalho C. Liraglutide modulates gut microbiota and reduces NAFLD in obese mice. *J Nutr Biochem.* 2018 Dec;62:143-154. doi: 10.1016/j.jnutbio.2018.07.009. Epub 2018 Aug 11. PMID: 30292107.
- [227] Galatou E, Mourelatou E, Hatziantoniou S, Vizirianakis IS. Nonalcoholic Steatohepatitis (NASH) and Atherosclerosis: Explaining Their Pathophysiology, Association and the Role of Incretin-Based Drugs. *Antioxidants (Basel).* 2022 May 27;11(6):1060. doi: 10.3390/antiox11061060. PMID: 35739957; PMCID: PMC9220192.

- [228] Tsiampali C, Papaioannidou P, Goulas A, Polyzos SA. The role of glucagon-like peptide-1 receptor agonists in nonalcoholic fatty liver disease. *Expert Rev Clin Pharmacol*. 2023 Jul-Dec;16(11):1063-1072. doi: 10.1080/17512433.2023.2274536. Epub 2023 Nov 22. PMID: 37864548.
- [229] Yadav P, Khurana A, Bhatti JS, Weiskirchen R, Navik U. Glucagon-like peptide 1 and fibroblast growth factor-21 in non-alcoholic steatohepatitis: An experimental to clinical perspective. *Pharmacol Res*. 2022 Oct;184:106426. doi: 10.1016/j.phrs.2022.106426. Epub 2022 Sep 6. PMID: 36075510.
- [230] Mastoor Z, Diz-Chaves Y, González-Matías LC, Mallo F. Renin-Angiotensin System in Liver Metabolism: Gender Differences and Role of Incretins. *Metabolites*. 2022 May 3;12(5):411. doi: 10.3390/metabo12050411. PMID: 35629915; PMCID: PMC9143858.
- [231] Hamed AE, Elsaahar M, Elwan NM, El-Nakeep S, Naguib M, Soliman HH, Ahmed Aboubakr A, AbdelMaqsood A, Sedrak H, Assaad SN, Elwakil R, Esmat G, Salh S, Mostafa T, Mogawer S, Sadek SE, Saber MM, Ezelarab H, Mahmoud AA, Sultan S, El Kassas M, Kamal E, ElSayed NM, Moussa S. Managing diabetes and liver disease association. *Arab J Gastroenterol*. 2018 Dec;19(4):166-179. doi: 10.1016/j.ajg.2018.08.003. Epub 2018 Nov 9. PMID: 30420265.
- [232] Itou M, Kawaguchi T, Taniguchi E, Sata M. Dipeptidyl peptidase-4: a key player in chronic liver disease. *World J Gastroenterol*. 2013 Apr 21;19(15):2298-306. doi: 10.3748/wjg.v19.i15.2298. PMID: 23613622; PMCID: PMC3631980.
- [233] Hanna S, Sethiadi J, Ali Q, Sinha S. Repurposing GLP-1 Receptor Agonists: A Perspective on Epigenetic Strategies to Combat Fibrosis and Hepatocellular Carcinoma in the Aged Liver. *Cancers (Basel)*. 2025 Aug 8;17(16):2600. doi: 10.3390/cancers17162600. PMID: 40867230; PMCID: PMC12384729.
- [234] Huynh DJ, Renelus BD, Jamorabo DS. Dual metformin and glucagon-like peptide-1 receptor agonist therapy reduces mortality and hepatic complications in cirrhotic patients with diabetes mellitus. *Ann Gastroenterol*. 2023 Sep-Oct;36(5):555-563. doi: 10.20524/aog.2023.0814. Epub 2023 Jul 3. PMID: 37664227; PMCID: PMC10433257.
- [235] Wang J, Qiu K, Zhou S, Gan Y, Jiang K, Wang D, Wang H. Risk factors for hepatocellular carcinoma: an umbrella review of systematic review and meta-analysis. *Ann Med*. 2025 Dec;57(1):2455539. doi: 10.1080/07853890.2025.2455539. Epub 2025 Jan 20. PMID: 39834076; PMCID: PMC11753015.
- [236] Arvanitakis K, Koufakis T, Kotsa K, Germanidis G. How Far beyond Diabetes Can the Benefits of Glucagon-like Peptide-1 Receptor Agonists Go? A Review of the Evidence on Their Effects on Hepatocellular Carcinoma. *Cancers (Basel)*. 2022 Sep 24;14(19):4651. doi: 10.3390/cancers14194651. PMID: 36230573; PMCID: PMC9562923.
- [237] Choi J, Nguyen VH, Przybyszewski E, Song J, Carroll A, Michta M, Almazan E, Simon TG, Chung RT. Association of Sodium-Glucose Cotransporter-2 Inhibitors With Reduced Hepatocellular Carcinoma Risk in Patients With Type 2 Diabetes. *Am J Gastroenterol*. 2025 Dec 16. doi: 10.14309/ajg.0000000000003889. Epub ahead of print. PMID: 41400268.
- [238] Titus J, Katukuri V, Boktor M, Mansi IA. Association of GLP1-Receptor Agonists with Risk of Hepatocellular Carcinoma: A Retrospective Cohort Study. *Drug Saf*. 2025 Oct;48(10):1089-1101. doi: 10.1007/s40264-025-01558-1. Epub 2025 Jun 30. PMID: 40587039.
- [239] Liu B, Peng G, Yin Y, Shen C, Yin X, Cai Z, Zhang B. Genetic evidence for repurposing of glucagon-like peptide-1 receptor agonists to prevent chronic liver diseases. *Gut*. 2024 Apr 5;73(5):879-882. doi: 10.1136/gutjnl-2024-332254. PMID: 38490731.
- [240] Liu Z, Shan D, Han X. GLP-1 Receptor Agonists' Role in Reducing Hepatocellular Carcinoma Risk. *Gastroenterology*. 2025 Feb;168(2):422-423. doi: 10.1053/j.gastro.2024.09.038. Epub 2024 Oct 18. PMID: 39424235.
- [241] Zacharia GS, Gongati SR, Kharel A, Jacob A. Semaglutide in Metabolic Dysfunction-Associated Steatohepatitis: A Narrative Review. *Cureus*. 2025 Oct 28;17(10):e95632. doi: 10.7759/cureus.95632. PMID: 41322896; PMCID: PMC12660513.
- [242] Cheraghpour M, Hatami B, Singal AG. Lifestyle and Pharmacologic Approaches to Prevention of Metabolic Dysfunction-associated Steatotic Liver Disease-related Hepatocellular Carcinoma. *Clin Gastroenterol Hepatol*. 2025 Apr;23(5):685-694.e6. doi: 10.1016/j.cgh.2024.09.041. Epub 2025 Jan 10. PMID: 39800201.
- [243] Hu Z, Tian D, Yang Z, Zhang J, Zhang L, Xu Y, Lu X. The mechanisms of GLP-1 receptor agonists in liver diseases: their multifaceted impact on immune response and metabolic regulation. *Front Pharmacol*. 2026 Mar 19;17:1754721. doi: 10.3389/fphar.2026.1754721. PMID: 41939830; PMCID: PMC13044122.
- [244] Abrahamsi D, Douros A, Yin H, Yu OH, Faillie JL, Montastruc F, Platt RW, Bouganin N, Azoulay L. Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study. *BMJ*. 2018 Dec 5;363:k4880. doi: 10.1136/bmj.k4880. PMID: 30518618; PMCID: PMC6278586.

- [245] Barbato GM, Cadamuro M, Fabris L. Incretin-based treatment in type 2 diabetes mellitus and risk of cholangiocarcinoma: Is it only adverse drug effect? *Clin Res Hepatol Gastroenterol*. 2019 Jun;43(3):232-235. doi: 10.1016/j.clinre.2019.01.009. Epub 2019 Mar 1. PMID: 30833185.
- [246] Giorda CB, Picariello R, Tartaglino B, Nada E, Costa G, Gnani R. Incretin-based therapy and risk of cholangiocarcinoma: a nested case-control study in a population of subjects with type 2 diabetes. *Acta Diabetol*. 2020 Apr;57(4):401-408. doi: 10.1007/s00592-019-01444-0. Epub 2019 Nov 5. PMID: 31691043.
- [247] Kaur RJ, Gomaz SB, Shaurya R, Aggarwal P, Porchezian P, Dhingra S, Sidhu P, Ambwani S, Charan J. Disproportionality analysis of semaglutide-associated bile-duct cancer: A vigibase study. *Indian J Gastroenterol*. 2026 Feb 4. doi: 10.1007/s12664-025-01891-4. Epub ahead of print. PMID: 41639322.
- [248] Ueda P, Wintzell V, Melbye M, Eliasson B, Svensson AM, Franzén S, Gudbjörnsdóttir S, Hveem K, Jonasson C, Svanström H, Pasternak B. Use of incretin-based drugs and risk of cholangiocarcinoma: Scandinavian cohort study. *Diabetologia*. 2021 Oct;64(10):2204-2214. doi: 10.1007/s00125-021-05508-1. Epub 2021 Jul 13. PMID: 34254177; PMCID: PMC8423638.
- [249] Krishnan A, Schneider CV, Arkenau HT, Mauro EM, Forner A, Scott Butsch W, Walsh D, Alqahtani SA. Association between incretin-based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: A large population-based matched cohort study. *J Clin Transl Endocrinol*. 2024 Sep 18;38:100370. doi: 10.1016/j.jcte.2024.100370. PMID: 39386155; PMCID: PMC11460491.
- [250] Yonatan ER, Jusni LFJ, Alvianto S, Widjanarko ND, Usman SY, Muzellina VN. Do Incretin-Based Therapies Influence the Risk of Cholangiocarcinoma in Type 2 Diabetes Patients? Insights from a Systematic Review and Meta-Analysis. *J Gastrointest Cancer*. 2025 Oct 11;56(1):198. doi: 10.1007/s12029-025-01330-9. PMID: 41075111.
- [251] Trakoonsenathong R, Chiu CF, Saengboonmee C. Glucagon-like peptide 1 receptor agonist: A potential game changer for cholangiocarcinoma. *World J Gastroenterol*. 2024 Sep 14;30(34):3862-3867. doi: 10.3748/wjg.v30.i34.3862. PMID: 39350782; PMCID: PMC11438652.
- [252] Chen BD, Zhao WC, Jia QA, Zhou WY, Bu Y, Wang ZZ, Wang F, Wu WJ, Wang Q. Effect of the GLP-1 analog exendin-4 and oxaliplatin on intrahepatic cholangiocarcinoma cell line and mouse model. *Int J Mol Sci*. 2013 Dec 13;14(12):24293-304. doi: 10.3390/ijms141224293. PMID: 24351817; PMCID: PMC3876111.
- [253] Chen BD, Zhao WC, Dong JD, Sima H. Expression of GLP-1R protein and its clinical role in intrahepatic cholangiocarcinoma tissues. *Mol Biol Rep*. 2014 Jul;41(7):4313-20. doi: 10.1007/s11033-014-3302-7. Epub 2014 Feb 28. PMID: 24577752.
- [254] Chen B, Zhou W, Zhao W, Yuan P, Tang C, Wang G, Leng J, Ma J, Wang X, Hui Y, Wang Q. Oxaliplatin reverses the GLP-1R-mediated promotion of intrahepatic cholangiocarcinoma by altering FoxO1 signaling. *Oncol Lett*. 2019 Aug;18(2):1989-1998. doi: 10.3892/ol.2019.10497. Epub 2019 Jun 19. PMID: 31423269; PMCID: PMC6607039.
- [255] Trakoonsenathong R, Kunprom W, Aphivatanasiri C, Yueangchantuek P, Pimkeeree P, Sorin S, Khawkhiauw K, Chiu CF, Okada S, Wongkham S, Saengboonmee C. Liraglutide exhibits potential anti-tumor effects on the progression of intrahepatic cholangiocarcinoma, in vitro and in vivo. *Sci Rep*. 2024 Jun 14;14(1):13726. doi: 10.1038/s41598-024-64774-2. PMID: 38877189; PMCID: PMC11178799.
- [256] Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med*. 2013 Apr 8;173(7):534-9. doi: 10.1001/jamainternmed.2013.2720. PMID: 23440284.
- [257] Funch D, Gydesen H, Tornøe K, Major-Pedersen A, Chan KA. A prospective, claims-based assessment of the risk of pancreatitis and pancreatic cancer with liraglutide compared to other antidiabetic drugs. *Diabetes Obes Metab*. 2014 Mar;16(3):273-5. doi: 10.1111/dom.12230. Epub 2013 Nov 26. PMID: 24199745; PMCID: PMC4237552.
- [258] Chalmer T, Almdal TP, Vilsbøll T, Knop FK. Adverse drug reactions associated with the use of liraglutide in patients with type 2 diabetes--focus on pancreatitis and pancreas cancer. *Expert Opin Drug Saf*. 2015 Jan;14(1):171-80. doi: 10.1517/14740338.2015.975205. Epub 2014 Nov 3. PMID: 25363438.
- [259] Nreu B, Dicembrini I, Tinti F, Mannucci E, Monami M. Pancreatitis and pancreatic cancer in patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonists: an updated meta-analysis of randomized controlled trials. *Minerva Endocrinol (Torino)*. 2023 Jun;48(2):206-213. doi: 10.23736/S2724-6507.20.03219-8. Epub 2020 Jul 23. PMID: 32720500.
- [260] Monami M, Nreu B, Scatena A, Cresci B, Andreozzi F, Sesti G, Mannucci E. Safety issues with glucagon-like peptide-1 receptor agonists (pancreatitis, pancreatic cancer and cholelithiasis): Data from randomized controlled trials. *Diabetes Obes Metab*. 2017 Sep;19(9):1233-1241. doi: 10.1111/dom.12926. Epub 2017 Jun 20. PMID: 28244632.

- [261] Wang H, Liu Y, Tian Q, Yang J, Lu R, Zhan S, Haukka J, Hong T. Incretin-based therapies and risk of pancreatic cancer in patients with type 2 diabetes: A meta-analysis of randomized controlled trials. *Diabetes Obes Metab.* 2018 Apr;20(4):910-920. doi: 10.1111/dom.13177. Epub 2018 Jan 3. PMID: 29193572.
- [262] Pinto LC, Falcetta MR, Rados DV, Leitão CB, Gross JL. Glucagon-like peptide-1 receptor agonists and pancreatic cancer: a meta-analysis with trial sequential analysis. *Sci Rep.* 2019 Feb 20;9(1):2375. doi: 10.1038/s41598-019-38956-2. PMID: 30787365; PMCID: PMC6382780.
- [263] Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials. *Endocrine.* 2020 Jun;68(3):518-525. doi: 10.1007/s12020-020-02223-6. Epub 2020 Feb 26. PMID: 32103407.
- [264] Cao M, Pan C, Tian Y, Wang L, Zhao Z, Zhu B. Glucagon-like peptide 1 receptor agonists and the potential risk of pancreatic carcinoma: a pharmacovigilance study using the FDA Adverse Event Reporting System and literature visualization analysis. *Int J Clin Pharm.* 2023 Jun;45(3):689-697. doi: 10.1007/s11096-023-01556-2. Epub 2023 Mar 28. PMID: 36977858.
- [265] Wen J, Nadora D, Bernstein E, How-Volkman C, Truong A, Joy B, Kou M, Muttalib Z, Alam A, Frezza E. Evaluating the Rates of Pancreatitis and Pancreatic Cancer Among GLP-1 Receptor Agonists: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Endocrinol Diabetes Metab.* 2025 Sep;8(5):e70113. doi: 10.1002/edm2.70113. PMID: 40988099; PMCID: PMC12457091.
- [266] Kalathiya UN, Herrin J, Swarna KS, Deng Y, Polley EC, Neumiller JJ, Galindo RJ, Umpierrez GE, Ross JS, Mickelson MM, McCoy RG. Comparative Risk of Adverse Pancreatic Events With GLP-1 Receptor Agonists, SGLT2 Inhibitors, DPP4 Inhibitors, and Sulfonylureas Among Adults With Type 2 Diabetes at Moderate Cardiovascular Disease Risk. *Endocr Pract.* 2026 Jan;32(1):23-30. doi: 10.1016/j.eprac.2025.09.004. Epub 2025 Sep 11. PMID: 40945659.
- [267] Lauri G, Arcidiacono PG, Facciorusso A, Capurso G, Tacelli M. Glucagon-like Peptide-1 receptor agonists are not associated with increased risk of pancreatic cancer: A systematic review and meta-analysis. *Pancreatology.* 2026 Apr 6:S1424-3903(26)00147-X. doi: 10.1016/j.pan.2026.04.005. Epub ahead of print. PMID: 41991368.
- [268] Tuersun A, Hou G, Cheng G. Pancreatitis and Pancreatic Cancer Risk Among Patients With Type 2 Diabetes Receiving Dipeptidyl Peptidase 4 Inhibitors: An Updated Meta-Analysis of Randomized Controlled Trials. *Clin Ther.* 2024 Aug;46(8):650-656. doi: 10.1016/j.clinthera.2024.06.015. Epub 2024 Jul 31. Erratum in: *Clin Ther.* 2025 Jan;47(1):113. doi: 10.1016/j.clinthera.2024.11.010. PMID: 39084911.
- [269] Ailawadi S, Murphy JE, Storandt MH, Mahipal A. Glucagon-like Peptide-1 Receptor Agonist Use and Pancreatic Cancer Risk in Patients with Chronic Pancreatitis. *Cancers (Basel).* 2026 Jan 6;18(2):179. doi: 10.3390/cancers18020179. PMID: 41595103; PMCID: PMC12839127.
- [270] Muhammed A, Thomas C, Kalaiselvan V, Undela K. Risk of pancreatitis and pancreatic carcinoma for anti-diabetic medications: findings from real-world safety data analysis and systematic review and meta-analysis of randomized controlled trials. *Expert Opin Drug Saf.* 2024 Jun;23(6):731-742. doi: 10.1080/14740338.2023.2284992. Epub 2023 Dec 11. PMID: 37986140.
- [271] Xie H, Xu Q, Zhao B, Wu W. Drug-associated pancreatic cancer: insights from real-world pharmacovigilance and network pharmacology. *Expert Opin Drug Saf.* 2025 Mar 6:1-11. doi: 10.1080/14740338.2025.2469273. Epub ahead of print. PMID: 40049721.
- [272] Faour O, Boktor M, Yau H, Kinaan M, Mansi IA. GLP-1 Receptor Agonists Initiation and Risk of Acute Pancreatitis and Pancreatic Cancer: A Real-World Comparative Study. *Am J Med Open.* 2025 Aug 20;14:100114. doi: 10.1016/j.ajmo.2025.100114. PMID: 41473903; PMCID: PMC12745096.
- [273] Zhang Z, Chen X, Lu P, Zhang J, Xu Y, He W, Li M, Zhang S, Jia J, Shao S, Xie J, Yang Y, Yu X. Incretin-based agents in type 2 diabetic patients at cardiovascular risk: compare the effect of GLP-1 agonists and DPP-4 inhibitors on cardiovascular and pancreatic outcomes. *Cardiovasc Diabetol.* 2017 Mar 1;16(1):31. doi: 10.1186/s12933-017-0512-z. PMID: 28249585; PMCID: PMC5333444.
- [274] Post Z, Rosario Lora D, Blogowski W. Unraveling the sweet connection between pancreatic cancer and hyperglycemia. *Trends Endocrinol Metab.* 2026 Mar;37(3):230-244. doi: 10.1016/j.tem.2025.06.003. Epub 2025 Jul 1. PMID: 40603165.
- [275] Williams JA. GLP-1 mimetic drugs and the risk of exocrine pancreatic disease: Cell and animal studies. *Pancreatology.* 2016 Jan-Feb;16(1):2-7. doi: 10.1016/j.pan.2015.11.008. Epub 2015 Dec 1. PMID: 26751948.
- [276] Zhao HJ, Jiang X, Hu LJ, Yang L, Deng LD, Wang YP, Ren ZP. Activation of GLP-1 receptor enhances the chemosensitivity of pancreatic cancer cells. *J Mol Endocrinol.* 2020 Feb;64(2):103-113. doi: 10.1530/JME-19-0186. PMID: 31855560.

- [277] Kiesewetter DO, Gao H, Ma Y, Niu G, Quan Q, Guo N, Chen X. 18F-radiolabeled analogs of exendin-4 for PET imaging of GLP-1 in insulinoma. *Eur J Nucl Med Mol Imaging*. 2012 Mar;39(3):463-73. doi: 10.1007/s00259-011-1980-0. Epub 2011 Dec 15. PMID: 22170321; PMCID: PMC3617488.
- [278] Cases AI, Ohtsuka T, Kimura H, Zheng B, Shindo K, Oda Y, Mizumoto K, Nakamura M, Tanaka M. Significance of expression of glucagon-like peptide 1 receptor in pancreatic cancer. *Oncol Rep*. 2015 Oct;34(4):1717-25. doi: 10.3892/or.2015.4138. Epub 2015 Jul 20. PMID: 26238361.
- [279] Zhang Y, Huang S, Li P, Chen Q, Li Y, Zhou Y, Wang L, Kang M, Zhang B, Yang B, Dong X, Wu Y. Pancreatic cancer-derived exosomes suppress the production of GIP and GLP-1 from STC-1 cells in vitro by down-regulating the PCSK1/3. *Cancer Lett*. 2018 Sep 1;431:190-200. doi: 10.1016/j.canlet.2018.05.027. Epub 2018 May 22. PMID: 29800682.
- [280] Wu J, Qian P, Han Y, Xu C, Xia M, Zhan P, Wei J, Dong J. GLP1 alleviates oleic acid-propelled lipocalin-2 generation by tumor-infiltrating CD8⁺ T cells to reduce polymorphonuclear MDSC recruitment and enhances viral immunotherapy in pancreatic cancer. *Cell Mol Immunol*. 2025 Mar;22(3):282-299. doi: 10.1038/s41423-025-01260-3. Epub 2025 Feb 5. PMID: 39910336; PMCID: PMC11868399.
- [281] Bao J, Liu D, Sun J, Su X, Cheng H, Qi L, Zhang Y, Lv Y, Ye Z, Yu X, Wei Q, Qiu Y, Su J, Li L. Pancreatic cancer-associated diabetes mellitus is characterized by reduced β -cell secretory capacity, rather than insulin resistance. *Diabetes Res Clin Pract*. 2022 Mar;185:109223. doi: 10.1016/j.diabres.2022.109223. Epub 2022 Feb 8. PMID: 35149166.
- [282] Buteau J, Foisy S, Joly E, Prentki M. Glucagon-like peptide 1 induces pancreatic beta-cell proliferation via transactivation of the epidermal growth factor receptor. *Diabetes*. 2003 Jan;52(1):124-32. doi: 10.2337/diabetes.52.1.124. PMID: 12502502.
- [283] Koehler JA, Drucker DJ. Activation of glucagon-like peptide-1 receptor signaling does not modify the growth or apoptosis of human pancreatic cancer cells. *Diabetes*. 2006 May;55(5):1369-79. doi: 10.2337/db05-1145. PMID: 16644694.
- [284] Cencioni C, Malatesta S, Vigiano Benedetti V, Licursi V, Perfetto L, Conte F, Ranieri D, Bartolazzi A, Kunkl M, Tuosto L, Larghi A, Piro G, Agostini A, Tortora G, Corbo V, Carbone C, Spallotta F. The GLP-1R agonist semaglutide reshapes pancreatic cancer associated fibroblasts reducing collagen proline hydroxylation and favoring T lymphocyte infiltration. *J Exp Clin Cancer Res*. 2025 Jan 20;44(1):18. doi: 10.1186/s13046-024-03263-w. PMID: 39828692; PMCID: PMC11744909.
- [285] Deng J, Guo Y, Du J, Gu J, Kong L, Tao B, Li J, Fu D. The Intricate Crosstalk Between Insulin and Pancreatic Ductal Adenocarcinoma: A Review From Clinical to Molecular. *Front Cell Dev Biol*. 2022 Feb 17;10:844028. doi: 10.3389/fcell.2022.844028. PMID: 35252207; PMCID: PMC8891560.
- [286] Xu W, Qadir MMF, Nasteska D, Mota de Sa P, Gorvin CM, Blandino-Rosano M, Evans CR, Ho T, Potapenko E, Veluthakal R, Ashford FB, Bitsi S, Fan J, Bhondeley M, Song K, Sure VN, Sakamuri SSVP, Schiffer L, Beatty W, Wyatt R, Frigo DE, Liu X, Katakam PV, Arlt W, Buck J, Levin LR, Hu T, Kolls J, Burant CF, Tomas A, Merrins MJ, Thurmond DC, Bernal-Mizrachi E, Hodson DJ, Mauvais-Jarvis F. Architecture of androgen receptor pathways amplifying glucagon-like peptide-1 insulinotropic action in male pancreatic β cells. *Cell Rep*. 2023 May 30;42(5):112529. doi: 10.1016/j.celrep.2023.112529. Epub 2023 May 17. PMID: 37200193; PMCID: PMC10312392.
- [287] Takano Y, Kasai K, Takagishi Y, Kikumori T, Imai T, Murata Y, Hayashi Y. Pancreatic Neuroendocrine Tumors in Mice Deficient in Proglucagon-Derived Peptides. *PLoS One*. 2015 Jul 20;10(7):e0133812. doi: 10.1371/journal.pone.0133812. PMID: 26192435; PMCID: PMC4508046.
- [288] Tong JCL, Frazer-Morris C, Shilleh AH, Vilorio K, de Bray A, Nair AM, Johnson PRV, Spiers R, Kobiita A, Olaniru OE, Persaud SJ, Hauffe R, Kleinridders A, Schultz C, Bruce Verchere C, Cui C, Campbell JE, Cyranka M, Epanchintsev A, Åmmälä C, Broichhagen J, Hodson DJ. Localized GLP1 receptor pre-internalization directs pancreatic alpha cell to beta cell communication. *Cell Metab*. 2025 Aug 5;37(8):1698-1714.e5. doi: 10.1016/j.cmet.2025.06.009. Epub 2025 Jul 14. PMID: 40664215; PMCID: PMC12276844.
- [289] Smith DK, Kates L, Durinck S, Patel N, Stawiski EW, Kljavin N, Foreman O, Sipos B, Solloway MJ, Allan BB, Peterson AS. Elevated Serum Amino Acids Induce a Subpopulation of Alpha Cells to Initiate Pancreatic Neuroendocrine Tumor Formation. *Cell Rep Med*. 2020 Aug 25;1(5):100058. doi: 10.1016/j.xcrm.2020.100058. PMID: 33205067; PMCID: PMC7659536.
- [290] Wada R, Yagihashi S. The expression of glucagon-like peptide-1 receptor and dipeptidyl peptidase-IV in neuroendocrine neoplasms of the pancreas and gastrointestinal tract. *Endocr Pathol*. 2014 Dec;25(4):390-6. doi: 10.1007/s12022-014-9326-7. PMID: 25119061.
- [291] Tiano JP, Tate CR, Yang BS, DiMarchi R, Mauvais-Jarvis F. Effect of targeted estrogen delivery using glucagon-like peptide-1 on insulin secretion, insulin sensitivity and glucose homeostasis. *Sci Rep*. 2015 May 13;5:10211. doi: 10.1038/srep10211. PMID: 25970118; PMCID: PMC4429560.

- [292] Talmon GA, Wren JD, Nguyen CL, Pour PM. Pancreatic Polypeptide Cell Proliferation in the Pancreas and Duodenum Coexisting in a Patient With Pancreatic Adenocarcinoma Treated With a GLP-1 Analog. *Pancreas*. 2017 Jul;46(6):820-824. doi: 10.1097/MPA.0000000000000844. PMID: 28609372.
- [293] Masjkur J, Arps-Forker C, Poser SW, Nikolakopoulou P, Toutouna L, Chenna R, Chavakis T, Chatzigeorgiou A, Chen LS, Dubrovskaya A, Choudhary P, Uphues I, Mark M, Bornstein SR, Androutsellis-Theotokis A. Hes3 is expressed in the adult pancreatic islet and regulates gene expression, cell growth, and insulin release. *J Biol Chem*. 2014 Dec 19;289(51):35503-16. doi: 10.1074/jbc.M114.590687. Epub 2014 Nov 4. PMID: 25371201; PMCID: PMC4271235.
- [294] Beyene E, Chirumamilla L, Bisrat M, Bowen A, Fetle Y, Wilkerson B, Wudeneh A, Gillani SF, Larbi D, Michael M. Liver gains beyond glycemic control: GLP-1 vs. SGLT2 in metabolic dysfunction-associated steatohepatitis (MASH): A real-world data analysis. *Clin Res Hepatol Gastroenterol*. 2026 Feb;50(2):102760. doi: 10.1016/j.clinre.2026.102760. Epub 2026 Jan 5. PMID: 41500355.
- [295] Shabil M, Khatib MN, Ballal S, Bansal P, Tomar BS, Ashraf A, Kumar MR, Sinha A, Rawat P, Gaidhane AM, Sah S, Daniel AS, Yappalparvi A, Bushi G. Risk of Hepatocellular Carcinoma with Glucagon-like Peptide-1 receptor agonist treatment in patients: a systematic review and meta-analysis. *BMC Endocr Disord*. 2024 Nov 18;24(1):246. doi: 10.1186/s12902-024-01775-2. PMID: 39551761; PMCID: PMC11571652.
- [296] Uttenthal LO, Ghiglione M, George SK, Bishop AE, Polak JM, Bloom SR. Molecular forms of glucagon-like peptide-1 in human pancreas and glucagonomas. *J Clin Endocrinol Metab*. 1985 Sep;61(3):472-9. doi: 10.1210/jcem-61-3-472. PMID: 2991321.
- [297] Felix K, Fakelman F, Hartmann D, Giese NA, Gaida MM, Schnölzer M, Flad T, Büchler MW, Werner J. Identification of serum proteins involved in pancreatic cancer cachexia. *Life Sci*. 2011 Jan 31;88(5-6):218-25. doi: 10.1016/j.lfs.2010.11.011. Epub 2010 Nov 19. PMID: 21094171.
- [298] Lagger M, Irmanesh P, Frossard JL, Adamina M, Buhler L. Is GLP-1 receptor agonist therapy safe for patients with intraductal papillary mucinous neoplasm? *Swiss Med Wkly*. 2025 Oct 15;155:4850. doi: 10.57187/s.4850. PMID: 41100817.
- [299] Laeeq T, Ahmed M, Sattar H, Zeeshan MH, Ali MB. Role of SGLT2 Inhibitors, DPP-4 Inhibitors, and Metformin in Pancreatic Cancer Prevention. *Cancers (Basel)*. 2024 Mar 28;16(7):1325. doi: 10.3390/cancers16071325. PMID: 38611003; PMCID: PMC11011099.
- [300] Cuomo RE. The Influence of GLP-1 Receptor Agonists on Five-Year Mortality in Colon Cancer Patients. *Cancer Invest*. 2025 Nov;43(10):982-991. doi: 10.1080/07357907.2025.2585512. Epub 2025 Nov 11. PMID: 41216819.
- [301] Dosda A, Fauchier G, Sabbah N, Fauchier L, Lecomte T, Ducluzeau PH. Association between glucagon-like peptide-1 receptor agonists and colorectal cancer survival: A population-based cohort study. *Diabetes Metab*. 2026 Mar;52(2):101734. doi: 10.1016/j.diabet.2026.101734. Epub 2026 Jan 16. PMID: 41547436.
- [302] Wang B, Huang J, Chen Z. Reassessing the role of GLP-1 receptor agonists in colorectal cancer Care. *Diabetes Metab*. 2026 Mar;52(2):101742. doi: 10.1016/j.diabet.2026.101742. Epub 2026 Feb 14. PMID: 41698477.
- [303] Guo M, Liu Y, Zeng Y, Chen J, Zeng C, Huang LL, Wang JY, Wu YH, Wu Q, Teng FY, Xu Y. Association Between GLP-1 Receptor Agonists and the Risk of Colon Cancer in Adults With Type 2 Diabetes or Obesity: A Systematic Review and Network Meta-Analysis. *Diabetes Metab Res Rev*. 2026 Feb;42(2):e70134. doi: 10.1002/dmrr.70134. PMID: 41668634.
- [304] Kamarudin MNA, Sarker MMR, Zhou JR, Parhar I. Metformin in colorectal cancer: molecular mechanism, preclinical and clinical aspects. *J Exp Clin Cancer Res*. 2019 Dec 12;38(1):491. doi: 10.1186/s13046-019-1495-2. PMID: 31831021; PMCID: PMC6909457.
- [305] Zhong Y, Wu T, Khan NU. Association between GLP-1 receptor agonists as a class and colorectal cancer risk: a meta-analysis of retrospective cohort studies. *BMC Gastroenterol*. 2025 Aug 22;25(1):614. doi: 10.1186/s12876-025-04211-4. PMID: 40847331; PMCID: PMC12372225.
- [306] Kakkar AK. GLP-1 receptor agonists and the risk of colorectal cancer. *Med Hypotheses*. 2014 Jun;82(6):796. doi: 10.1016/j.mehy.2014.03.028. Epub 2014 Apr 3. PMID: 24746383.
- [307] Zhang Y, Xie Y, Xia S, Ge X, Li J, Liu F, Jia F, Wang S, Zhou Q, Gao M, Fang W, Zheng C. The Novel Dual GIP and GLP-1 Receptor Agonist Tirzepatide Attenuates Colon Cancer Development by Regulating Glucose Metabolism. *Adv Sci (Weinh)*. 2025 May;12(19):e2411980. doi: 10.1002/advs.202411980. Epub 2025 Mar 24. PMID: 40125821; PMCID: PMC12097124.
- [308] Wenjing H, Shuang Y, Weisong L, Haipeng X. Exendin-4 does not modify growth or apoptosis of human colon cancer cells. *Endocr Res*. 2017 Aug;42(3):209-218. doi: 10.1080/07435800.2017.1292525. Epub 2017 Mar 20. PMID: 28318339.

- [309] Sun Y, Fan L, Meng J, Zhang F, Zhang D, Mei Q. Should GLP-1 receptor agonists be used with caution in high risk population for colorectal cancer? *Med Hypotheses*. 2014 Mar;82(3):255-6. doi: 10.1016/j.mehy.2013.11.034. Epub 2013 Dec 6. PMID: 24424394.
- [310] Kissow H, Hartmann B, Holst JJ, Viby NE, Hansen LS, Rosenkilde MM, Hare KJ, Poulsen SS. Glucagon-like peptide-1 (GLP-1) receptor agonism or DPP-4 inhibition does not accelerate neoplasia in carcinogen treated mice. *Regul Pept*. 2012 Nov 10;179(1-3):91-100. doi: 10.1016/j.regpep.2012.08.016. Epub 2012 Sep 15. PMID: 22989472.
- [311] Masur K, Schwartz F, Entschladen F, Niggemann B, Zaenker KS. DPP-IV inhibitors extend GLP-2 mediated tumor promoting effects on intestinal cancer cells. *Regul Pept*. 2006 Dec 10;137(3):147-55. doi: 10.1016/j.regpep.2006.07.003. Epub 2006 Aug 14. PMID: 16908079.
- [312] Jin T. Why diabetes patients are more prone to the development of colon cancer? *Med Hypotheses*. 2008 Aug;71(2):241-4. doi: 10.1016/j.mehy.2008.03.025. Epub 2008 May 5. PMID: 18456417.
- [313] Zac-Varghese S, Trapp S, Richards P, Sayers S, Sun G, Bloom SR, Reimann F, Gribble FM, Rutter GA. The Peutz-Jeghers kinase LKB1 suppresses polyp growth from intestinal cells of a proglucagon-expressing lineage in mice. *Dis Model Mech*. 2014 Nov;7(11):1275-86. doi: 10.1242/dmm.014720. Epub 2014 Sep 4. PMID: 25190708; PMCID: PMC4213731.
- [314] Yorifuji N, Inoue T, Iguchi M, Fujiwara K, Kakimoto K, Nouda S, Okada T, Kawakami K, Abe Y, Takeuchi T, Higuchi K. The dipeptidyl peptidase-4 inhibitor sitagliptin suppresses mouse colon tumorigenesis in type 2 diabetic mice. *Oncol Rep*. 2016 Feb;35(2):676-82. doi: 10.3892/or.2015.4429. Epub 2015 Nov 16. PMID: 26573958.
- [315] Phuah P, Norton M, Cheng S, Roberts AG, Pirri D, Meyer L, Chung PE, Dunsterville C, Karwowski R, Lam BYH, Otsubo E, Aleksashina S, Gribble FM, Reimann F, Hanyaloglu AC, Yeo GSH, Bewick GA, Jones B, Owen B, Murphy KG. The microbial tryptophan metabolite indole acts on the gastrointestinal tract to improve glucose homeostasis in a mouse model of diabetes by enhancing GLP-1 secretion and L cell differentiation. *Diabetologia*. 2026 Jun;69(6):1659-1674. doi: 10.1007/s00125-026-06688-4. Epub 2026 Mar 4. PMID: 41776124.
- [316] Glass LL, Calero-Nieto FJ, Jawaid W, Larraufie P, Kay RG, Göttgens B, Reimann F, Gribble FM. Single-cell RNA-sequencing reveals a distinct population of proglucagon-expressing cells specific to the mouse upper small intestine. *Mol Metab*. 2017 Oct;6(10):1296-1303. doi: 10.1016/j.molmet.2017.07.014. Epub 2017 Aug 1. PMID: 29031728; PMCID: PMC5641633.
- [317] Jiang Y, Rose AJ, Sijmonsma TP, Bröer A, Pfenninger A, Herzig S, Schmoll D, Bröer S. Mice lacking neutral amino acid transporter B(0)AT1 (Slc6a19) have elevated levels of FGF21 and GLP-1 and improved glycaemic control. *Mol Metab*. 2015 Feb 16;4(5):406-17. doi: 10.1016/j.molmet.2015.02.003. PMID: 25973388; PMCID: PMC4421019.
- [318] Ueda P, Wintzell V, Melbye M, Eliasson B, Söderling J, Gudbjörnsdóttir S, Hveem K, Jonasson C, Svanström H, Hviid A, Pasternak B. Use of DPP4 Inhibitors and GLP-1 Receptor Agonists and Risk of Intestinal Obstruction: Scandinavian Cohort Study. *Clin Gastroenterol Hepatol*. 2024 Jun;22(6):1226-1237.e14. doi: 10.1016/j.cgh.2023.08.034. Epub 2023 Sep 15. PMID: 37716613.
- [319] Chen JJ, Hsu CW, Hung CM, Suen MW, Wang HY, Yang WC, Stubbs B, Chen YW, Chen TY, Lei WT, Carvalho AF, Hsu SP, Shiue YL, Zeng BY, Li CT, Su KP, Liang CS, Zeng BS, Tseng PT. Agent- and Dose-Specific Intestinal Obstruction Safety of GLP-1 Receptor Agonists and SGLT2 Inhibitors: A Network Meta-Analysis of Randomized Trials. *Int J Mol Sci*. 2026 Jan 7;27(2):608. doi: 10.3390/ijms27020608. PMID: 41596262; PMCID: PMC12841245.
- [320] Yuan B, Yang Z, Wang C, Zong G, Qiu J, Feng C, Geng X. Genetic evidence for a causal protective effect of GLP-1 receptor agonists on paralytic ileus but not on other gastrointestinal events. *Medicine (Baltimore)*. 2026 Mar 20;105(12):e48089. doi: 10.1097/MD.00000000000048089. PMID: 41861181; PMCID: PMC13008193.
- [321] Saghafi S, Yaghoubi MA, Safarpour H, Raeisi H, Mousavi Z. Protecting the endocrine axis in immuno-oncology: GLP-1 receptor agonists as host-directed modulators in colorectal cancer. *Biomed Pharmacother*. 2026 Jan;194:118948. doi: 10.1016/j.biopha.2025.118948. Epub 2026 Jan 6. PMID: 41496347.
- [322] Temperley HC, Coalter M, Creavin B, Jordan P, Hogan A, O'Sullivan J, O'Shea D, McCormick PH, Harrold E, Kelly ME. Evaluating the impact of GLP-1 receptor agonists in combination with total neoadjuvant therapy for locally advanced rectal cancer. *Br J Surg*. 2026 Apr 9;113(4):znag029. doi: 10.1093/bjs/znag029. PMID: 41806363.
- [323] Nguyen L, Shanmugan S. A Review Article: The Relationship Between Obesity and Colorectal Cancer. *Curr Diab Rep*. 2024 Dec 2;25(1):8. doi: 10.1007/s11892-024-01556-0. PMID: 39621160; PMCID: PMC11611961.
- [324] Skriver C, Friis S, Knudsen LB, Catarig AM, Clark AJ, Dehlendorff C, Mørch LS. Potential preventive properties of GLP-1 receptor agonists against prostate cancer: a nationwide cohort study. *Diabetologia*. 2023 Nov;66(11):2007-2016. doi: 10.1007/s00125-023-05972-x. Epub 2023 Aug 3. PMID: 37532786.

- [325] Lu S, Yin H, Yu OHY, Azoulay L. Incretin-Based Drugs and the Incidence of Prostate Cancer Among Patients With Type 2 Diabetes. *Epidemiology*. 2022 Jul 1;33(4):563-571. doi: 10.1097/EDE.0000000000001486. Epub 2022 Mar 29. PMID: 35394977.
- [326] Lin Y, Xu G, Li L, Xiang J, Zhai L. Incretin-based drugs decrease the incidence of prostate cancer in type 2 diabetics: A pooling-up analysis. *Medicine (Baltimore)*. 2024 May 17;103(20):e38018. doi: 10.1097/MD.00000000000038018. PMID: 38758855; PMCID: PMC11098233.
- [327] Chou OHI, Lu L, Chung CT, Chan JSK, Chan RNC, Lee AYH, Dee EC, Ng K, Pui HHH, Lee S, Cheung BMY, Tse G, Zhou J. Comparisons of the risks of new-onset prostate cancer in type 2 diabetes mellitus between SGLT2I and DPP4I users: A population-based cohort study. *Diabetes Metab*. 2025 Jan;51(1):101571. doi: 10.1016/j.diabet.2024.101571. Epub 2024 Aug 23. PMID: 39182669.
- [328] Sharma N, Khatib MN, Balaraman AK, Roopashree R, Kaur M, Srivastava M, Barwal A, Prasad GVS, Rajput P, Syed R, Sharma G, Kumar S, Singh MP, Bushi G, Chilakam N, Pandey S, Brar M, Mehta R, Sah S, Gaidhane AM, Shabil M. Effect of GLP-1 receptor agonists on prostate cancer risk reduction: a systematic review and meta-analysis. *Int Urol Nephrol*. 2025 Apr;57(4):1039-1049. doi: 10.1007/s11255-024-04266-4. Epub 2024 Nov 4. PMID: 39495435.
- [329] Fang A, Frigo DE, Hahn A, Razouki Z, Hwang J, Koutroumpakis E, Lawen T, Smith M, Hamilton-Reeves J, DiGiovanni J, Higgason N, Garcia RS, Chapin BF, Pettaway C, Chery L, Troncoso P, Logothetis C, Daniel CR, Wei P, Gregg JR. GLP-1 Agonist Use Among Men With Localized Prostate Cancer: A Narrative Review and Rationale for Prospective Clinical Trials. *Urology*. 2025 Jul;201:152-158. doi: 10.1016/j.urology.2025.04.056. Epub 2025 May 29. PMID: 40348027; PMCID: PMC13036752.
- [330] Drewa J, Lazar-Juszczak K, Adamowicz J, Juszczak K. May Patients Receiving GLP-1 Agonists Be at Lower Risk of Prostate Cancer Aggressiveness and Progression? *Cancers (Basel)*. 2025 May 6;17(9):1576. doi: 10.3390/cancers17091576. PMID: 40361502; PMCID: PMC12071316.
- [331] Alhajjah A, Al-Faouri R, Bahmad HF, Bader T, Dobbs RW, Abdullelah AA, Abou-Kheir W, Davicioni E, Lee DI, Shahait M. From Diabetes to Oncology: Glucagon-like Peptide-1 (GLP-1) Receptor Agonist's Dual Role in Prostate Cancer. *Cancers (Basel)*. 2024 Apr 18;16(8):1538. doi: 10.3390/cancers16081538. PMID: 38672620; PMCID: PMC11048615.
- [332] Bera S, Gutgesell LC, Darden B, Sargis RM, Maienschein-Cline M, Gaber CE, Reizine NM, Vander Griend DJ, Vellky JE. GLP1 receptor agonism alters growth and therapeutic response in prostate cancer. *Endocr Relat Cancer*. 2025 Dec 2;32(12):e250185. doi: 10.1530/ERC-25-0185. PMID: 41257454; PMCID: PMC12713343.
- [333] Iwaya C, Nomiya T, Komatsu S, Kawanami T, Tsutsumi Y, Hamaguchi Y, Horikawa T, Yoshinaga Y, Yamashita S, Tanaka T, Terawaki Y, Tanabe M, Nabeshima K, Iwasaki A, Yanase T. Exendin-4, a Glucagonlike Peptide-1 Receptor Agonist, Attenuates Breast Cancer Growth by Inhibiting NF- κ B Activation. *Endocrinology*. 2017 Dec 1;158(12):4218-4232. doi: 10.1210/en.2017-00461. PMID: 29045658.
- [334] Li XN, Bu HM, Ma XH, Lu S, Zhao S, Cui YL, Sun J. Glucagon-like Peptide-1 Analogues Inhibit Proliferation and Increase Apoptosis of Human Prostate Cancer Cells in vitro. *Exp Clin Endocrinol Diabetes*. 2017 Feb;125(2):91-97. doi: 10.1055/s-0042-112368. Epub 2016 Dec 22. PMID: 28008585.
- [335] Wenjing H, Shao Y, Yu Y, Huang W, Feng G, Li J. Exendin-4 enhances the sensitivity of prostate cancer to enzalutamide by targeting Akt activation. *Prostate*. 2020 Apr;80(5):367-375. doi: 10.1002/pros.23951. Epub 2020 Jan 22. PMID: 31967357.
- [336] Stein MS, Kalff V, Williams SG, Murphy DG, Colman PG, Hofman MS. The GLP-1 receptor is expressed *in vivo* by human metastatic prostate cancer. *Endocr Oncol*. 2024 Jan 22;4(1):e230015. doi: 10.1530/EO-23-0015. PMID: 38313829; PMCID: PMC10831528.
- [337] Besschetnova A, Han W, Liu M, Gao Y, Li M, Wang Z, Labaf M, Patalano S, Venkataramani K, Muriph RE, Macoska JA, Siegfried KR, Evans J, Balk SP, Gao S, Han D, Cai C. Demethylation of EHMT1/GLP Protein Reprograms Its Transcriptional Activity and Promotes Prostate Cancer Progression. *Cancer Res Commun*. 2023 Aug 31;3(8):1716-1730. doi: 10.1158/2767-9764.CRC-23-0208. PMID: 37663929; PMCID: PMC10470473.
- [338] Murphy A, Shyanti RK, Mishra M. Targeting obesity, metabolic syndrome, and prostate cancer: GLP-1 agonists as emerging therapeutic agents. *Discov Oncol*. 2025 Mar 1;16(1):258. doi: 10.1007/s12672-025-01878-9. PMID: 40024963; PMCID: PMC11872791.
- [339] Knura M, Garczor W, Borek A, Drzymała F, Rachwał K, George K, Francuz T. The Influence of Anti-Diabetic Drugs on Prostate Cancer. *Cancers (Basel)*. 2021 Apr 12;13(8):1827. doi: 10.3390/cancers13081827. PMID: 33921222; PMCID: PMC8068793.

- [340] Kajitani N, Takahashi J, Honda H, Hamahara J, Ando S. Severe Visceral Obesity, Fatty Liver and Diabetes after Orchiectomy for Prostate Cancer. *Intern Med.* 2020 Sep 15;59(18):2281-2285. doi: 10.2169/internalmedicine.4653-20. Epub 2020 Jun 9. PMID: 32522924; PMCID: PMC7578597.
- [341] Andrianu K, Works D, Christiansen A, Enke C, Chaiken L, Baine M. Exploring the Impact of Sodium-Glucose Cotransporter-2 Inhibitors on Genitourinary Toxicities in Prostate Cancer Patients Undergoing Radiation Therapy: A Case Study and Discussion. *Pract Radiat Oncol.* 2024 Sep-Oct;14(5):373-376. doi: 10.1016/j.prro.2024.04.006. Epub 2024 May 16. PMID: 38752974.
- [342] Model JFA, Lima MV, Ohlweiler R, Sarapio E, Vogt ÉL, Rocha DS, de Souza SK, Vinagre AS. Liraglutide treatment counteracts alterations in adipose tissue metabolism induced by orchiectomy in rats. *Life Sci.* 2021 Aug 1;278:119586. doi: 10.1016/j.lfs.2021.119586. Epub 2021 May 3. PMID: 33957171.
- [343] Mercola D. Obesity-linked genes may promote prostate cancer among Asian and Hispanic immigrants to North America. *Front Public Health.* 2026 Feb 9;14:1742476. doi: 10.3389/fpubh.2026.1742476. PMID: 41737617; PMCID: PMC12926505.
- [344] Piccoli GF, Mesquita LA, Stein C, Aziz M, Zoldan M, Degobi NAH, Spiazzi BF, Lopes Junior GL, Colpani V, Gerchman F. Do GLP-1 Receptor Agonists Increase the Risk of Breast Cancer? A Systematic Review and Meta-analysis. *J Clin Endocrinol Metab.* 2021 Mar 8;106(3):912-921. doi: 10.1210/clinem/dgaa891. PMID: 33248445.
- [345] Hicks BM, Yin H, Yu OH, Pollak MN, Platt RW, Azoulay L. Glucagon-like peptide-1 analogues and risk of breast cancer in women with type 2 diabetes: population based cohort study using the UK Clinical Practice Research Datalink. *BMJ.* 2016 Oct 20;355:i5340. doi: 10.1136/bmj.i5340. PMID: 27797785.
- [346] Sarti S, Viansone AA, Serra O, Casadei C, Cecconetto L, Di Menna G, Farolfi A, Gianni C, Mariotti M, Merloni F, Palleschi M, Sirico M, Zoppoli G, Musolino A. Pharmacological Prevention in Breast Cancer: Current Evidence, Challenges, and Future Directions. *Cancers (Basel).* 2025 Nov 7;17(22):3597. doi: 10.3390/cancers17223597. PMID: 41300964; PMCID: PMC12651551.
- [347] Xande JG, Del Giglio A. GLP-1 Receptor Agonists in Breast Cancer: A New Frontier in Obesity and Prognosis Management. *Int J Mol Sci.* 2025 Aug 11;26(16):7744. doi: 10.3390/ijms26167744. PMID: 40869064; PMCID: PMC12386789.
- [348] Parsons K, Montalvo M, Fischbach N, Taylor M, Alfaro S, Lustberg M. The Impact and Safety of GLP-1 Agents and Breast Cancer. *Cancer Med.* 2025 Jun;14(12):e70932. doi: 10.1002/cam4.70932. PMID: 40552446; PMCID: PMC12186097.
- [349] Naaman SC, Shen S, Zeytinoglu M, Iyengar NM. Obesity and Breast Cancer Risk: The Oncogenic Implications of Metabolic Dysregulation. *J Clin Endocrinol Metab.* 2022 Jul 14;107(8):2154-2166. doi: 10.1210/clinem/dgac241. PMID: 35453151; PMCID: PMC9282365.
- [350] Ligumsky H, Wolf I, Israeli S, Haimsohn M, Ferber S, Karasik A, Kaufman B, Rubinek T. The peptide-hormone glucagon-like peptide-1 activates cAMP and inhibits growth of breast cancer cells. *Breast Cancer Res Treat.* 2012 Apr;132(2):449-61. doi: 10.1007/s10549-011-1585-0. Epub 2011 Jun 3. PMID: 21638053.
- [351] Ligumsky H, Amir S, Arbel Rubinstein T, Guion K, Scherf T, Karasik A, Wolf I, Rubinek T. Glucagon-like peptide-1 analogs activate AMP kinase leading to reversal of the Warburg metabolic switch in breast cancer cells. *Med Oncol.* 2024 May 6;41(6):138. doi: 10.1007/s12032-024-02390-w. Erratum in: *Med Oncol.* 2026 Mar 27;43(5):177. doi: 10.1007/s12032-026-03285-8. PMID: 38705935.
- [352] Hashimoto Takigami N, Kuniyoshi S, Miki Y, Tamaki K, Kamada Y, Uehara K, Tsuchiya S, Terukina S, Iwabuchi E, Kanai A, Miyashita M, Ishida T, Tamaki N, Sasano H. Breast Cancer, Diabetes Mellitus and Glucagon-Like Peptide-1 Receptor Toward Exploring Their Possible Associations. *Breast Cancer Res Treat.* 2021 Aug;189(1):39-48. doi: 10.1007/s10549-021-06288-3. Epub 2021 Jul 2. Erratum in: *Breast Cancer Res Treat.* 2022 Jan;191(1):221. doi: 10.1007/s10549-021-06380-8. PMID: 34213657.
- [353] Tanaka Y, Iwaya C, Kawanami T, Hamaguchi Y, Horikawa T, Shigeoka T, Yanase T, Kawanami D, Nomiyama T. Combined treatment with glucagon-like peptide-1 receptor agonist exendin-4 and metformin attenuates breast cancer growth. *Diabetol Int.* 2021 Nov 25;13(3):480-492. doi: 10.1007/s13340-021-00560-z. PMID: 35693999; PMCID: PMC9174406.
- [354] Liu ZZ, Duan XX, Yuan MC, Yu J, Hu X, Han X, Lan L, Liu BW, Wang Y, Qin JF. Glucagon-like peptide-1 receptor activation by liraglutide promotes breast cancer through NOX4/ROS/VEGF pathway. *Life Sci.* 2022 Apr 1;294:120370. doi: 10.1016/j.lfs.2022.120370. Epub 2022 Feb 3. PMID: 35124000.
- [355] Shadboorestan A, Tarighi P, Koosha M, Faghihi H, Ghahremani MH, Montazeri H. Growth Promotion and Increased ATP-Binding Cassette Transporters Expression by Liraglutide in Triple Negative Breast Cancer Cell

Line MDA-MB-231. *Drug Res (Stuttg)*. 2021 Jul;71(6):307-311. doi: 10.1055/a-1345-7890. Epub 2021 Jan 21. PMID: 33477190.

- [356] Stanisavljevic I, Pavlovic S, Simovic Markovic B, Jurisevic M, Krajnovic T, Mijatovic S, Spasojevic M, Mitrovic S, Corovic I, Jovanovic I. Semaglutide decelerates the growth and progression of breast cancer by enhancing the acquired antitumor immunity. *Biomed Pharmacother*. 2024 Dec;181:117668. doi: 10.1016/j.biopha.2024.117668. Epub 2024 Nov 12. PMID: 39536536.
- [357] Atasoy O, Anadol E, Yar Saglam AS, Akdemir EY, Coskun YS, Atak E, Dincer S, Usta DD, Emniyet Sert A, Kaplanoglu GT, Guney Y. Synergistic Potential of GLP-1 Receptor Agonists and Radiotherapy in Breast Cancer Treatment: A New Therapeutic Avenue (TROD-GROG 006). *Curr Radiopharm*. 2025;18(4):318-332. doi: 10.2174/0118744710381356250429045716. PMID: 40329735.
- [358] Santos B, Marção M, Durdana I, Lee B, Vumma L, Segato-Dezem F, Chasteen H, Zhang S, Lewis C, Peng Y, LeVee A, Wong M, Mortimer J, McArthur H, Scherer PE, Plummer JT, Gruber J. GLP-1 Targeting Agents Impair Chemoimmunotherapy Effectiveness in Triple-Negative Breast Cancer. *Res Sq [Preprint]*. 2026 Jan 9:rs.3.rs-8380296. doi: 10.21203/rs.3.rs-8380296/v1. PMID: 41542041; PMCID: PMC12803343.
- [359] Lemon LS, Orr B, Modugno F, Buckanovich RJ, Coffman L, Edwards RP, Taylor S. Metformin and survival: Is there benefit in a cohort limited to diabetic women with endometrial, breast, or ovarian cancer? *Gynecol Oncol*. 2022 Apr;165(1):60-66. doi: 10.1016/j.ygyno.2022.01.022. Epub 2022 Feb 6. PMID: 35140015.
- [360] Sukumar JS, Raghavendra AS, Pasyar S, Bassett RL, Tripathy D, Barcenas CH, Basen-Engquist KM, Arun BK. Weight Loss Patterns and Clinical Outcomes of GLP1 Receptor Agonists in Breast Cancer Survivors. *Cancer Res Commun*. 2026 Mar 1;6(3):447-455. doi: 10.1158/2767-9764.CRC-25-0554. PMID: 41677473; PMCID: PMC13043164.
- [361] Fujiwara K, Inoue T, Henmi Y, Hirata Y, Naka Y, Hara A, Kakimoto K, Nouda S, Okada T, Kawakami K, Takeuchi T, Higuchi K. Sitagliptin, a dipeptidyl peptidase-4 inhibitor, suppresses CXCL5 and SDF-1 and does not accelerate intestinal neoplasia formation in *ApcMin*/+ mice fed a high-fat diet. *Oncol Lett*. 2017 Oct;14(4):4355-4360. doi: 10.3892/ol.2017.6698. Epub 2017 Aug 1. PMID: 28943949; PMCID: PMC5604155.
- [362] Cornelio CK, Cowart K, Perkins J, Alomar ME, Gayoso RP, Miranda AC, Phan AT, White RT. Real-World Cardiovascular Outcomes of GLP-1 Receptor Agonists in Women With Type 2 Diabetes and Breast Cancer. *Pharmacotherapy*. 2026 Apr;46(4):e70130. doi: 10.1002/phar.70130. PMID: 41801847.
- [363] Brown S, Tadros AB, Montagna G, Bell T, Crowley F, Gallagher EJ, Dayan JH. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may reduce the risk of developing cancer-related lymphedema following axillary lymph node dissection (ALND). *Front Pharmacol*. 2024 Sep 4;15:1457363. doi: 10.3389/fphar.2024.1457363. PMID: 39318780; PMCID: PMC11420520.
- [364] Santella C, Yin H, Hicks BM, Yu OHY, Bouganin N, Azoulay L. Weight-lowering Effects of Glucagon-like Peptide-1 Receptor Agonists and Detection of Breast Cancer Among Obese Women with Diabetes. *Epidemiology*. 2020 Jul;31(4):559-566. doi: 10.1097/EDE.0000000000001196. PMID: 32282437.
- [365] Bourou MZ, Matsas A, Valsamakis G, Vlahos N, Panoskaltsis T. The Potential Role of Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists as a Type of Conservative Treatment of Endometrial Cancer in Women of Reproductive Age: A Review of the Literature and a Call for Study. *Cureus*. 2024 Sep 18;16(9):e69678. doi: 10.7759/cureus.69678. PMID: 39429275; PMCID: PMC11489137.
- [366] Riedinger CJ, Sakach J, Maples JM, Fulton J, Chippior J, O'Donnell B, O'Malley DM, Chambers LM. Glucagon-like peptide-1 (GLP-1) receptor agonists for weight management: A review for the gynecologic oncologist. *Gynecol Oncol*. 2024 Nov;190:1-10. doi: 10.1016/j.ygyno.2024.07.008. Epub 2024 Aug 7. PMID: 39116625.
- [367] Kong W, Deng B, Shen X, John C, Haag J, Sinha N, Lee D, Sun W, Chen S, Zhang H, Clontz A, Hursting SD, Zhou C, Bae-Jump V. Tirzepatide as an innovative treatment strategy in a pre-clinical model of obesity-driven endometrial cancer. *Gynecol Oncol*. 2024 Dec;191:116-123. doi: 10.1016/j.ygyno.2024.10.004. Epub 2024 Oct 10. PMID: 39388742; PMCID: PMC12419173.
- [368] Hagemann AR, Hagemann IS, Mutch DG, Devor EJ, Malmrose PK, Zhang Y, Morrison AM, Thiel KW, Leslie KK. Enhancing Progestin Therapy with a Glucagon-Like Peptide 1 Agonist for the Conservative Management of Endometrial Cancer. *Cancers (Basel)*. 2025 Feb 10;17(4):598. doi: 10.3390/cancers17040598. PMID: 40002193; PMCID: PMC11853405.
- [369] Hsieh TYJ, Yen TT, Hacker MR, Dottino J, Esselen KM. Impact of GLP-1 RA plus progestin therapy on fertility-sparing management of endometrial intraepithelial neoplasia and endometrial cancer. *Gynecol Oncol*. 2026 Apr;207S:23-29. doi: 10.1016/j.ygyno.2026.03.010. PMID: 42000371.
- [370] Podder V, Coleman RL, Hagemann AR, Singhanian P, Powell MA, Herzog TJ, Slomovitz BM. Repositioning GLP-1 Receptor Agonists in Endometrial Cancer: Molecular Rationale, Preclinical Insights, and Translational

Opportunities. *Clin Cancer Res.* 2026 Feb 4;32(3):447-454. doi: 10.1158/1078-0432.CCR-25-2819. PMID: 41329840.

- [371] Rothman SM, Yin H, Yu OHY, Pollak M, Azoulay L. Incretin-Based Drugs and the Incidence of Endometrial Cancer Among People with Type 2 Diabetes: Active Comparator New-User Design. *Drug Saf.* 2025 Sep;48(9):1023-1033. doi: 10.1007/s40264-025-01551-8. Epub 2025 May 10. PMID: 40347221.
- [372] Tseng PT, Zeng BY, Hsu CW, Sun CK, Suen MW, Carvalho AF, Stubbs B, Chen YW, Chen TY, Lei WT, Chen PH, Chen JJ, Shiue YL, Zeng BS, Su KP, Liang CS. The gynecologic tumor risk related to GLP-1 receptor agonists and SGLT2 inhibitors use: a network meta-analysis of 91 randomized controlled trials. *J Hematol Oncol.* 2025 Nov 27;18(1):109. doi: 10.1186/s13045-025-01750-x. PMID: 41310711; PMCID: PMC12661836.
- [373] Yen TT, Hsieh TY, Lee GY, Toy EP, Wei JC, Tanner EJ. GLP-1 Receptor Agonists Plus Progestins and Endometrial Cancer Risk in Nonmalignant Uterine Diseases. *JAMA Netw Open.* 2026 Feb 2;9(2):e2558205. doi: 10.1001/jamanetworkopen.2025.58205. PMID: 41665904; PMCID: PMC12892152.
- [374] Moshayedi N, Clair K, Francoeur AA. Obesity management in the setting of endometrial cancer and hyperplasia: A narrative review. *Gynecol Oncol Rep.* 2025 Aug 24;61:101929. doi: 10.1016/j.gore.2025.101929. PMID: 40917133; PMCID: PMC12408227.
- [375] Violette CJ, Agarwal R, Mandelbaum RS, González JL, Hong KM, Roman LD, Klar M, Wright JD, Paulson RJ, Obermair A, Matsuo K. The potential role of GLP-1 receptor agonist targeting in fertility-sparing treatment in obese patients with endometrial malignant pathology: a call for research. *Expert Rev Anticancer Ther.* 2023 Apr;23(4):385-395. doi: 10.1080/14737140.2023.2194636. Epub 2023 Mar 28. PMID: 36944434.
- [376] Karkia R, Zahra E, Min C, Hirai K, Makarov E, Karteris E, Chatterjee J. Evaluating plasma adipokines and their cognate receptors as biomarkers for non-invasive diagnosis of endometrial cancer. *Biosci Rep.* 2025 Sep 22;45(9):517--29. doi: 10.1042/BSR20253508. PMID: 40902078; PMCID: PMC12599288.
- [377] Kosowska A, Gallego-Colon E, Garczorz W, Klych-Ratuszny A, Aghdam MRF, Woz Niak M, Witek A, Wróblewska-Czech A, Cygal A, Wojnar J, Francuz T. Exenatide modulates tumor-endothelial cell interactions in human ovarian cancer cells. *Endocr Connect.* 2017 Nov;6(8):856-865. doi: 10.1530/EC-17-0294. Epub 2017 Oct 17. PMID: 29042458; PMCID: PMC5682419.
- [378] He W, Yu S, Wang L, He M, Cao X, Li Y, Xiao H. Exendin-4 inhibits growth and augments apoptosis of ovarian cancer cells. *Mol Cell Endocrinol.* 2016 Nov 15;436:240-9. doi: 10.1016/j.mce.2016.07.032. Epub 2016 Aug 3. PMID: 27496641.
- [379] Liu J, Chen Z, Yang Q, Lin H, Wang S, Li M, Wang T, Zhao Z, Xu M, Chen Y, Xu Y, Lu J, Gong Q, Ning G, Wang L, Wang W, Bi Y, Zheng J. Mendelian randomization study of GLP-1R effects on ovarian cancer subtypes mediated by metabolic factors. *Commun Med (Lond).* 2026 Jan 12;6(1):113. doi: 10.1038/s43856-026-01379-y. PMID: 41526703; PMCID: PMC12901151.
- [380] Tang E, Zeng J, Shi X, Wang Y, Sun Y, Wu L. Subtype-Specific Causal Effects of Antidiabetic Drug Targets on Ovarian Cancer: Mendelian Randomization and Colocalization Evidence. *Int J Womens Health.* 2026 Mar 10;18:578124. doi: 10.2147/IJWH.S578124. PMID: 41835849; PMCID: PMC12988754.
- [381] Khan D, Sridhar A, Moffett CR. GLP-1R/NPY2R regulate gene expression, ovarian and adrenal morphology in HFD mice. *J Endocrinol.* 2025 Jan 10;264(2):e240189. doi: 10.1530/JOE-24-0189. PMID: 39692365; PMCID: PMC11798413.
- [382] Zhu XX, Feng ZH, Liu LZ, Zhang Y. Liraglutide suppresses the proliferation of endometrial cancer cells through the adenosine 5'-monophosphate (AMP)-activated protein kinase signaling pathway. *Chin Med J (Engl).* 2021 Jan 19;134(5):576-578. doi: 10.1097/CM9.0000000000001363. PMID: 33470656; PMCID: PMC7929608.
- [383] Li W, Gu Y, Liu S, Ruan F, Lv W. GLP1R inhibits the progression of endometrial carcinoma through activation of cAMP/PKA pathway. *J Clin Lab Anal.* 2022 Oct;36(10):e24604. doi: 10.1002/jcla.24604. Epub 2022 Aug 21. PMID: 35989517; PMCID: PMC9551121.
- [384] Zhang Y, Xu F, Liang H, Cai M, Wen X, Li X, Weng J. Exenatide inhibits the growth of endometrial cancer Ishikawa xenografts in nude mice. *Oncol Rep.* 2016 Mar;35(3):1340-8. doi: 10.3892/or.2015.4476. Epub 2015 Dec 8. PMID: 26648451.
- [385] Zhang Y, Cheng J, Li J, He J, Li X, Xu F. The GLP-1R Agonist Exendin-4 Attenuates Hyperglycemia-Induced Chemoresistance in Human Endometrial Cancer Cells Through ROS-Mediated Mitochondrial Pathway. *Front Oncol.* 2021 Dec 20;11:793530. doi: 10.3389/fonc.2021.793530. PMID: 34988025; PMCID: PMC8721044.
- [386] Kanda R, Hiraike H, Wada-Hiraike O, Ichinose T, Nagasaka K, Sasajima Y, Ryo E, Fujii T, Osuga Y, Ayabe T. Expression of the glucagon-like peptide-1 receptor and its role in regulating autophagy in endometrial cancer. *BMC Cancer.* 2018 Jun 15;18(1):657. doi: 10.1186/s12885-018-4570-8. PMID: 29907137; PMCID: PMC6003019.

- [387] Devis-Jauregui L, Eritja N, Davis ML, Matias-Guiu X, Llobet-Navàs D. Autophagy in the physiological endometrium and cancer. *Autophagy*. 2021 May;17(5):1077-1095. doi: 10.1080/15548627.2020.1752548. Epub 2020 May 13. PMID: 32401642; PMCID: PMC8143243.
- [388] Irons EE, Pfeil KA, Perez JA, van Besien K. Incidence of hematologic malignancies and mortality associated with GLP-1 receptor agonist and SGLT2 inhibitor use in type 2 diabetes mellitus: results of a retrospective cohort study of electronic health records. *EClinicalMedicine*. 2026 Jan 14;91:103749. doi: 10.1016/j.eclinm.2025.103749. PMID: 41583363; PMCID: PMC12830215.
- [389] Lin A, Ding Y, Li Z, Jiang A, Liu Z, Wong HZH, Cheng Q, Zhang J, Luo P. Glucagon-like peptide 1 receptor agonists and cancer risk: advancing precision medicine through mechanistic understanding and clinical evidence. *Biomark Res*. 2025 Mar 27;13(1):50. doi: 10.1186/s40364-025-00765-3. PMID: 40140925; PMCID: PMC11948983.
- [390] Lin PY, Zeng BS, Chen JJ, Zeng BY, Suen MW, Hung CM, Hsu CW, Stubbs B, Chen YW, Chen TY, Lei WT, Hsu SP, Shiue YL, Su KP, Li CT, Wang HY, Tseng PT, Liang CS. Agent-specific, histopathology-stratified hematologic malignancy risk among dpp-4 inhibitors, glp-1 receptor agonists, and SGLT2 inhibitors: a network meta-analysis of 270,471 participants. *J Hematol Oncol*. 2026 Apr 9;19(1):23. doi: 10.1186/s13045-026-01788-5. PMID: 41957612; PMCID: PMC13063595.
- [391] Grandhi N, Liu L, Wang M, Thomas T, Schoen M, Sanfilippo K, Gao F, Colditz GA, Carson KR, Janakiram M, Chang SH. Association between glucagon-like peptide-1 receptor agonist use and progression of monoclonal gammopathy of uncertain significance to multiple myeloma among patients with diabetes. *JNCI Cancer Spectr*. 2024 Nov 1;8(6):pkae095. doi: 10.1093/jncics/pkae095. PMID: 39514091; PMCID: PMC11643351.
- [392] Tentolouris A, Ntanas-Stathopoulos I, Filippatos C, Terpos E, Kastritis E, Duque ER, Dimopoulos MA, Gavriatopoulou M, Briasoulis A. GLP-1 receptor agonists in patients with MGUS: A real-world propensity-matched study. *Eur J Clin Invest*. 2026 Jan;56(1):e70140. doi: 10.1111/eci.70140. Epub 2025 Oct 22. PMID: 41123105.
- [393] Lopez DS, Abdelgadir O, Hernández-Pérez JG, Ernest D, Hong AS, DeSantis SM, Cowell LG, Almandoz JP, Messiah SE. GLP-1 RAs and Kidney Cancer Risk: Methodological Considerations in Active-Comparator Selection. *Diabetes Obes Metab*. 2026 Mar 19. doi: 10.1111/dom.70700. Epub ahead of print. PMID: 41852253.
- [394] Ebbesen MS, Kissow H, Hartmann B, Grell K, Gørløv JS, Kielsen K, Holst JJ, Müller K. Glucagon-Like Peptide-1 Is a Marker of Systemic Inflammation in Patients Treated with High-Dose Chemotherapy and Autologous Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2019 Jun;25(6):1085-1091. doi: 10.1016/j.bbmt.2019.01.036. Epub 2019 Feb 5. PMID: 30731250.
- [395] Pradhan R, Yu OHY, Platt RW, Azoulay L. Glucagon like peptide-1 receptor agonists and the risk of skin cancer among patients with type 2 diabetes: Population-based cohort study. *Diabet Med*. 2024 Apr;41(4):e15248. doi: 10.1111/dme.15248. Epub 2023 Nov 10. PMID: 37876318.
- [396] Feng H, Shang S, Chen K, Sun X, Yue X. Impact of metformin on melanoma: a meta-analysis and systematic review. *Front Oncol*. 2024 May 23;14:1399693. doi: 10.3389/fonc.2024.1399693. PMID: 38846983; PMCID: PMC11153730.
- [397] Haq Z, Mirza FN, Abdi P, Diaz MJ, Libby TJ. Metformin Use and Risk of Non-Melanoma Skin Cancer: A Propensity-Matched Case-Control Study. *J Drugs Dermatol*. 2024 Dec 1;23(12):1089-1095. doi: 10.36849/jdd.8249. PMID: 39630677.
- [398] Pimenta EM, Garza AE, Camp SY, Park J, Hoffman SE, Valderrábano L, Fu J, Bi K, Carson MT, Karam J, Titchen BM, Medjahed S, Khandekar MJ, Shannon E, Kang YJ, Coy S, Lin JR, Nag A, Thorner AR, Gibson WJ, Santagata S, Raut CP, Hornick JL, Merriam P, Solimini NL, George S, Demetri GD, Van Allen EM. Epigenetic dysregulation of metabolic programs mediates liposarcoma cell plasticity. *Sci Transl Med*. 2026 Jan 21;18(833):eadw4689. doi: 10.1126/scitranslmed.adw4689. Epub 2026 Jan 21. PMID: 41564157; PMCID: PMC13062979.
- [399] Honors MA, Kinzig KP. Chronic exendin-4 treatment prevents the development of cancer cachexia symptoms in male rats bearing the Yoshida sarcoma. *Horm Cancer*. 2014 Feb;5(1):33-41. doi: 10.1007/s12672-013-0163-9. Epub 2013 Oct 8. PMID: 24101584; PMCID: PMC3947106.