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Semaglutide and cancer: A systematic review and meta-analysis

Lakshmi Nagendra [a], Harish BG [b], Meha Sharma [c], Deep Dutta [d,*]

[a] Department of Endocrinology, JSS Academy of Higher Education and Research, Mysore, India
[b] Department of Anaesthesiology, JSS Academy of Higher Education and Research, Mysore, India
[c] Department of Rheumatology, Center for Endocrinology Diabetes Arthritis & Rheumatism (CEDAR) Superspeciality Healthcare, Dwarka, New Delhi, India
[d] Department of Endocrinology, Center for Endocrinology Diabetes Arthritis & Rheumatism (CEDAR) Superspeciality Healthcare, Dwarka, New Delhi, India

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ABSTRACT

Background: French national health care insurance system database has suggested 1–3 years use of glucagon like peptide-1 receptor agonists (GLP1RA) (exenatide, liraglutide and dulaglutide) may be linked with increased occurrence of thyroid cancer. Similar data on semaglutide is not-available. Hence, we undertook this systematic review to look at the safety of semaglutide focussing on different cancers.

Methods: Databases were searched for randomized controlled trials (RCTs) and real-world studies involving patients receiving semaglutide in the intervention-arm. Primary outcome was to evaluate the occurrence of pancreatic and thyroid cancers. Secondary outcomes were to the evaluate occurrence of any other malignancies or severe adverse-events.

Results: Data from 37 RCTs and 19 real-world studies having 16,839 patients in placebo-control group, 16,550 patients in active-control group and 13,330 patients in real-world studies were analysed. Compared to placebo, occurrence of pancreatic cancer [OR 0.25 (95%CI: 0.03–2.24); P = 0.21], thyroid cancer [OR 2.04 (95%CI: 0.33–12.61); P = 0.44; I^2 = 0%] and all neoplasms (benign, malignant and otherwise unspecified) [OR 0.95 (95% CI:0.62–1.45); P = 0.82; I^2 = 0%] was similar in the semaglutide group. Compared to active controls, occurrence of pancreatic cancer [OR 0.40 (95%CI:0.09–1.87); P = 0.26; I^2 = 0%], thyroid cancer [OR 1.19 (95% CI:0.15–9.66); P = 0.87; I^2 = 0%] and all neoplasms (benign, malignant and otherwise unspecified) [OR 0.91 (95% CI: 0.44–1.89); P = 0.79; I^2 = 0%] were similar in the semaglutide group. Real-world data analysis revealed single case each of pancreatic cancer and B-cell lymphoma.

Conclusion: Semaglutide use in RCTs and real-world studies was not associated with an increased risk of any types of cancer, and this conclusion is supported by a high grade of evidence.

1. Introduction

Gastrointestinal side effects are the most common and well-established side effects reported with the use of semaglutide, similar to other glucagon like peptide-1 receptor agonists (GLP1RA). A review of the United States Food and Drug Agency (USFDA) adverse event reporting system suggested gastrointestinal side effects were more likely in females, people with higher body mass index and middle-aged patients (18–65 years age) [1]. Data from a recently published nested case-control analysis of the French national health care insurance system database by Bezin et al. [2] analysing data from people living with type-2 diabetes (T2D) from 2006 to 2018 revealed that people treated with glucagon like peptide-1 receptor agonists (GLP1RA) for 1–3 years had an increased risk of all thyroid cancer (hazard ratio [HR] 1.58; 95% CI: 1.27–1.95) and specifically even higher risks of medullary thyroid cancer (HR 1.78; 95%CI: 1.04–3.05). This analysis was primarily based on data coming from use of exenatide, liraglutide and dulaglutide [2].

Since injectable and oral semaglutide was approved by USFDA in December 2017 and September 2019 only, and was available for clinical use across the globe even later, data from semaglutide was missing from the nested case-control analysis by Bezin et al. [2]. An analysis of aggregated electronic health record database (Explorys) at Ohio USA for data from January 2005 till June 2019 (619,340 and 64,230 patients in the metformin and GLP1RA respectively) by Wang et al. [3] revealed significantly lower incident risk of prostate cancer [adjusted odds ratio (aOR) 0.81; p = 0.03)], lung cancer (aOR 0.81; p = 0.05), and colon

* Corresponding author. Center for Endocrinology, Diabetes, Arthritis & Rheumatism (CEDAR) Super-speciality Healthcare, Dwarka, New Delhi, 110075, India.
E-mail addresses: drlakshminagendra@gmail.com, drlakshminagendra@jssuni.edu.in (L. Nagendra), bgharish07@gmail.com (H. BG), docmsharma@gmail.com (M. Sharma), deepdutta2000@yahoo.com (D. Dutta).

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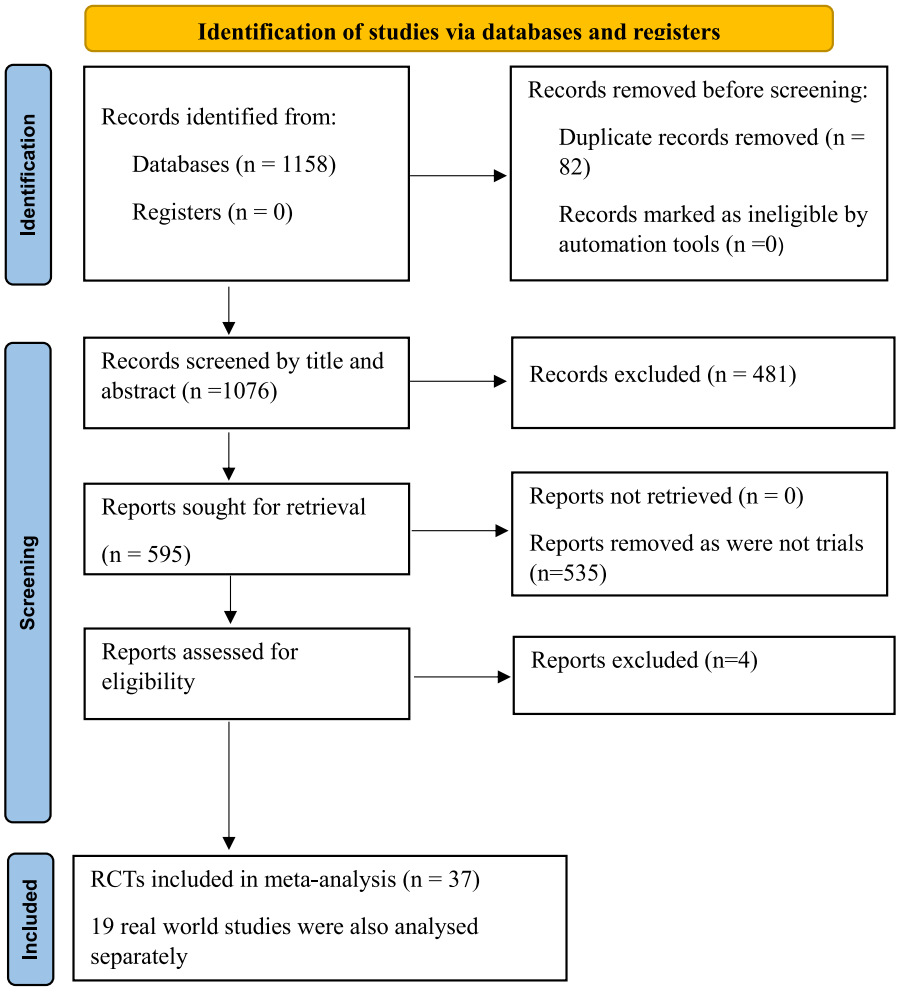

Fig. 1. Flowchart elaborating on study retrieval and inclusion in this systematic review.

cancer (aOR 0.85; p = 0.03), but increased risks for thyroid cancer (aOR 1.65; p < 0.01). The analysis by Wang et al. [3] was also primarily based on data coming from use of exenatide, liraglutide and dulaglutide. A review of all reported cases of thyroid cancer under European pharmacovigilance database (EudraVigilance) with regards to GLP1RA since their approval for clinical use in Europe till January 2020 noted increased risks for thyroid cancer with liraglutide followed by exenatide and lastly dulaglutide [4]. In a meta-analysis reviewing data from 52 trials (48,267 patients on GLP1RA vs. 40,755 controls), use of GLP1RA was not associated with increased risk of breast cancer (relative risk [RR] 0.98; 95%CI: 0.76–1.26) [5]. Analysis of data from 43 trials using GLP1RA for >52 weeks did not note any increased risk for pancreatitis (OR 1.24; 95%CI: 0.94–1.64; P = 0.13) and pancreatic cancer (OR 1.28; 95%CI:0.87–1.89; P = 0.20) ([6]). A review of data from 113 trials using different GLP1RA, a significantly increased risk of cholelithiasis (OR 1.30; 95% CI:1.01–1.68, P = 0.041) was noted with the use of GLP1RA [7].

Extensive literature review revealed that till date, 22 systematic reviews/meta-analysis/network meta-analysis have been published evaluating different aspects of use of injectable/oral semaglutide in clinical practice, primarily focussing on glycaemic control in T2D, as a weight loss medicine in people with or without T2D and as a medication against metabolic-dysfunction associated steatotic liver disease (MASLD) (Supplementary Table-1) [8–29]. However surprisingly, only one of the systematic reviews (Supplementary Table-1) looked at the risk of cancer with use of semaglutide [15]. Since then, many more RCTs have been published with semaglutide. Also, a lot of real-world studies have also been published from different countries elaborating on their experience of use of semaglutide in clinical practice. Hence the aim of this systematic review and meta-analysis was to look at the safety profile of semaglutide focussing on the risks of occurrence of different cancers.

2. Methods

The systematic review was done using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The pre-written protocol for the systematic review has been registered with PROSPERO having a registration number of CRD42023425828 ([30]). RCTs involving people receiving injectable or oral semaglutide in the study group and placebo/any other medication in the control group were considered for this systematic review. The primary outcome was to evaluate the occurrence of pancreatic cancers and thyroid cancers. The secondary outcomes were to evaluate the occurrence of any other types of malignancies or any other severe adverse events (SAEs). We did not separately analyse all the different types of treatment-emergent adverse events (TAEs) as the common side effects, specifically different types of gastro-intestinal side effects of GLP1RAs including semaglutide is already well known. Analysis was done separately for controls receiving placebo defined as placebo control group (PCG), and for controls receiving other anti-diabetes medications defined as active control group (ACG).

Table-1
Summary of all the major side effect profile from randomized controlled trials on semaglutide vs passive control group published till April 2023.

Author; Year	Number of patients; Condition	Major side effects noted	Data on cancer
Aroda et al. [36] 2019/PIONEER 1	Semaglutide: 525 Placebo: 178 T2D	Semaglutide: severe hypoglycaemia: 8; pancreatitis 0; retinopathy 9; AKI 1; Placebo: severe hypoglycaemia: 1; pancreatitis 0; retinopathy 3; AKI 1;	Semaglutide: PC 0; TC 0 Placebo: PC 0; TC 0
Pratley et al. [39] 2019/PIONEER 4	Semaglutide: 285 Placebo 142 T2D	Semaglutide: severe hypoglycaemia: 2; pancreatitis 0; retinopathy 8; AKI 0; Placebo: severe hypoglycaemia: 3; pancreatitis 1; retinopathy 2; AKI 1;	Semaglutide: PC 0; TC 1 Placebo: PC 0; TC 0
Mosenzon et al. [40] 2019/PIONEER 5	Semaglutide:163 Placebo: 161 T2D	Semaglutide: severe hypoglycaemia: 9; pancreatitis 0; retinopathy 5; AKI 3; Placebo: severe hypoglycaemia: 3; pancreatitis 0; retinopathy 2; AKI 1;	Semaglutide: PC 0; TC 0 Placebo: PC 0; TC 0
Husain et al. [41] 2019/PIONEER 6	Semaglutide:1591 Placebo: 1592 T2D	Semaglutide: severe hypoglycaemia: 0; pancreatitis 1; retinopathy 93; AKI 32; Placebo: severe hypoglycaemia: 0; pancreatitis 3; retinopathy 76; AKI 37;	Semaglutide: PC 0; TC 0 Placebo: PC 0; TC 0
Zinman et al. [43] 2019/PIONEER 8	Semaglutide:547 Placebo: 184 T2D	Semaglutide: severe hypoglycaemia: 147; pancreatitis 0; retinopathy 24; AKI 3; Placebo: severe hypoglycaemia: 54; pancreatitis 0; retinopathy 8; AKI 0;	Semaglutide: PC 0; TC 0 Placebo: PC 0; TC 0
Yamada et al. [44] 2020/PIONEER 9	Semaglutide:146 Placebo: 49 T2D	Semaglutide: severe hypoglycaemia:0; pancreatitis 0; retinopathy 2; AKI 0; Placebo: severe hypoglycaemia: 0; pancreatitis 0; retinopathy 2; AKI 0;	Semaglutide: PC 0; TC 1 Placebo: PC 0; TC 0
Wilding et al. [58] 2021/STEP 1	Semaglutide:1306 Placebo: 655 Obesity	Semaglutide:Severe hypoglycaemia: 8; pancreatitis:3; AKI 3 Placebo: Severe hypoglycaemia: 5; pancreatitis:0; AKI:2	Semaglutide: Malignant neoplasms:14 Placebo: Malignant neoplasms: 7
Davies et al. [59] 2021/STEP 2	Semaglutide:805 Placebo: 402 Obesity	Semaglutide: severe hypoglycaemia:45; pancreatitis 1; retinopathy 27; AKI 6; Placebo: severe hypoglycaemia: 12; pancreatitis 1; retinopathy 11; AKI 2;	Semaglutide: Malignant neoplasms:12; Placebo: Malignant neoplasms: 8
Wadden et al. [60] 2021/STEP 3	Semaglutide:407 Placebo: 204 Obesity	Semaglutide: severe hypoglycaemia:2; pancreatitis 0; AKI 0; Placebo: severe hypoglycaemia: 0; pancreatitis 0; AKI 0;	Semaglutide: Malignant neoplasms:3; Placebo: Malignant neoplasms: 1
Rubino et al. [61] 2021/STEP 4	Semaglutide:535 Placebo: 268 Obesity	Semaglutide: severe hypoglycaemia:3; pancreatitis 0; AKI 1; Placebo: severe hypoglycaemia: 3; pancreatitis 0; AKI 1;	Semaglutide: Malignant neoplasms:6; Placebo: Malignant neoplasms: 1
Garvey et al. [62] 2022/STEP 5	Semaglutide:152 Placebo: 152 Obesity	Semaglutide: severe hypoglycaemia:4; pancreatitis 0; AKI 0; Placebo: severe hypoglycaemia: 0; pancreatitis 0; AKI 0;	Semaglutide: Malignant neoplasms:2; Placebo: Malignant neoplasms: 4
Kadowaki et al. [63] 2022/STEP 6	Semaglutide:152 Placebo: 152 Obesity	Semaglutide: severe hypoglycaemia:0; pancreatitis 0; AKI 2; Placebo: severe hypoglycaemia: 0; pancreatitis 0; AKI 0;	Semaglutide: Malignant neoplasms:2; Placebo: Malignant neoplasms: 1
Rubino et al. [65] 2022/STEP 8	Semaglutide:126 Placebo: 85 Obesity	Semaglutide: severe hypoglycaemia:0; pancreatitis 0; AKI 1; Placebo: severe hypoglycaemia: 0; pancreatitis 0; AKI 1;	Semaglutide: Malignant neoplasms: 3; Placebo: Malignant neoplasms: 1
Weghuber et al. [64] 2022/STEP TEENS	Semaglutide:133 Placebo: 67 Obesity	Semaglutide: Fatal adverse events 0 Placebo: Fatal adverse events 0	Semaglutide: Malignant neoplasms:0; Placebo: Malignant neoplasms:0
Sorli et al. [46] 2017/SUSTAIN 1	Semaglutide:258 Placebo: 129 T2D	Semaglutide: severe hypoglycaemia:0; pancreatitis 0; retinopathy 0; AKI 0; Placebo: severe hypoglycaemia: 3; pancreatitis 0; retinopathy 3; AKI 0;	Semaglutide: PC 0; TC 1 Placebo: PC 0; TC 0
Rodbard et al. [50] 2018/SUSTAIN 5	Semaglutide:263 Placebo: 133 T2D	Semaglutide: severe hypoglycaemia:25; pancreatitis 0; retinopathy 0; AKI 0; Placebo: severe hypoglycaemia: 7; pancreatitis 0; retinopathy 0; AKI 0;	Semaglutide: PC 0; TC 0 Placebo: PC 0; TC 0
Marso et al. [51] 2016/SUSTAIN 6	Semaglutide:1648 Placebo: 1649 T2D	Semaglutide: severe hypoglycaemia:369; pancreatitis 9; retinopathy 50; AKI 65; Placebo: severe hypoglycaemia: 350; pancreatitis 12; retinopathy 29; AKI 34;	Semaglutide: PC 1; TC 0 Placebo: PC 4; TC 0
Zinman et al. [54] 2019/SUSTAIN 9	Semaglutide:151 Placebo: 151 T2D	Semaglutide: severe hypoglycaemia:17; pancreatitis 0; retinopathy 3; AKI 1; Placebo: severe hypoglycaemia: 3; pancreatitis 0; retinopathy 8; AKI 0;	Semaglutide: PC 0; TC 0 Placebo: PC 4; TC 0
Loomba et al. [68] 2023	Semaglutide:47 Placebo: 24 NASH- related cirrhosis	Semaglutide: severe hypoglycaemia:0; severe GI disorders 3; AKI 1; Placebo: severe hypoglycaemia: 0; severe GI disorders 2; AKI 0;	Semaglutide: Malignant neoplasms:0; Placebo: Malignant neoplasms: 0
Newsome et al. [69] 2022	Semaglutide:239 Placebo: 80 NASH	Semaglutide: severe hypoglycaemia:0; severe GI disorders 8; AKI 0; Placebo: severe hypoglycaemia: 0; severe GI disorders 0; AKI 0;	Semaglutide: Malignant neoplasms:3; Placebo: Malignant neoplasms: 0

(*continued on next page*)

Table-1 (*continued*)

Author; Year	Number of patients; Condition	Major side effects noted	Data on cancer
O'Neil et al. [70] 2018	Semaglutide:718 Placebo: 136 Obesity	Semaglutide: severe hypoglycaemia:41; Pancreatitis:3; AKI 0; Placebo: severe hypoglycaemia: 8; Pancreatitis:1; AKI 0;	Semaglutide: Malignant neoplasms:12; Placebo: Malignant neoplasms:4

AKI: Acute kidney injury; NASH: Non-alcoholic steatohepatitis; PC: Pancreatic cancer; TC: Thyroid cancer; T2D: Type 2 Diabetes mellitus; GI: gastrointestinal; PIONEER: Peptide Innovation for Early Diabetes Treatment; SUSTAIN: Semaglutide Unabated Sustainability in Treatment of Type-2 Diabetes; STEP: Semaglutide Treatment Effect in People with obesity.

We systematically searched PubMed (Medline) with key-words or MESH terms: (semaglutide) OR (injectable semaglutide) OR (oral semaglutide). We then searched Embase using the following search strategy: 'semaglutide' OR 'injectable semaglutide' OR 'oral semaglutide'. Thereafter we searched Cochrane database using: "semaglutide" OR "injectable semaglutide" OR "oral semaglutide". A check search was also done on CNKI database, clinicaltrials.gov, ctri.nic.in, and Google scholar to ensure that we have not missed out on any relevant article. Methodologic details have been elaborated in previous meta-analysis published by our group [31]. The risk of bias assessment was done by 3 authors using the risk of bias assessment tool in Review Manager (Revman) Version 5.4 software. The different types of bias looked for have been elaborated in a previous metanalyses by our group [31,32]. Random effect model for analysis. Forest plots generated for all the different outcomes were used to assess heterogeneity. We specifically used Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test [33]. The details of heterogeneity analysis have been elaborated in previous published meta-analysis [32]. The grading/certainty of the evidence of the major outcome was done using Grades of Recommendation, Assessment, Development and Evaluation approach [34], with procedural details elaborated in a previous publication by us [31]. Publication bias was assessed by plotting Funnel Plots [34,35], elaborated in supplementary figure-1. Key outcomes table was generated using the GRADE software (https://gdt.gradepro.org/app/).

3. Results

A total of 1158 articles were found after the initial search (Fig. 1). Following removal of duplicates (82 articles), screening of the titles and abstracts, the search was reduced down to 595 studies which were evaluated in detail for inclusion in this systematic review (Fig. 1). As per the inclusion and exclusion criteria, we analysed data from the Peptide Innovation for Early Diabetes Treatment (PIONEER) series of RCTs (10 RCTs) [36–45], Semaglutide Unabated Sustainability in Treatment of Type-2 Diabetes (SUSTAIN) series of RCTs (12 RCTs) [46–57], 8 Semaglutide Treatment Effect in People with obesity (STEP) series of RCTs [58–65], 7 other RCTs [66–72] and 19 real world studies for analysis in our study [73–92]. Data from RCTs involving semaglutide in comparison to PCG (n = 16,839) and ACG (n = 16,559) have been elaborated separately in Table-1 and Table-2 respectively. Real world studies (n = 13,330) have been elaborated in Table-4.

The summaries of risk of bias of the studies have been elaborated in Fig. 2a and b. Selection bias, attrition bias and, reporting bias, allocation concealment bias, detection bias was judged to be at low risk of bias in all the 37 RCTs (100%). Performance bias was judged to be at low risk of bias in 27 out of 37 RCTs (72.97%). Source of funding, especially pharmaceutical and conflict of interests were considered under "other bias" section which was found to be at high risk in all the 37 RCTs (100%) (Fig. 2a,b)

3.1. Effect of semaglutide on primary and secondary outcomes

3.1.1. Semaglutide vs passive control group

Data from 21 RCTs involving 16,839 people either on semaglutide or placebo was analysed to find out the impact of semaglutide on the occurrence of cancers. As compared to placebo, the occurrence of pancreatic cancer [OR 0.25 (95% CI: 0.03–2.24); P = 0.21; high certainty of evidence (HCE); Fig. 3a], thyroid cancer [OR 2.04 (95% CI: 0.33–12.61); P = 0.44; I^2 = 0% (Low heterogeneity(LH)); HCE; Fig. 3b] and all neoplasms (benign, malignant and otherwise unspecified) [OR 0.95 (95% CI: 0.62–1.45); P = 0.82; I^2 = 0% (LH); HCE); Fig. 3c] was similar in the semaglutide group.

3.1.2. Semaglutide vs active control group

Data from 19 studies involving 16,559 people either on semaglutide or active controls was analysed to find out the impact of semaglutide on the occurrence of cancers. As compared to active controls (other diabetes medications), the occurrence of pancreatic cancer [OR 0.40 (95% CI: 0.09–1.87); P = 0.26; I^2 = 0% (LH); HCE; Fig. 4a], thyroid cancer [OR 1.19 (95% CI: 0.15–9.66); P = 0.87; I^2 = 0% (LH); HCE; Fig. 4b] and all neoplasms (benign, malignant and otherwise unspecified) [OR 0.91 (95% CI: 0.44–1.89); P = 0.79; I^2 = 0% (LH); HCE; Fig. 4c] was similar in the semaglutide group.

Funnel plots were plotted to evaluate of the presence of publication bias, and have been elaborated in Supplementary Fig. 1. Summary of findings of the key outcomes of this study have been elaborated in Table-3. The summary of finding table highlights that the odds ratio for thyroid cancer, pancreatic cancer and all neoplasms were not increased with the use of semaglutide as compared to both placebo controls and active controls, an observation supported by a high grade of evidence (Table-3).

3.1.3. Semaglutide in real world studies

Data from 19 real world studies involving 13,330 patient was analysed to look at the occurrence of cancer during the course of the studies (Table-4) (73–92). All of these were single arm studies from different parts of the globe. Only a single patient with pancreatic cancer and another patient with B-cell lymphoma was documented in these 13,330-patient having a follow up duration ranging from 30 weeks to 18 months (Table-4). There were no reports of thyroid cancer or specifically medullary thyroid carcinoma. 381 patients (2.86%) had to prematurely discontinue the treatment during the course of the study due to adverse events (Table-4). There were 5 reports of pancreatitis, 5 reports of severe hypoglycaemia and 2 deaths from the analysis of data from 13,330 patients. The occurrence of different cardiovascular events during the real-world studies have been elaborated in Table-4.

4. Discussion

Diabetes per se has been recognised as an independent risk factor for cancer incidence as well as mortality [93]. Although the mechanism is still not well established, persistent hyperglycemia, hyperinsulinemia with insulin resistance, increased circulating levels of different growth factors and inflammatory cytokines are believed to have some role [93]. Virtually, almost every medication used for the treatment for diabetes have been linked with cancer at one point of time or other. Pioglitazone at one point of time was linked with bladder cancer. However subsequent data published in the last few years have been more reassuring. A review of Chang Gung Research Database in Taiwan from January 2016 till December 2019, involving 97,024 people living with T2D receiving

Table-2
Summary of all the major side effect profile from randomized controlled trials on semaglutide vs active control group published till April 2023.

Author; Year	Number of patients; Condition	Major side effects noted	Data on cancer
Rodbard et al. [37] 2019/PIONEER 2	Semaglutide: 175 Empagliflozin: 178 T2D	Semaglutide: severe hypoglycaemia: 7; pancreatitis 1; retinopathy 14; AKI 2; Empagliflozin: severe hypoglycaemia: 8; pancreatitis 1; retinopathy 5; AKI 1;	Semaglutide: PC 0; TC 0 Empagliflozin: PC 0; TC 0
Rosenstock et al. [38] 2019/PIONEER 3	Semaglutide: 1397 Sitagliptin: 467 T2D	Semaglutide: severe hypoglycaemia: 83; pancreatitis 3; retinopathy 14; AKI 10; Sitagliptin: severe hypoglycaemia: 39; pancreatitis 1; retinopathy 5; AKI 3;	Semaglutide: PC 1; TC 0 Sitagliptin: PC 1; TC 0
Pratley et al. [39] 2019/PIONEER 4	Semaglutide: 285 Liraglutide: 284 T2D	Semaglutide: severe hypoglycaemia: 2; pancreatitis 0; retinopathy 8; AKI 0; Liraglutide: severe hypoglycaemia: 7; pancreatitis 1; retinopathy 4; AKI 1;	Semaglutide: PC 0; TC 1 Liraglutide: PC 1; TC 1
Pieber et al. [42] 2019/PIONEER7	Semaglutide: 253 Sitagliptin: 251 T2D	Semaglutide: severe hypoglycaemia: 14; pancreatitis 0; retinopathy 6; AKI 1; Sitagliptin: severe hypoglycaemia: 14; pancreatitis 0; retinopathy 6; AKI 0;	Semaglutide: PC 0; TC 0 Sitagliptin: PC 0; TC 0
Yamada et al. [44] 2020/PIONEER 9	Semaglutide: 146 Liraglutide: 48 T2D	Semaglutide: severe hypoglycaemia: 0; pancreatitis 0; retinopathy 2; AKI 0; Liraglutide: severe hypoglycaemia: 2; pancreatitis 0; retinopathy 0; AKI 0;	Semaglutide: PC 0; TC 1 Liraglutide: PC 0; TC 0
Yabe et al. [45] 2020/PIONEER 10	Semaglutide: 393 Dulaglutide: 65 T2D	Semaglutide: severe hypoglycaemia: 10; pancreatitis 0; retinopathy 28; AKI 0; Dulaglutide: severe hypoglycaemia: 0; pancreatitis 0; retinopathy 3; AKI 0;	Semaglutide: PC 0; TC 1 Dulaglutide: PC 0; TC 0
Frias et al. [72] 2021/SURPASS 2	Semaglutide: 469 Tirzepatide: 1409 T2D	Semaglutide: severe hypoglycaemia: 2; pancreatitis 4; Tirzepatide: severe hypoglycaemia: 0; pancreatitis 3;	Semaglutide: PC 0; TC 1 Tirzepatide: PC 0; TC 0
Ahren et al. [47] 2017/SUSTAIN 2	Semaglutide: 818 Sitagliptin: 407 T2D	Semaglutide: severe hypoglycaemia: 9; pancreatitis 4; retinopathy 1; AKI 0; Sitagliptin: severe hypoglycaemia: 5; pancreatitis 0; retinopathy 3; AKI 0;	Semaglutide: PC 0; TC 1 Sitagliptin: PC 0; TC 0
Ahmann et al. [48] 2017/SUSTAIN 3	Semaglutide: 404 Exenatide: 405 T2D	Semaglutide: severe hypoglycaemia: 33; pancreatitis 2; retinopathy 0; AKI 0; Exenatide: severe hypoglycaemia: 33; pancreatitis 3; retinopathy 0; AKI 0;	Semaglutide: PC 0; TC 0 Exenatide: PC 0; TC 0
Aroda et al. [49] 2017/SUSTAIN 4	Semaglutide: 722 Insulin glargine: 360 T2D	Semaglutide: severe hypoglycaemia: 36; pancreatitis 2; retinopathy 4; AKI 0; Insulin glargine: severe hypoglycaemia: 38; pancreatitis 0; retinopathy 1; AKI 0;	Semaglutide: PC 1; TC 0 Insulin glargine: PC 0; TC 0
Pratley et al. [52] 2017/SUSTAIN 7	Semaglutide: 601 Dulaglutide: 600 T2D	Semaglutide: severe hypoglycaemia: 7; pancreatitis 2; retinopathy 4; AKI 0; Dulaglutide: severe hypoglycaemia: 8; pancreatitis 0; retinopathy 5; AKI 0;	Semaglutide: PC 0; TC 1 Dulaglutide: PC 0; TC 1
Lingvay et al. [53] 2019/SUSTAIN 8	Semaglutide: 394 Canagliflozin: 394 T2D	Semaglutide: severe hypoglycaemia: 53; pancreatitis 0; retinopathy 9; AKI 4; Canagliflozin: severe hypoglycaemia: 32; pancreatitis 0; retinopathy 15; AKI 0;	Semaglutide: PC 0; TC 0 Canagliflozin: PC 0; TC 0
Capehorn et al. [55] 2019/SUSTAIN 10	Semaglutide: 290 Liraglutide: 287 T2D	Semaglutide: severe hypoglycaemia: 5; pancreatitis 0; retinopathy 3; AKI 0; Liraglutide: severe hypoglycaemia: 7; pancreatitis 2; retinopathy 4; AKI 0;	Semaglutide: PC 0; TC 0 Liraglutide: PC 0; TC 0
Kellerer et al. [56] 2022/SUSTAIN11	Semaglutide:874 Insulin aspart: 864 T2D	Semaglutide: Fatal adverse events: 12 Insulin aspart: Fatal adverse events: 1	Semaglutide: All neoplasms: 6 Insulin aspart: All neoplasmas: 1
Rubino et al. [65] 2022/STEP 8	Semaglutide: 126 Liraglutide: 127 Obesity	Semaglutide: severe hypoglycaemia: 0; pancreatitis 0; AKI 1 Liraglutide: severe hypoglycaemia: 1; pancreatitis 1; AKI 0	Semaglutide: Malignant neoplasms: 3 Liraglutide: malignant neoplasms: 3
Ji et al. [66] 2021	Semaglutide: 578 Sitagliptin: 290 T2D	Semaglutide: severe hypoglycaemia: 8; pancreatitis 1; retinopathy 33; AKI 0; Sitagliptin: severe hypoglycaemia: 4; pancreatitis 0; retinopathy 10; AKI 0;	Semaglutide: PC 0; TC 0 Sitagliptin: PC 0; TC 0
O'Neil et al. [70] 2018	Semaglutide: 718 Liraglutide: 103 T2D	Semaglutide: severe hypoglycaemia: 41; pancreatitis 3; Liraglutide: severe hypoglycaemia: 4; pancreatitis 0;	Semaglutide: Malignant neoplasms: 12 Liraglutide: malignant neoplasms: 3
Seino et al. [71] 2017	Semaglutide: 105 Sitagliptin: 103 T2D	Semaglutide: severe hypoglycaemia: 1; pancreatitis 0; retinopathy 6; AKI 0; Sitagliptin: severe hypoglycaemia: 0; pancreatitis 0; retinopathy 4; AKI 0;	Semaglutide: PC 0; TC 0 Sitagliptin: PC 1; TC 0
Kaku et al. [67] 2017	Semaglutide: 480 Additional OAD: 121 T2D	Semaglutide: severe hypoglycaemia: 9; pancreatitis 0; retinopathy 27; AKI 0; Additional OAD: severe hypoglycaemia: 2; pancreatitis 0; retinopathy 6; AKI 0;	Semaglutide: PC 0; TC 0 Additional OAD: PC 0; TC 0

AKI: Acute kidney injury; OAD: Oral anti-diabetes drug; PC: Pancreatic cancer; TC: Thyroid cancer; T2D: Type 2 Diabetes mellitus; GI: gastrointestinal; PIONEER: Peptide Innovation for Early Diabetes Treatment; SUSTAIN: Semaglutide Unabated Sustainability in Treatment of Type-2 Diabetes; STEP: Semaglutide Treatment Effect in People with obesity.

Table-3
Summary of findings of the key outcomes of this metanalysis.

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)
	Risk with PCG	Risk Semaglutide			
Thyroid cancer	0 per 1000	0 per 1000 (0–0)	OR 2.04 (0.33–12.61)	11823 (11 RCTs)	⨁⨁⨁⨁ High
Pancreatic cancer	1 per 1000	0 per 1000 (0–2)	OR 0.25 (0.03–2.24)	9945 (10 RCTs)	⨁⨁⨁⨁ High
All neoplasms	5 per 1000	5 per 1000 (3–8)	OR 0.95 (0.62–1.45)	16839 (21 RCTs)	⨁⨁⨁⨁ High
Outcomes	Risk with ACG	Risk with Semaglutide	Relative effect (95% CI)	N° of participants (studies)	Certainty of the evidence (GRADE)
Thyroid cancer	0 per 1000	0 per 1000 (0–2)	OR 1.19 (0.15–9.66)	13170 (16 RCTs)	⨁⨁⨁⨁ High
Pancreatic cancer	1 per 1000	0 per 1000 (0–1)	OR 0.40 (0.09–1.87)	11869 (15 RCTs)	⨁⨁⨁⨁ High
All neoplasms	1 per 1000	1 per 1000 (1–3)	OR 0.91 (0.44–1.89)	16559 (19 RCTs)	⨁⨁⨁⨁ High

[a] The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); CI: confidence interval; OR: odds ratio; ACG: active control group; PCG: placebo control group.

pioglitazone and SGLT2i in different permutations and combinations did not document any increased risk of bladder cancer over 2.8 years of clinical use. In a meta-analysis analysing data from 77 RCTs, comprising 45,162 and 43,811 patients on SGLT2i and controls respectively, the use of SGLT2i was not associated with any increased risk of malignancies [RR = 1.05, 95% CI = 0.97–1.14, P = 0.20] [94]. The same has been replicated in 2 other meta-analysis involving smaller number of RCTs [95,96].

GLP1RA has also been linked with different cancers at different points of time. However, a recently published multicentric retrospective cohort study from Virginia USA analysing data from 492,760 patients started in GLP1RA as compared to 918,711 patients started on metformin between 2006 and 2021 in people with obesity and/or T2D noted significantly lower risks for pancreatic cancer with use of GLP1RA [HR 0.47; 95%CI: 0.42–0.52], providing us with reassuring data against pancreatic cancer with use of GLP1RA [97]. In another recently published systematic review and meta-analysis reviewing data from observational studies, incretin-based therapies were not linked with pancreatic cancer [98].

Thompson et al. [99] have suggested that the increased risk of thyroid cancers with use of GLP1RA (exenatide, liraglutide and dulaglutide) as reported by Bezin et al., should be taken in the context that diabetes per se is associated with increased risk of thyroid cancer by 20–30%, detection bias (overdiagnosis) for picking up well differentiated papillary thyroid micro-carcinoma due to increased surveillance in the clinical trial settings; absolute increase in risk of thyroid cancer being very small due to

Table-4
Summary of all the major side effect profile from real world studies published on semaglutide till April 2023.

Author; Year	Number of patients; Condition	Major side effects noted	Data on cancer
Napoli et al. [73]; 2023; Italy	579 pts; 30 weeks; T2D	Severe hypoglycaemia = 0; Cardiac disorders = 13	N/A
Mohammedi et al. [74]; 2023; France	497 pts; 30 weeks; T2D	Pancreatitis = 3; Discontinuation = 43	N/A
Berra et al. [75]; 2023; Italy	594 pts; 1 year follow-up; T2D	elevated lipase = 3; elevated amylase = 1; intolerance = 1; severe hypoglycaemia = 1; mild hypoglycaemic = 0.5%	N/A
Menzen et al. [76]; 2023; Germany	669 pts; 30 weeks follow-up; T2D	Hypoglycaemia = 18; discontinuation = 44; SAE = 3; pancreatitis = 1	N/A
Wolffenbuttel et al. [77]; 2023; Netherlands	211 pts; 1-year; T2D	Cholecystitis = 1; SAEs = 14; Discontinuation = 8; Hypoglycaemia = 14; severe hypoglycaemia = 1	N/A
Flor et al., 2022 [78]; Spain	3 pts on hemodialysis	N/A	N/A
Volpe et al. [79]; 2022; Italy	48 pts; 52 weeks; MASLD in T2D	N/A	N/A
Lucas et al. [80]; 2022; Spain	166 pts; 24 months; T2D	Stroke = 1; Myocardial infarction = 1; Severe hypoglycaemia = 0.2%	N/A
Bellido et al. [81]; 2022; Spain	227 pts; 30 weeks; T2D	Atrial fibrillation, left ventricular failure, and AMI = 2; death following AMI = 1; Discontinuation = 1	N/A
Yamada et al. [82]; 2022	77 pts; 6 months; T2D	Hypoglycaemia = 0; Discontinuation = 0	N/A
Blanco et al. [83]; 2022; Spain	117 pts; 53 weeks; T2D	Hypoglycemia = 0; Discontinuation = 17;	N/A
Fererro et al. [84]; 2022; Italy	154 pts; 12 months; T2D	Discontinuation = 15.1% (n = 23)	N/A
Holmes et al. [85]; 2021; UK	215 pts; 30 weeks; T2D	Discontinuation = 22; SAE = 8; Pancreatitis = 1; Sudden death = 1; Hypoglycaemia = 14; severe hypoglycaemia = 0	N/A
Hansen et al. [86]; 2021; Denmark	119 pts; 12 months; T2D	Stroke = 1; AMI = 1; Strangulated hernia = 1; Hypoglycaemia = 0; Pancreatitis = 0	Nil
Ekberg et al. [87]; 2021; Sweden	331; 30 weeks; T2D	Gastrointestinal haemorrhage = 1; Severe hypoglycaemia = 1	pancreatic cancer and death = 1; B-cell lymphoma = 1
Yale et al. [88]; 2021; Canada	452; 30 weeks; T2D	SAEs = 9; Discontinuation = 10; Severe hypoglycaemia = 1; Death-1	N/A
Visaria et al. [89]; 2021; USA	1888; 18 months; T2D	N/A	N/A
Jain et al. [90]; 2021; Canada	164; 6 months; T2D	Discontinuation = 17	N/A
Mody et al. [91]; 2021; USA (91)	3852; 11 months; T2D	N/A	N/A
Brown et al. [92]; 2021; Canada	2967; 18 months; T2D	Discontinuation = 196	N/A

RCT: randomized controlled trial; Meta: meta-analysis; SR: systematic review; T2D: type-2 diabetes; * evaluated only oral semaglutide; sc: subcutaneous; MASLD: metabolic dysfunction associated steatotic liver disease; N/A: not available; AMI: acute myocardial infarction; SAE: severe adverse events; N/A: not available.

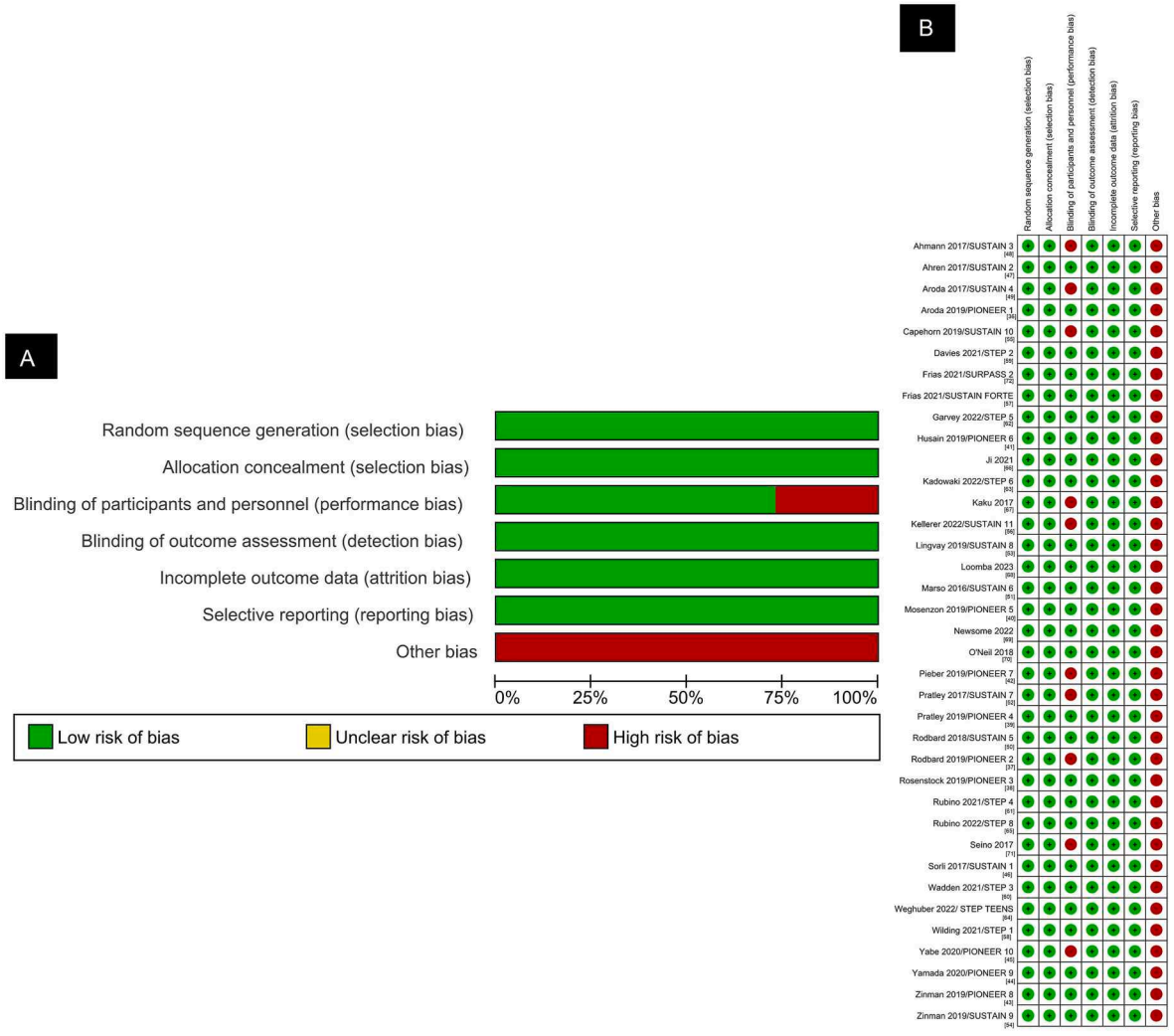

Fig. 2. (2A) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (2B) Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

very low incidence of thyroid cancer, in contrast to a much greater quantum of benefit in cardiovascular risk reduction in T2D, thus benefits largely outweighing the harm. The observations of Thompson et al. [99] is supported by a previous publication evaluating the risk of thyroid cancer with the use of liraglutide in USA by analysing data from commercially insured population from 2010 to 2014 [100]. In that study, Funch et al. [100] noted that the risk of thyroid cancer with use of liraglutide vs metformin was not increased [OR 1.00 (95%CI: 0.56–1.79). Review of medical records revealed that 85% of all documented thyroid cancers were papillary thyroid carcinoma or a follicular variant of papillary thyroid carcinoma, of which 46% were thyroid microcarcinomas $\leq$10 mm in diameter, which were more prevalent in the liraglutide cohort (67% versus 43% in all comparators) [100]. Screening for such cancers has been discouraged as diagnosing and treating them offers no survival benefit. Medullary thyroid cancer is different from papillary thyroid cancer, has totally different origins, is more aggressive and likely to have metastasis. In animal models and rodents, liraglutide has been demonstrated to activate the GLP-1 receptors on C-cells, causing an increased incidence of C-cell neoplasia [101]. However similar effects were reassuringly not seen in studies on monkeys [101]. However, an continues actively surveillance for medullary thyroid carcinoma with the use of GLP1RA may be a good clinical practice.

Our analysis of a very large number of patients receiving semaglutide in the clinical trial setting (n = 33,398) as well as real word setting (n = 13,330) provides us with reassuring data on lack of increased risks of any cancer (pancreatic cancer, thyroid cancer and any other neoplasm) with use of semaglutide, an observation supported by a high grade of evidence.

Limitations of the current systematic review is that the currently available published real-world data has a maximum follow-up duration of 18 months. Carcinogenesis is often a slow process over many years to decades. Hence future publications from patient record database and real-world data having many years of follow-up are likely to provide us with more concrete data with regards to long-term cancer risks with semaglutide.

Strengths of our systematic review include being the first systematic review to specifically look at the occurrence of cancer with use of semaglutide as a primary end-point. This is the largest systematic review on semaglutide written till data analysing data from 37 studies having 46,719 patients. This systematic review provides us with reassuring data on the safety of use of semaglutide over initial 18 months of therapy.

To conclude it may be said that this systematic review based on the current available data provides us with reassuring information with regards to risks of cancer with use of semaglutide.

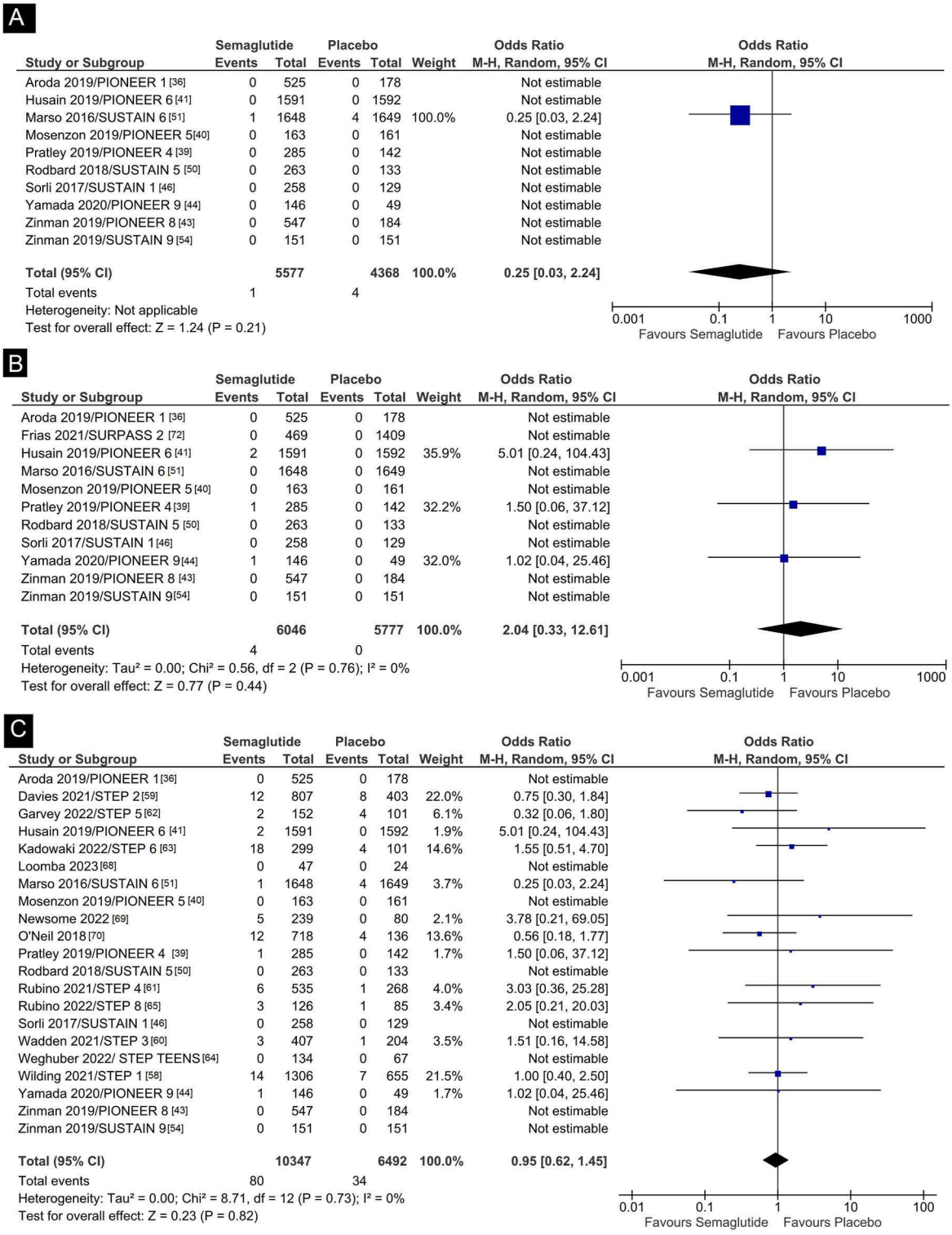

Fig. 3. Forest plot comparing the occurrence of (A): Pancreatic cancer; (B): thyroid cancer; (C) All neoplasms, in patients receiving semaglutide as compared to placebo (placebo control group).

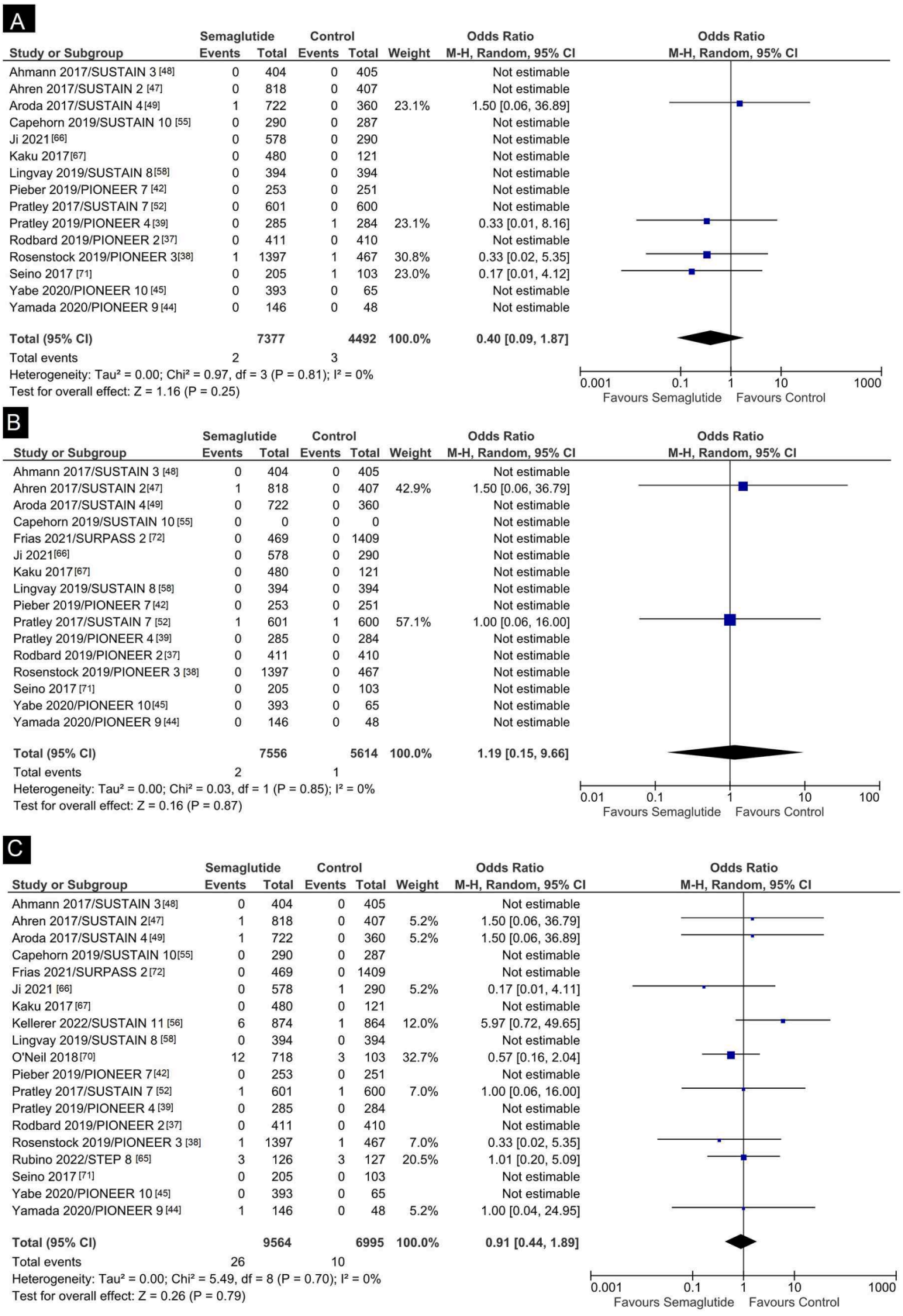

Fig. 4. Forest plot comparing the occurrence of (A): Pancreatic cancer; (B): thyroid cancer; (C) All neoplasms, in patients receiving semaglutide as compared to those receiving anti-diabetes medications (active control group).

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None for all the authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2023.102834.

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