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ORIGINAL ARTICLE

Risk of cancer in patients treated with dipeptidyl peptidase-4 inhibitors: an extensive meta-analysis of randomized controlled trials

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Abstract

Aims Observational studies and meta-analyses of randomized trials on dipeptidyl peptidase-4 inhibitors (DPP4i) reported discordant results on the risk of malignancies with this class of drugs. Aim of the present meta-analysis is the assessment of the effect of DPP4i treatment on the incidence of different types of cancer, collecting all available evidence from randomized controlled trials.

Methods An extensive MEDLINE, EMBASE, and Cochrane database search for sitagliptin or vildagliptin or omarigliptin or saxagliptin or alogliptin or trelagliptin or anagliptin or linagliptin or gemigliptin or evogliptin or teneligliptin was performed up to September 30th, 2019. All trials performed on type 2 diabetes, with duration ≥ 24 weeks, and comparing of DPP4i with placebo or active drugs were collected. The study has been registered on PROSPERO (#153344). Mantel–Haenszel odds ratio (MH-OR) with 95% confidence interval (95% CI) was calculated for all outcomes.

Results A total of 157 eligible trials were identified. DPP-4i were not associated with an increased risk of overall cancer (MH-OR 0.93 [0.86, 1.00]; $p = 0.07$), with no significant differences across individual molecules of the class. When compared with placebo/none, a lower risk of cancer with DPP-4i was observed in placebo-controlled trials (MH-OR 0.90 [0.82, 0.99], $p = 0.030$), whereas no significant differences have been detected with any other comparators. DPP-4i was associated with a significant reduction in colorectal cancer (MH-OR 0.70 [0.53, 0.94], $p = 0.020$).

Conclusions Available data do not support the hypothesis of an association of DPP4i treatment with malignancies, with a possible beneficial effect for colon-rectal cancer.

Keywords DPP-4 inhibitors · Meta-analysis · Cancer

Introduction

Type 2 diabetes is associated with an increased risk of several types of cancer. The mechanisms underlying this association are complex, and they include common pathogenetic factors (e.g., obesity, hyperinsulinemia, low-grade inflammation) and possible detrimental effects of hyperglycemia [1–3]. In addition, it is possible that some drugs used for the treatment of diabetes interfere, either positively or negatively, with the risk of developing some specific malignancies [4–6].

The effect of dipeptidyl peptidase-4 inhibitors (DPP-4i) on hyperglycemia in patients with type 2 diabetes is believed to be mainly due to increased availability of active glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). However, substrates of DPP4 also include many other growth factors, chemokines, and neuropeptides [7]. The complexity of the actions of DPP4i could raise concerns on their safety; however, a growing body of clinical evidence from randomized trials and observational studies confirms that these drugs have a remarkably positive comprehensive safety profile, at least in the short- and medium term.

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Ilaria Dicembrini and Besmir Nreu have contributed equally to this work.

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The exploration of the association between drug treatments and malignancies, which often have a very long latency, is particularly challenging, because of the limited duration of follow-up of most studies. Some experimental evidence in animal models suggested that DPP-4 inhibition is related to several types of malignancies, such as pancreatic, ovarian, prostate, skin, and lung cancer [8]. In addition, some studies postulated that DPP-4i could increase the risk of metastasis in mouse models by the activation of the nuclear factor E2-related factor 2, which is capable of up-regulating the expression of metastasis-associated proteins, thus increasing cancer cell migration and promoting metastasis [9]. Population-based cohort studies in type 2 diabetic patients showed a correlation between DPP-4i treatment and pancreatic cancer [10], cholangiocarcinoma [11], and thyroid cancer [12]. In addition, several pharmacovigilance studies, exploring the FDA adverse event reporting system database, suggested an increased risk of pancreatic cancer with sitagliptin [13, 14]. On the other hand, several other observational studies failed to show any association of DPP4i with any type of cancer [15–17]. In addition, some preclinical studies have hypothesized an antitumoral property of DPP-4i, particularly in in vitro and animal models for colorectal cancer [18–20].

A recent meta-analysis of observational studies reported reassuring results for DPP-4i with respect to incident malignancies, with a possible favorable effect for breast cancer in comparison with other glucose-lowering agents [7]. However, the interpretation of retrospective observational data is problematic, since confounders cannot be entirely accounted for in adjusted models. Only randomized clinical trials (RCTs) can avoid such confounding bias. Pooled analyses of placebo-controlled trials performed with individual molecules failed to detect significant associations between any DPP-4i and malignancies [21–23]. However, the number of events recorded with each individual drug is limited. A meta-analysis of RCTs including all DPP-4i could, therefore, be more informative. Several meta-analyses published some years ago did not report any increased risk of cancer [7, 24–26]; interestingly, one of these meta-analyses reported a nonsignificant trend toward reduction for colorectal cancer [7], in line with several preclinical studies [18–20]. However, these meta-analyses could not consider the most recent trials, including two large-scale cardiovascular outcome trials (CARMELINA [27] and CAROLINA [28]).

Aim of the present meta-analysis is the assessment of the effect of DPP4i treatment on the incidence of malignancies, collecting all available evidence from randomized controlled trials.

Materials and Methods

The present meta-analysis is a part of a wider and currently ongoing systematic review, which has been registered on the PROSPERO Web site (request for registration #153344; https://www.crd.york.ac.uk/PROSPERO/); the protocol can be found in Supplementary materials (Appendix 1). This meta-analysis is reported following the criteria of PRISMA statement [16] (Table S1 in Supplementary materials).

Search strategy and selection criteria

A MEDLINE, Cochrane database, EMBASE, and clinicaltrials.gov search was performed to identify all clinical trials (English only), up to September 30th, 2019, with duration of follow-up of at least 24 weeks, in which DPP-4i (sitagliptin or vildagliptin or omarigliptin or saxagliptin or alogliptin or trelagliptin or anagliptin or linagliptin or gemigliptin or evogliptin or teneligliptin) were compared with either placebo or active comparators. Medical reviews of the same drugs by EMA and FDA were also searched for further unpublished trials. An attempt to retrieve results of completed, but yet unpublished, trials was performed by searching the www.clinicaltrials.gov register. Detailed information on the search string is reported in Supplementary materials (Table 2S).

The identification of relevant abstracts, the selection of studies, and extraction were performed independently by two of the authors (I.D. and B.N.) and conflicts resolved by a third investigator (M.M.).

The following parameters/information were extracted: first author, year of publication, name, and dose of investigational drug, comparator, add-on therapy, duration of follow-up, number of patients and malignancies in each arm (total and site-specific), mean age, duration of diabetes, HbA1c, and body mass index (BMI).

Data analysis

For all published trials, results reported in published papers were used as the primary source of information; when data on the endpoints considered were not available in the primary publication, an attempt of retrieving information was made on clinicaltrials.gov. The quality of trials was assessed using the parameters proposed by the Cochrane Collaboration.

The principal endpoint was the incidence of any malignancies; when they were not listed as adverse events of special interest, we collected only cases reported as serious adverse events.

The secondary endpoint was the incidence of:

(a) Cancer of thyroid
(b) Cholangiocarcinoma
(c) Pancreatic cancer
(d) Gastrointestinal cancer (any cancer from the esophagus to the small intestine)
(e) Colorectal cancer
(f) Bladder cancer
(g) Breast cancer
(h) Prostate cancer
(i) Upper and lower airways cancer
(j) Melanoma

Statistical analyses

Mantel–Haenszel odds ratio (MH-OR) with 95% confidence interval (95% CI) was calculated for all outcomes defined above, on an intention-to-treat basis. This calculation excludes trials with zero events. In the case of trials with zero events in which the number of patients treated with the active drug is different from that of comparators, this exclusion could lead to distortion. For this reason, for the principal endpoint, a sensitivity analysis was performed with continuity correction, imputing one event for each treatment group in trials with zero events. For the same reason, the Peto-OR was calculated for the primary endpoint. Heterogeneity was assessed using I^2 statistics. A random-effect model was applied in the primary analysis, whereas a fixed-effect model was applied in a further sensitivity analysis. For the principal endpoint, a Trial Sequential Analysis was also performed using the TSA software (version 1.0 beta, http://www.ctu.dk/tools-and-links), with alpha 0.05, power 0.80, relative risk reduction 7%, and estimated incidence in control group 2.63%. This method allows reducing the risk of type 1 error due to repetitive testing of accumulating data [17]. Funnel plot for the principal endpoint was examined in order to estimate possible publication/disclosure bias.

Subgroup analyses were performed, whenever possible, for all endpoints for different drugs of the class, different classes of comparators, for cardiovascular outcomes and non/cardiovascular outcomes trials. All analyses specified above were performed using Review Manager 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Results

Trial characteristics

Figure 1 reports the trial flow summary. A total of 192 trials fulfilling inclusion criteria were identified. Of those, 35 reported neither specific information on the endpoints considered in the present meta-analysis, nor a complete list of serious adverse events (Table 3S), and were therefore excluded from the analysis.

The principal characteristics of the 157 trials included in the analysis are reported in Table 4S and Table 5S. The overall quality was satisfactory in the majority of trials for all items of the Cochrane tool, with the exception of "blinding of participants and personnel" which cannot be completely ruled out for several trials (open-label design or methods not satisfactorily described) and of "selective reporting" due to lack of adjudication of cases of malignancies (Fig. 1S).

Out of 157 studies (66,825 patients in DPP-4 inhibitors and 61,524 patients in control group), 109 reported at least one event of malignancy (1383 and 1437 with DPP-4 inhibitors and comparators, respectively). No publication bias was detected at a visual analysis of the Funnel plot (Fig. 2S).

DPP-4 inhibitors were not associated with a significant increase in the risk of cancer (MH-OR: 0.93 [0.86, 1.00]; $p=0.065$; Fig. 2); no significant differences were observed across individual molecules of the class. No heterogeneity (I^2: 0%) was detected for this endpoint. Similar results were obtained using a fixed-effect model (MH-OR 0.94 [0.87, 1.01], $p=0.09$), as well as in a sensitivity analysis with continuity correction (MH-OR 0.93 [0.86, 1.000]; $p=0.050$), and when using Peto's method (0.94 [0.87, 1.01]; $p=0.11$, I^2: 30%). Trial sequential analysis showed that the required information size is far from being reached, and the cumulative z curve remains inside the monitoring boundaries (Fig. 3S). In the analysis of subgroups of trials with different comparators, a lower risk of cancer with DPP-4 inhibitors was observed in placebo-controlled trials (MH-OR 0.90 [0.82, 0.99], $p=0.030$; $I^2=0\%$), whereas no significant differences were detected with any other comparators (Fig. 4S).

When analyzing trials with (0.90 [0.83, 0.98], $p=0.01$) and without (MH-OR: 1.11 [0.91, 1.34], $p=0.83$) cardiovascular endpoint, a between-group difference could not be completely ruled out (p for interaction: 0.06) with respect to cancer (Fig. 5S).

Only 2 trials did not report information on individual types of cancer and therefore were excluded from further analyses [29, 30]. No association was observed for any different form of cancer, with the exception of a nonsignificant trend toward reduction for colorectal cancer (Table 1). A further, post hoc analysis limited to placebo-controlled trials showed a significant association of DPP-4 inhibitors with a reduced incidence

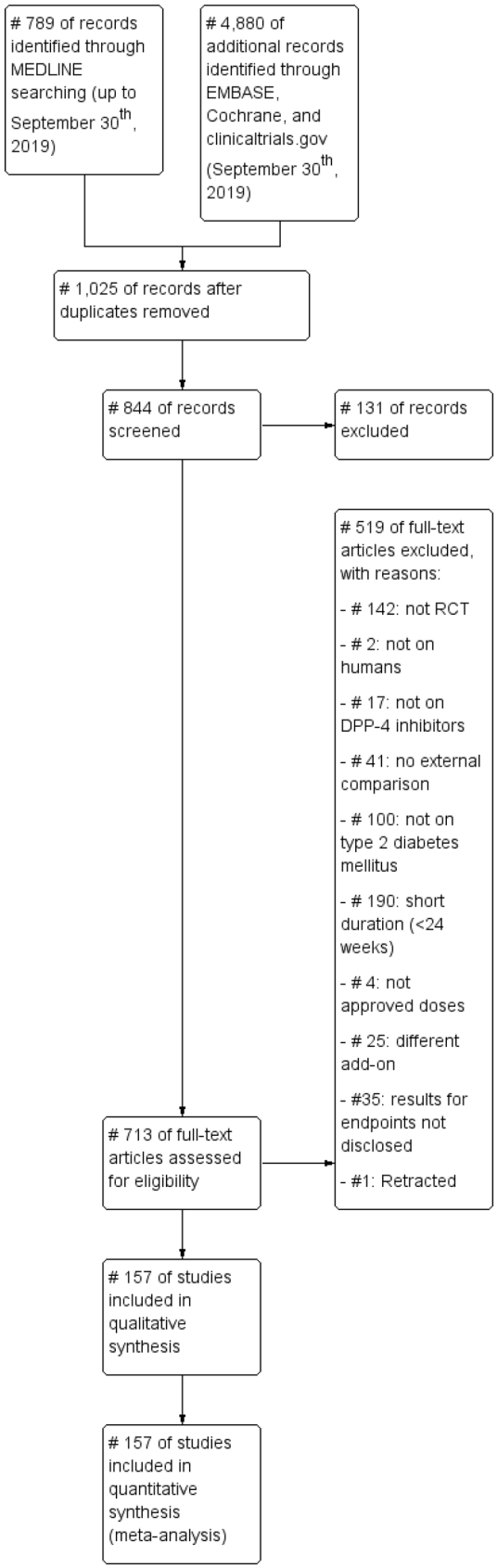

Fig. 1 Trial flow diagram

of colorectal cancer (MH-OR 0.70 [0.53, 0.94], $p=0.020$, I^2:15%; Fig. 6S).

Discussion

The present meta-analysis does not suggest any increase in the incidence of cancer with DPP-4 inhibitors. These results confirm, in a larger sample, those of several previous pooled analyses [21–23] and meta-analyses [7, 24–26]. The trial sequential analysis suggests that wider samples are needed to reach a conclusive result.

Cancer is a very heterogeneous group of diseases, differing for pathogenesis and risk factors. Therefore, analyses on the overall incidence of malignancies could be misleading, diluting either beneficial or detrimental effects of treatment on the risk of individual types of cancer. In this respect, DPP-4 inhibitors have been associated with an increased risk of pancreatic cancer [13, 14], thyroid cancer [12], and cholangiocarcinoma [11]. The present analysis seems to exclude an increased risk of breast cancer, with an upper confidence limit lower than 1.30. On the other hand, no reliable information can be retrieved for thyroid cancer and cholangiocarcinoma, because of the paucity of observed cases (13 and 7 cases, respectively).

Preclinical studies also suggested that DPP-4 inhibitors could reduce the risk of colorectal cancer. In randomized clinical trials, the risk of this malignancies is lower with DPP-4 inhibitors than with comparators, although the difference does not reach statistical significance ($p=0.06$). In addition, the protective effect of DPP-4 inhibitors with respect to colorectal cancer is statistically significant when placebo-controlled trials are analyzed separately. This result, although promising, needs to be confirmed on larger samples of patients.

Some limitations of this meta-analysis should be considered when interpreting its results. Malignancies were not the principal endpoints of the trials included but were reported only as serious adverse events, at investigators' discretion. No pre-defined diagnostic criteria or screening procedures were used, and no specific adjudication of events was performed by independent committees. Furthermore, patients enrolled in clinical trials are not representative of those of the general population; in particular, the largest samples of subjects enrolled in trials with DPP-4 inhibitors are those included in cardiovascular outcome studies, which were selected for high cardiovascular risk. Finally, the relatively short duration of available trials does not allow any inference on the long-term effects of DPP-4 inhibitors, which will need to be assessed through specifically designed studies.

In conclusion, available data do not support the hypothesis of an association of DPP-4 inhibitors treatment with

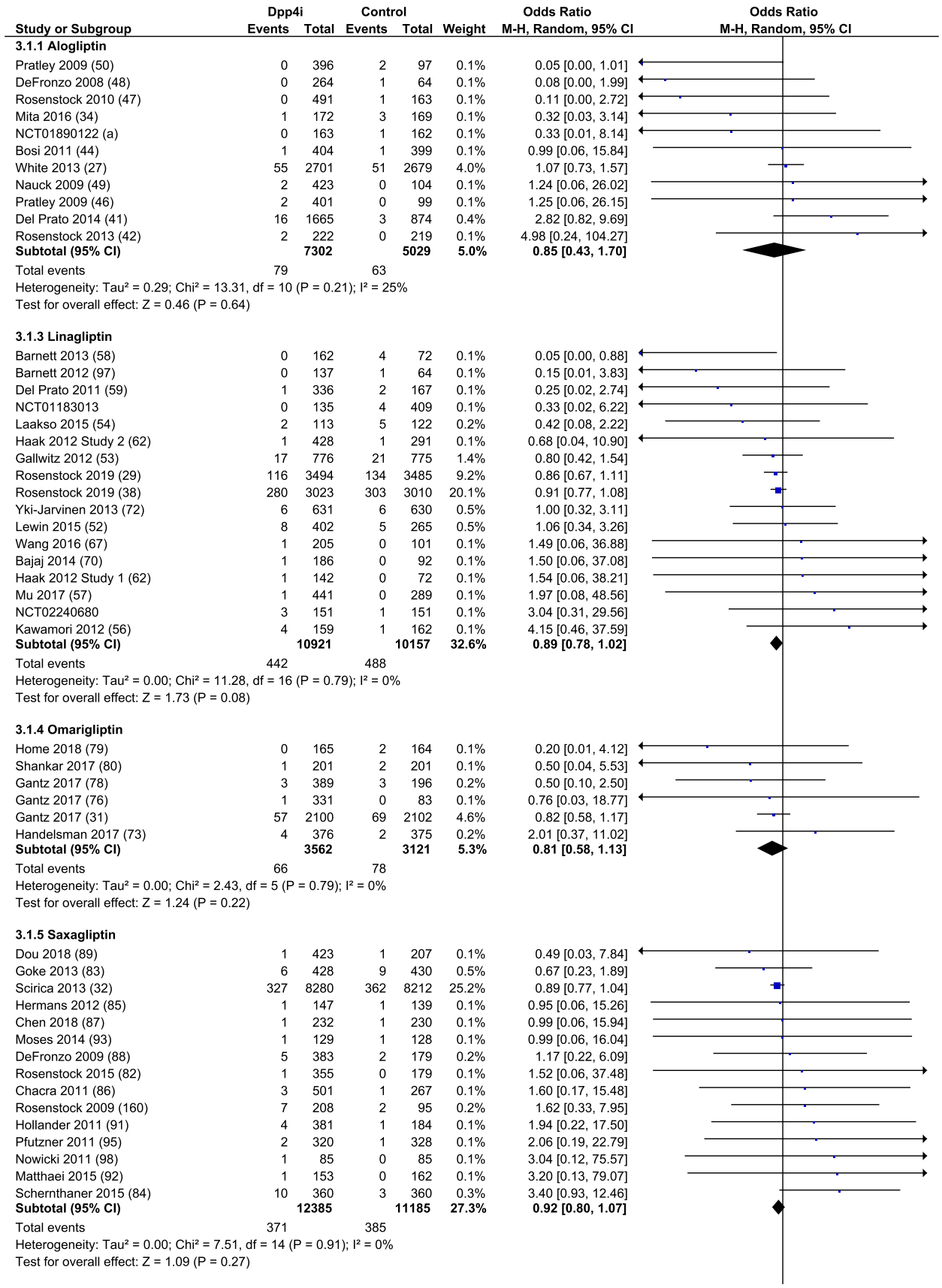

Fig. 2 Overall cancer risk with DPP-4 inhibitors versus other comparators (MH-OR, 95% CI: Mantel-Haenszel odds ratio, with 95% of confidence intervals). For references, see Supplementary Materials

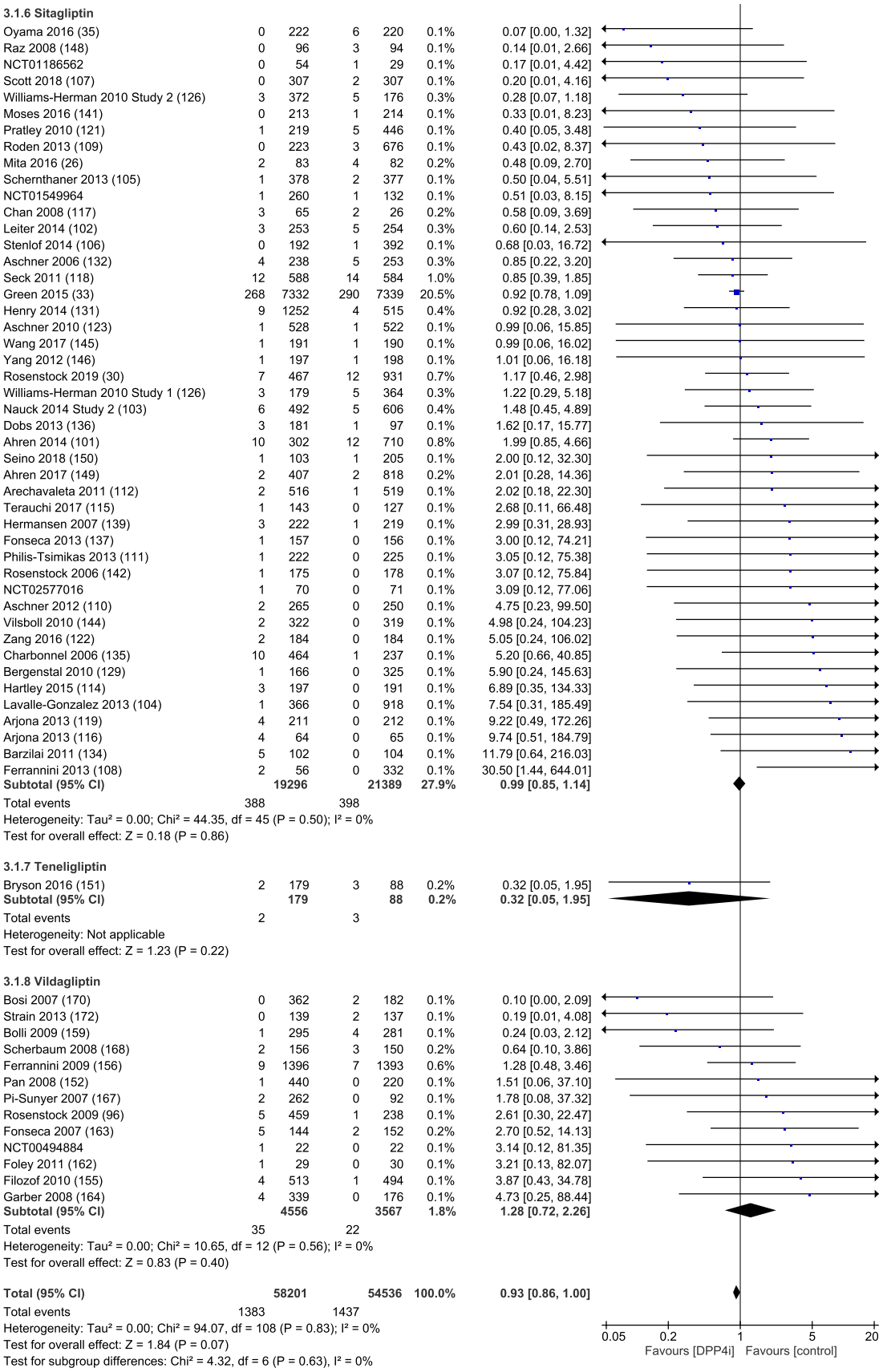

Fig. 2 (continued)

Table 1 DPP-4 inhibitors and risk of different types of cancer

Type of cancer	#trials with at least one event	# of patients (DPP-4i/C)	# of cancers (DPP-4i/C)	I^2 (%)	MH-OR 95%, CI	Overall effect *p*	Subgroup differences* *p*	Subgroup differences* I^2
Colorectal	38	66,474/61,176	131/161	0	0.80 [0.63, 1.01]	0.065	0.84	0
Other gastrointestinal	30	66,474/61,176	56/47	0	1.03 [0.70, 1.51]	0.90	0.29	18
Breast	44	29.913/27.529	65/73	0	0.89 [0.64, 1.24]	0.50	0.45	0
Upper/lower airways	39	66,474/61,176	138/115	0	1.16 [0.91, 1.48]	0.24	0.61	0
Bladder	24	66,474/61,176	69/92	0	0.77 [0.56, 1.06]	0.11	0.17	35
Prostate	39	36,561/3,647	144/133	0	1.03 [0.81, 1.29]	0.83	0.88	0
Thyroid	6	66,474/61,176	9/4	0	2.28 [0.78, 6.65]	0.13	0.95	0
Cholangiocarcinoma	3	66,474/61,176	3/4	16	0.91 [0.16, 5.24]	0.91	0.30	16
Melanoma	21	66,474/61,176	42/43	0%	1.13 [0.73, 1.75]	0.57	0.82	0
Pancreatic	21	66,474/61,176	58/63	0%	0.86 [0.60, 1.24]	0.42	0.50	0

C comparators, *MH-OR* Mantel–Haenszel odds ratio, *CI* confidence intervals, *DPP-4i* dipeptidyl peptidase-4 inhibitors

*For different molecules of the class

cancer, suggesting possible beneficial effects on colorectal cancer, which deserves further investigation.

Author contribution MM and EM were involved in design, data collection, analysis, and writing manuscript. ID, BN, and CM were involved in data collection and manuscript revision.

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Compliance with ethical standards

Conflict of interest ID has received speaking fees from Novonordisk; CM has no conflict of interest; BN is presently employee of Novo Nordisk; FT has no conflicts of interest to declare MM has received speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Bristol Myers Squibb; EM has received consultancy fees from Merck and Novartis speaking fees from Astra Zeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Eli-Lilly, Merck, Novo Nordisk, Sanofi, and Novartis and research grants from Merck, Novartis, and Takeda. All the authors approved the final version of this manuscript. Dr. Matteo Monami is the person who takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of article, informed consent is not necessary.

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