Incretin-based drugs and the incidence of colorectal cancer in patients with type 2 diabetes

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ABSTRACT

Background: Evidence on the safety of the incretin-based drugs (glucagon-like peptide-1 [GLP-1] analogues and dipeptidyl peptidase-4 [DPP-4] inhibitors) with respect to colorectal cancer is contradictory. The objective of this study was to determine whether use of incretin-based drugs is associated with risk of incident colorectal cancer in patients with type 2 diabetes.

Methods: Using data from the United Kingdom Clinical Practice Research Datalink, we identified a cohort of 112,040 patients newly treated with antidiabetic drugs between 1 January 2007 and 31 March 2015. We modeled use of GLP-1 analogues and DPP-4 inhibitors as time-varying variables and compared them with use of sulfonylureas. We lagged exposures by one year for latency and to reduce reverse causality and detection bias. We used time-dependent Cox proportional hazards models to estimate hazard ratios with 95% confidence intervals of incident colorectal cancer associated with the use of GLP-1 analogues and DPP-4 inhibitors overall, by cumulative duration of use, and by time since initiation.

Results: During 388,619 person–years of follow-up, there were 733 incident colorectal cancer events (incidence rate: 1.9 per 1,000 person–years). Use of GLP-1 analogues was not associated with colorectal cancer incidence (hazard ratio: 1.0, 95% confidence interval: 0.7, 1.6), nor was use of DPP-4 inhibitors (hazard ratio: 1.2, 95% confidence interval: 1.0, 1.5). There was no evidence of a duration–response relationship for either drug.

Conclusions: The results of this large population-based study indicate that use of incretin-based drugs is not associated with colorectal cancer incidence among patients with type 2 diabetes.

INTRODUCTION

Incretin-based drugs, which include glucagon-like peptide-1 (GLP-1) analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors, are used as second- to third-line therapies in the management of type 2 diabetes.[1] While these drugs lower glucose levels and reduce the risk of hypoglycemia compared to other antidiabetic drugs,[2] there are concerns that their use may increase the risk of certain malignancies, including colorectal cancer.[3 4]

The current evidence associating the use of incretin-based drugs with the incidence of colorectal cancer is mixed. According to safety reviews of randomized controlled trials (RCTs) conducted by the US Food and Drug Administration and the European Medicines Agency, no imbalance of colon events was observed with the 1.8 mg formulation of liraglutide (a GLP-1 analogue) compared with placebo.[5 6] However, the Food and Drug Administration reported two rectal cancer events [0.05%; 0.06 events per 100 person–years] among users of 1.8 mg liraglutide, compared with no events in the placebo group.[5] Furthermore, in the Food and Drug Administration's review of the 3 mg formulation of liraglutide (used in weight management), two malignant colorectal events were observed in the treatment group [0.06%; 0.04 events per 100 person–years], while no events were observed in the placebo group.[7] The evidence continued to be mixed after the publication of large post-marketing RCTs of GLP-1 analogues and DPP-4 inhibitors.[8-15] While the majority of these RCTs reported no associations with colorectal cancer,[8-13] saxagliptin (a DPP-4 inhibitor) was associated with a decreased risk of colon cancer (HR: 0.51, 95% CI: 0.27, 0.92) in a post-hoc analysis of the SAVOR-TIMI 53 trial.[14] In contrast, in a pooled analysis of 25 RCTs of sitagliptin (a DPP-4 inhibitor), there was an imbalance in the incidence rate of colon cancer compared with placebo (0.09% per year vs 0.04% per year, respectively).[15] To date, to our knowledge, only one observational study has

been conducted to assess this safety concern and did not observe an association between the use of incretin-based drugs and the incidence of colorectal cancer.[16]

The biologic evidence on this potential association is limited, with few studies publishing contradictory findings. On the one hand, there is some evidence that the use of GLP-1 analogues and DPP-4 inhibitors may increase the development of malignant colorectal neoplasms.[17-19] On the other, there is competing evidence that these drugs may have anti-cancer properties in vitro.[20-23] Thus, given the discordant information on the association between the use of incretin-based drugs and colorectal cancer incidence, there is an urgent need to assess their safety in the real-world setting. Therefore, the objective of this population-based study was to determine whether the use of GLP-1 analogues and DPP-4 inhibitors is associated with the incidence of colorectal cancer in patients with type 2 diabetes.

METHODS

Data source

We conducted this study using the United Kingdom (UK) Clinical Practice Research Datalink. This database contains anonymized, longitudinal clinical records of over 15 million patients from approximately 700 general practices, and has been shown to be largely representative of the general UK population.[24] Collected data include information on anthropometric and lifestyle variables, referrals, prescriptions and diagnoses; the data have been shown to be of high quality and validity.[25 26] Furthermore, colorectal cancer diagnoses in the Clinical Practice Research Datalink have been shown to be well recorded when compared with the UK National Cancer Data Repository.[27]

The study protocol was approved by the Independent Scientific Advisory Committee of the Clinical Practice Research Datalink (protocol number 16_264Mn) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

Study population

We identified a base cohort of patients newly treated with non-insulin antidiabetic drugs (including; metformin, sulfonylureas, prandial glucose regulators, thiazolidinediones, acarbose, DPP-4 inhibitors, GLP-1 analogues, and sodium-glucose co-transporter-2 inhibitors) between 1 January 1988 and 31 March 2015, with follow-up until 31 March 2016. Patients were required to be at least 40 years of age, and with at least 1 year of medical history in the Clinical Practice Research Datalink before their initial prescription. We excluded patients with advanced type 2 diabetes, identified on the basis of an insulin prescription written before their first non-insulin antidiabetic prescription. Female patients with a prior diagnosis of gestational diabetes or polycystic ovary syndrome were also excluded, as these are other indications for metformin.

Using the base cohort, we assembled a study cohort of patients who initiated a new class of an antidiabetic drug in or after 2007 (the year the first incretin-based drugs entered the UK market).[2] New users included those newly treated with an antidiabetic drug class (i.e. first-ever antidiabetic prescription) as well as those who added-on or switched to an antidiabetic drug class not previously used in their treatment history. Cohort entry was defined by the date of this new antidiabetic drug prescription. We excluded all patients with a history of colorectal cancer (in situ and malignant) and Lynch syndrome[28] at any time prior to cohort entry, as well as patients with less than one year of follow-up after cohort entry for latency purposes (this included patients diagnosed with colorectal cancer within one year of cohort entry).

All patients meeting the study inclusion criteria were followed starting one year after cohort entry (i.e. person–time at risk) until a first-ever diagnosis of colorectal cancer (in situ and malignant), or censored upon death from any cause, end of registration with the general practice, or the end of the study period (31 March 2016), whichever occurred first.

Exposure definition

Exposure to the different antidiabetic drugs was modelled as a time-varying variable, allowing patients to transition between different exposure groups during the follow-up period. For the GLP-1 analogue analysis, exposure was defined according to the following hierarchical definition: use of GLP-1 analogues (alone or in combination with other antidiabetic drugs), then use of sulfonylureas (alone or in combination with other antidiabetic drugs), and finally use of all other antidiabetic drugs. All drug exposures were lagged by one year for latency purposes, and to reduce reverse causality and detection bias. Based on this exposure definition, patients were considered unexposed to the drug of interest until one year after treatment initiation, and considered exposed thereafter for the remainder of follow-up, analogous to an intention-to-treat exposure definition. A similar exposure definition was used for the DPP-4 inhibitor analysis, where the following hierarchical exposure definition was used: DPP-4 inhibitors (alone or in combination with other antidiabetic drugs), then use of sulfonylureas (alone or in combination with other antidiabetic drugs), and finally use of all other antidiabetic drugs (eFigure 1; http://links.lww.com/EDE/B304). To avoid confounding by indication,[29] the reference category for all analyses was the use of sulfonylureas, as these represent an alternative second- to third-line treatment option. We considered, and rejected, the use of metformin as the reference category, as metformin is typically prescribed as a first-line treatment and thus it is not used at the same stage of disease as the incretin-based drugs.[30]

We also defined the use of GLP-1 analogues and DPP-4 inhibitors in terms of cumulative duration of use and time since initiation, which were modeled as time-dependent variables. Cumulative duration of use was calculated by summing the durations associated with each prescription from cohort entry until the time of event (risk set). Time since initiation was defined as the time between the first ever prescription of a GLP-1 analogue or DPP-4 inhibitor and the risk set date.

Potential confounders

The models were adjusted for the following potential confounders measured at cohort entry: age, sex, year of cohort entry, alcohol-related disorders (including alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic failure), smoking status (current, former, never, unknown), body mass index (BMI) (<25 kg/m^2, 25-29 kg/m^2, ≥30 kg/m^2, unknown), hemoglobin A1c (last laboratory result before cohort entry), duration of treated diabetes (defined as the time between first non-insulin prescription and cohort entry), previous cancer (other than non-melanoma skin cancer), inflammatory bowel disease (Crohn's disease and ulcerative colitis) and Charlson comorbidity score. We also adjusted the models for the presence of microvascular complications of diabetes (neuropathy, renal disease, retinopathy, and peripheral arteriopathy; measured at any time before cohort entry) and the number of unique antidiabetic drugs received in the year before cohort entry, both as proxies for diabetes severity. Models were adjusted for the total number of unique non-antidiabetic drugs in the year before cohort entry, as a general measure of comorbidity.[31] Finally, models were adjusted for use of aspirin and statins at any time before cohort entry, as these drugs have been associated with a decreased risk of colorectal cancer in some studies.[32 33]

Statistical analyses

We calculated crude incidence rates of colorectal cancer for the entire cohort, and for each exposure group. For the primary analysis, time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident colorectal cancer associated with the overall use of GLP-1 analogues and DPP-4 inhibitors compared with the use of sulfonylureas. All models were adjusted for the potential confounders listed previously.

Secondary analyses

We conducted four secondary analyses. First, we assessed whether there was a duration-response relation for GLP-1 analogue and DPP-4 inhibitor cumulative duration of use on the incidence of colorectal cancer. For this time-dependent analysis, HRs were estimated for three predefined duration categories: ≤1 year, 1.1-2 years, and > 2 years. Second, we assessed the association between time since initiation of GLP-1 analogues and DPP-4 inhibitors and colorectal cancer incidence (≤2 years and >2 years). Third, we assessed the association with the most common individual drugs within each incretin-based drug class (GLP-1 analogues: exenatide and liraglutide; DPP-4 inhibitors: sitagliptin, saxagliptin). Finally, the analyses were repeated after stratifying on colon versus rectal cancer.

Sensitivity analyses

We conducted seven sensitivity analyses to assess the robustness of our findings. First, we repeated the primary analysis after increasing the exposure lag period to 2 years, as there are uncertainties related to the length of the latency time window. Conversely, to explore the possibility that the previously reported increased risk was due to a tumor promoter effect, we repeated the analyses by removing the lag period. Third, to assess possible detection bias of

undiagnosed colorectal cancer, we stratified the cohort based on referrals to colonoscopy screening or fecal occult blood testing, measured in the 5 years before cohort entry.[34] Fourth, to address the possibility of outcome misclassification, we repeated the analysis upon restricting to malignant colorectal cancer and censoring on in situ colorectal cancer diagnoses. In the last three sensitivity analyses, we addressed possible residual confounding by repeating the primary analyses using the disease risk score method, marginal structural models, and multiple imputation for variables with missing information (eMethods 1-3; http://links.lww.com/EDE/B304). All analyses were conducted with SAS version 9.4 (SAS institute, Cary, NC).

RESULTS

A total of 112,040 patients met the study inclusion criteria (Figure), and were followed for a mean (standard deviation [SD]) of 3.5 (2.2) years after completing the 1-year post-cohort entry latency period. During 388,619 person–years of follow-up, there were 733 incident colorectal cancer events, generating a crude incidence rate of 1.9 (95% CI: 1.8, 2.0) per 1000 person–years. Among these events, 715 (incidence rate 1.8, 95% CI: 1.7, 2.0 per 1000 person–years) were malignant versus 18 (incidence rate 0.05, 95% CI: 0.03, 0.07 per 1000 person–years) in situ colorectal cancers. A total of 5724 (5.1%) patients were prescribed GLP-1 analogues during the study period, and 22,276 (19.9%) patients were prescribed DPP-4 inhibitors.

Table 1 presents baseline characteristics for the cohort overall, and stratified by use of GLP-1 analogues, DPP-4 inhibitors, and sulfonylureas at cohort entry. Compared with sulfonylurea users, GLP-1 analogue users were younger, more likely to have had alcohol-related disorders, and less likely to be current smokers. Additionally, GLP-1 analogue users were more likely to have a higher BMI, to have a higher hemoglobin A1c level, and were more likely to

have neuropathy and retinopathy. Compared with sulfonylurea users, DPP-4 inhibitor users were older, more likely to have had alcohol-related disorders, and less likely to be current smokers. DPP-4 inhibitor users were more likely to have a higher BMI, to have a higher hemoglobin Alc level and a higher Charlson comorbidity score. DPP-4 inhibitor users were also more likely to have neuropathy and retinopathy.

The results of primary and secondary analyses are shown in Tables 2 and 3. Compared with the use of sulfonylureas (1.6 cases per 1000 per year), the use of GLP-1 analogues (2.0 per 1000 per year) was not associated with the incidence of colorectal cancer (HR: 1.0, 95% CI: 0.7, 1.6). Furthermore, there was no evidence of a duration–response relationship both in terms of cumulative duration of use and time since initiation (Table 2).

Compared with the use of sulfonylureas (1.9 cases per 1000 per year), the use of DPP-4 inhibitors (2.1 cases per 1000 per year), was not associated with the incidence of colorectal cancer overall (HR: 1.2, 95% CI: 1.0, 1.5), or by cumulative duration of use and time since initiation (Table 3). Similar findings were observed when analyses were repeated stratifying on individual drug type and when stratifying on colon versus rectal cancer (eTables 1 to 4; http://links.lww.com/EDE/B304).

Sensitivity analyses

The results of the sensitivity analyses were consistent with those of the primary analysis (eFigure 2; http://links.lww.com/EDE/B304, eTables 5 to 18; http://links.lww.com/EDE/B304) For GLP-1 analogues, the adjusted HRs ranged between 0.9 and 1.9, while for DPP-4 inhibitors, the adjusted HRs ranged between 0.8 and 1.2.

DISCUSSION

In this large population-based cohort study with a mean follow-up of 3.5 years (after accounting for a 1-year post-cohort entry latency period) and with up to 9.5 years of potential follow-up, the use of GLP-1 analogues or DPP-4 inhibitors was not associated with incident colorectal cancer, when compared with the use of sulfonylureas. Furthermore, there were no associations by cumulative duration of use or time since initiation and the findings remained highly consistent in sensitivity analyses that considered different sources of bias.

Overall, our findings are consistent with the vast majority of RCTs, which showed no association between different incretin-based drugs and colorectal cancer incidence.[8-13] Moreover, our findings provide some reassurance that the diabetic dose of liraglutide (1.8 mg) is not associated with an increased risk of colorectal cancer. However, it is not possible to rule out a potential increased risk of colorectal cancer with higher doses of liraglutide, such as those used in weight management trials. Indeed, our study population did not include users of the 3 mg formulation, which is commonly used for treatment of obesity among non-diabetic patients. With respect to DPP-4 inhibitors, we did not observe any association with colorectal cancer incidence either overall or by individual drug types. This is inconsistent with prior RCTs that produced contradictory evidence; both decreased[14] and increased incidences[15] have been reported with saxagliptin and sitagliptin, respectively. However, these RCTs were not designed or powered to assess cancer incidence, and thus generated few events limiting the interpretation of their findings.

To our knowledge, only one observational study has been conducted to assess this possible association.[16] Using US Medicare data from 2007 to 2013 and an as-treated exposure definition, there was no association between the use of DPP-4 inhibitors and incident colorectal

cancer, regardless of whether these drugs were compared to thiazolidinediones (HR: 1.2, 95% CI: 0.9, 1.7) or sulfonylureas (HR: 1.0, 95% CI: 0.7, 1.3).[16] Similar findings were observed for the use of GLP-1 analogues, when compared with the use of long-acting insulin (HR: 0.8, 95% CI: 0.4, 1.6).[16] While our findings confirm those of the previous study,[16] the previous study was limited by its short duration of follow-up, which ranged between 0.7 and 1.2 years. Such short durations limit the interpretation of safety for outcomes such as colorectal cancer.[8-16]

The existing biologic evidence on the relation between the use of incretin-based drugs and colorectal cancer is contradictory.[17-23] While our study did not find an increase in the incidence of colorectal cancer with these drugs, it is not possible to completely rule out a tumor promoter effect with the use of GLP-1 analogues. Indeed, GLP-1 analogues may enhance the growth of the small and large bowel via fibroblast growth factor 7 (FGF7), and activation of the GLP-1 signaling pathway may promote gut growth and crypt fission.[17] This effect may be masked by the possible anti-cancer properties of GLP-1 analogues observed in vitro, whereby increased activation of the GLP-1 receptor has been shown to alter cell morphology, induce apoptosis, and inhibit proliferation of colon cancer cells.[20 23]

The evidence on DPP-4 inhibitors is lacking; these drugs have been shown to be cytotoxic agents against colon carcinoma cells and lower colon carcinogenesis in rat models.[21 22] However, there is competing evidence that long-term inhibition of the DPP-4 enzyme can lead to immune dysregulation and increased cancer risk,[18] and that DPP-4 inhibitor use may support the metastasis of colon cancer cells.[19] Overall, such experimental studies should be interpreted with caution, as animal models do not represent the complex pathophysiology of patients with type 2 diabetes, a population that is already at an increased risk of colorectal cancer.[35] Overall, our findings suggest that the incretin-based drugs are likely to have neutral effects on colorectal

carcinogenesis in the relative short-term, and thus future studies with longer follow-up will be needed to confirm our findings.

This study has several strengths. First, our study generated 388,619 person–years of follow-up, allowing for the identification of a substantial number of incident colorectal cancer events. Second, we used a new-user study design to reduce biases associated with the inclusion of prevalent users.[36] Third, we used a time-dependent exposure definition that took into account the dynamic nature of the pharmacologic management of type 2 diabetes, while eliminating the possibility of immortal time bias.[37] Fourth, a lag period was used for latency purposes and to reduce detection bias and reverse causality. Fifth, all models were adjusted for a number of potential confounders including smoking status, alcohol-related disorders, and BMI, which are all known risk factors of colorectal cancer. Finally, the results remained consistent across several sensitivity analyses, illustrating the robustness of our findings.

This study also has some limitations. Some exposure misclassification is possible as prescriptions in the Clinical Practice Research Datalink represent those written by general practitioners and not specialists. However, in the UK, general practitioners are responsible for maintaining the long-term care of patients with type 2 diabetes, and thus we expect such misclassification to have had an unimportant impact on our exposure definition. Although colorectal cancer diagnoses have been shown to be well recorded in the Clinical Practice Research Datalink,[27] outcome misclassification remains possible. However, we expect this potential misclassification to be non-differential between the treatment groups. As with all observational studies, residual confounding from unmeasured variables (such as family history or race/ethnicity) is possible, although it is unclear how these unmeasured variables would influence the prescribing of incretin-based drugs. Furthermore, we obtained consistent results in

sensitivity analyses using the disease risk score method and marginal structural models to control for time-dependent confounding. This study is also limited by its mean follow-up of 3.5 years after accounting for a 1-year latency after cohort entry, which may be considered short to assess cancer incidence. However, the rational for conducting this study was based on signals from short duration RCTs (12 weeks to 2.1 years),[14 15] and thus our study had long enough follow-up to assess colorectal cancer incidence in the relative short-term. Furthermore, based on the upper limits of the CIs of the main analyses (1.6 for use of GLP-1 analogues and 1.5 for use of DPP-4 inhibitors), our study was sufficiently powered to rule out strong associations between the use of the incretin-based drugs and colorectal cancer; though the possibility of weaker associations remains. Finally, given the rarity of the outcome, some of the secondary analyses resulted in wide CIs.

In summary, the results of this large population-based study indicate that, compared with the use of sulfonylureas, the use of incretin-based drugs is not associated with a substantial increase in the incidence, and may be unassociated with the incidence of colorectal cancer, among patients with type 2 diabetes.

REFERENCES

1. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. The Lancet 2006;**368**(9548):1696-705.
2. Nauck MA, Vilsbøll T, Gallwitz B, et al. Incretin-Based Therapies Viewpoints on the way to consensus. Diabetes Care 2009;**32**(suppl 2):S223-S31.
3. Halfdanarson TR, Pannala R. Incretins and risk of neoplasia. BMJ : British Medical Journal 2013;**346**.
4. Tseng C-H, Lee K-Y, Tseng F-H. An Updated Review on Cancer Risk Associated with Incretin Mimetics and Enhancers. Journal of Environmental Science and Health, Part C 2015;**33**(1):67-124.
5. Liraglutide (injection) for the Treatment of Patients with Type 2 Diabetes Food and Drug Administration.
6. Assessment Report for Victoza. European Medicines Agency.
7. Summary Review for Regulatory Action SAXENDA (liraglutide [rDNA origin] injection)
8. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;**373**(3):232-42.
9. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;**375**(4):311-22.
10. Pi-Sunyer X, Astrup A, Fujioka K, et al. A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 2015;**373**(1):11-22.
11. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;**369**(14):1327-35.

12. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016;**375**(19):1834-44.

13. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med 2015;**373**(23):2247-57.

14. Leiter L, Teoh H, Mosenzon O, et al. Frequency of cancer events with saxagliptin in the SAVOR-TIMI 53 trial. Diabetes, Obesity and Metabolism 2016;**18**(2):186-90.

15. Engel SS, Round E, Golm GT, et al. Safety and tolerability of sitagliptin in type 2 diabetes: pooled analysis of 25 clinical studies. Diabetes Ther 2013;**4**(1):119-45.

16. Htoo PT, Buse JB, Gokhale M, et al. Effect of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors on colorectal cancer incidence and its precursors. Eur J Clin Pharmacol 2016;**72**(8):1013-23.

17. Koehler JA, Baggio LL, Yusta B, et al. GLP-1R agonists promote normal and neoplastic intestinal growth through mechanisms requiring Fgf7. Cell Metab 2015;**21**(3):379-91.

18. Stulc T, Sedo A. Inhibition of multifunctional dipeptidyl peptidase-IV: Is there a risk of oncological and immunological adverse effects? Diabetes Res Clin Pract 2010;**88**(2):125-31.

19. Masur K, Schwartz F, Entschladen F, et al. DPPIV inhibitors extend GLP-2 mediated tumour promoting effects on intestinal cancer cells. Regul Pept 2006;**137**(3):147-55.

20. 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;**152**(9):3362-72.

21. Amritha C, KumArAvelu P, ChellAthAi DD. Evaluation of Anti Cancer Effects of DPP-4 Inhibitors in Colon Cancer-An Invitro Study. Journal of clinical and diagnostic research: JCDR 2015;**9**(12):FC14.

22. Femia AP, Raimondi L, Maglieri G, et al. Long-term treatment with Sitagliptin, a dipeptidyl peptidase-4 inhibitor, reduces colon carcinogenesis and reactive oxygen species in 1,2-dimethylhydrazine-induced rats. Int J Cancer 2013;**133**(10):2498-503.

23. Tawfik MK, Mohamed MI. Exenatide suppresses 1,2-dimethylhydrazine-induced colon cancer in diabetic mice: Effect on tumor angiogenesis and cell proliferation. Biomed Pharmacother 2016;**82**:106-16.

24. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol 2015;**44**(3):827-36.

25. Jick SS, Kaye JA, Vasilakis-Scaramozza C, et al. Validity of the general practice research database. Pharmacotherapy 2003;**23**(5):686-9.

26. Lawrenson R, Williams T, Farmer R. Clinical information for research; the use of general practice databases. J Public Health Med 1999;**21**(3):299-304.

27. Boggon R, Staa TP, Chapman M, et al. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. Pharmacoepidemiol Drug Saf 2013;**22**(2):168-75.

28. Lynch H, Lynch P, Lanspa S, et al. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. Clin Genet 2009;**76**(1):1-18.

29. Suissa S, Azoulay L. Metformin and the Risk of Cancer: Time-related biases in observational studies. Diabetes Care 2012;**35**(12):2665-73.

30. Raz I. Guideline approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;**36**(Supplement 2):S139-S44.

31. Schneeweiss S, Seeger JD, Maclure M, et al. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol 2001;**154**(9):854-64.

32. Garcia-Albeniz X. Aspirin for the prevention of colorectal cancer. 2011;**25**(0):461-72.

33. Liu Y, Tang W, Wang J, et al. Association between statin use and colorectal cancer risk: a meta-analysis of 42 studies. Cancer Causes Control 2014;**25**(2):237-49.

34. Public Health England. NHS bowel cancer screening (BCSP) programme. Secondary Public Health England. NHS bowel cancer screening (BCSP) programme. https://www.gov.uk/topic/population-screening-programmes/bowel

35. Berster JM, Göke B. Type 2 diabetes mellitus as risk factor for colorectal cancer. Arch Physiol Biochem 2008;**114**(1):84-98.

36. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;**158**(9):915-20.

37. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol 2008;**167**(4):492-9.

FIGURE LEGENDS

Figure. Study flow chart of patients included in the base and study cohorts

Table 1. Baseline Demographic and Clinical Characteristics of the Cohort and Stratified by Drug Use at Cohort Entry

Characteristic	Entire Cohort	Use at Cohort Entry [a]		
		GLP-1 analogues	DPP-4 inhibitors	Sulfonylureas
Total	112,040	1177	6002	18,513
Male, n (%)	65,166 (58)	666 (57)	3465 (58)	10,953 (59)
Year of cohort entry, n (%)				
2007	18,439 (17)	51 (4)	115 (2)	4362 (24)
2008	16,820 (15)	229 (20)	476 (8)	3715 (20)
2009	16,944 (15)	305 (26)	947 (16)	3076 (17)
2010	15,696 (14)	257 (22)	1385 (23)	2347 (13)
2011	13,097 (12)	153 (13)	1022 (17)	1807 (10)
2012	11,741 (11)	105 (9)	880 (15)	1362 (7)
2013	10,102 (9)	47 (4)	646 (11)	1007 (5)
2014	7805 (7)	S[b]	452 (8)	735 (4)
2015	1396 (1)	S[b]	79 (1)	102 (1)
Alcohol-related disorders, n (%)	16,329 (15)	221 (20)	1158 (19)	2775 (15)
Smoking status, n (%)				
Current	17,183 (15)	142 (12)	758 (13)	2741 (15)
Past	42,659 (38)	S[b]	S[b]	7129 (39)
Never	51,899 (46)	511 (43)	2788 (47)	8573 (46)
Unknown	299 (0.3)	S[b]	S[b]	70 (0.4)
Body mass index, n (%)				
< 25 kg/m^2	11,384 (10)	9 (1)	576 (10)	3183 (17)
25-30 kg/m^2	33,976 (30)	81 (7)	1809 (30)	6216 (34)
≥30.0	64,582 (58)	1087 (92)	3601 (60)	8691 (47)
Unknown	2098 (2)	0 (0.0)	16 (0.3)	423 (2)
Hemoglobin A1c, n (%)				
≤7.0%	17,187 (15)	147 (13)	674 (11)	1972 (11)
7.1%-8.0%	31,439 (28)	208 (18)	1941 (32)	4995 (27)
>8.0%	47,866 (43)	811 (69)	3333 (56)	9298 (50)
Unknown	15,548 (14)	11 (1)	54 (1)	2248 (12)
Cancer, n (%)	11,770 (11)	103 (9)	756 (13)	2293 (12)
Inflammatory bowel disease, n (%)	1350 (1)	16 (1)	87 (1)	302 (2)
Charlson comorbidity score, n (%)				
0	42,139 (38)	309 (26)	1036 (17)	6075 (33)
1-2	52,390 (47)	603 (51)	3207 (53)	8349 (45)
≥3	17,511 (16)	265 (23)	1759 (29)	4089 (22)
Neuropathy, n (%)	12,235 (11)	320 (27)	1528(26)	2778 (15)
Renal disease, n (%)	18,438 (17)	249 (21)	1613(27)	4583 (25)
Retinopathy, n (%)	12,562 (11)	325 (28)	1881 (31)	2787 (15)
Peripheral arteriopathy, n (%)	4365 (4)	52 (4)	358 (6)	921 (5)
Aspirin use, n (%)	52,018 (46)	808 (69)	4076 (68)	10,358 (56)
Statins use, n (%)	80,644 (72)	1072 (91)	5464 (91)	14,177 (77)
Number of non-antidiabetic drugs, n (%)				
0	4188 (4)	S[b]	29 (1)	570 (3)
1	5049 (5)	S[b]	81 (1)	549 (3)
2	6455 (6)	13 (1)	131(2)	794 (4)
3	7525 (7)	29 (3)	188 (3)	934 (5)
≥4	88,823 (79)	1128 (96)	5573 (93)	15,666 (85)

Number of unique antidiabetic drugs, n (%)				
0	85,778 (77)	42 (4)	427 (7)	7736 (42)
1	16,127 (14)	190 (16)	2234 (37)	8863 (48)
2	8303 (7)	537 (46)	2696 (45)	1750 (9)
3	1661 (2)	359 (31)	587 (10)	149 (1)
≥4	171 (0.1)	49 (4)	58 (1)	15 (0.1)
Class of unique antidiabetic drugs, n (%) [c]				
Metformin	23,975 (21)	1125 (96)	5528 (92)	10,516 (57)
Sulfonylureas	12,009 (11)	885 (75)	3510 (59)	1296 (7.0)
Thiazolidinediones	6212 (6)	645 (55)	2148 (36)	1975 (11)
Insulins	897 (1)	332 (28)	273 (5)	57 (0.3)
Others	825 (1)	114 (10)	256 (4)	144 (1)
Age, years (mean, SD)	64 (12)	60 (8.1)	67 (10)	66 (12)
Duration of treated diabetes in years (mean, SD)	1.4 (3.0)	8.0 (3.9)	7.7 (3.9)	2.9 (3.2)

Abbreviations: SD, standard deviation; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4

[a] Patients using other antidiabetic drugs (n=86,348) are not displayed in the table.

[b] Numbers less than 5 are not displayed, as per the confidentiality policies of the Clinical Practice Research Datalink.

[c] Non-mutually exclusive groups measured any time before (not including) cohort entry.

Note: Some categories may not add up to 100% due to rounding.

Table 2. Crude and Adjusted HRs for the Association Between the Use of GLP-1 Analogues and the Risk of Colorectal Cancer

Exposure [a]	Events	Person-years	Incidence rate [b] (95% CI)	Crude HR	Adjusted HR (95% CI) [c]
Sulfonylureas	302	151,949	2.0 (1.8, 2.2)	1.0	1.0 [Reference]
GLP-1 analogues	26	16,135	1.6 (1.1, 2.4)	0.8	1.0 (0.7, 1.6)
Duration of GLP-1 analogue use, years					
≤ 1	7	6504	1.1 (0.4, 2.2)	0.5	0.7 (0.3, 1.5)
1.1-2	12	5610	2.1 (1.1, 3.7)	1.1	1.4 (0.8, 2.6)
> 2	7	4021	1.7 (0.7, 3.6)	0.8	1.1 (0.5, 2.3)
Time since first GLP-1 analogue use, years					
≤ 2	9	5177	1.7 (0.8, 3.3)	0.9	1.2 (0.6, 2.4)
> 2	17	10,958	1.6 (0.9, 2.5)	0.7	1.0 (0.6, 1.6)

Abbreviations: HR, hazard ratio; CI, confidence interval; GLP-1, glucagon-like peptide-1

[a] Use of other antidiabetic drugs was considered in the model, but not presented in the table.

[b] Per 1000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, body mass index (BMI), smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic failure), hemoglobin A1c, duration of treated diabetes, previous cancer, presence of inflammatory bowel disease, Charlson comorbidity score, neuropathy, renal disease, retinopathy, peripheral arteriopathy, aspirin, statins, the number of unique antidiabetic drugs and the total number of unique non-diabetic drugs in the year before cohort entry.

Table 3. Crude and Adjusted HRs for the Association Between the Use of DPP-4 Inhibitors and the Risk of Colorectal Cancer

Exposure [a]	Events	Person-years	Incidence rate [b] (95% CI)	Crude HR	Adjusted HR (95% CI) [c]
Sulfonylureas	241	127,443	1.9 (1.7, 2.2)	1.0	1.0 [Reference]
DPP-4 inhibitors	117	56,613	2.1 (1.7, 2.5)	1.1	1.2 (1.0, 1.5)
Duration of DPP-4 inhibitor use, years					
≤ 1	38	16,248	2.3 (1.7, 3.2)	1.2	1.4 (1.0, 2.0)
1.1-2	34	19,820	1.7 (1.2, 2.4)	0.9	1.0 (0.7, 1.5)
> 2	45	20,545	2.2 (1.6, 2.9)	1.1	1.2 (0.9, 1.7)
Time since first DPP-4 inhibitor use, years					
≤ 2	43	19,625	2.2 (1.6, 3.0)	1.2	1.3 (1.0, 1.9)
> 2	74	36,988	2.0 (1.6, 2.5)	1.0	1.1 (0.9, 1.5)

Abbreviations: HR, hazard ratio; CI, confidence interval; DPP-4, dipeptidyl peptidase-4

[a] Use of other anti-diabetic drugs was considered in the model, but not presented in the table.

[b] Per 1000 Person-Years.

[c] Adjusted for age, sex, year of cohort entry, body mass index (BMI), smoking, alcohol-related disorders (including for example alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and hepatic failure), hemoglobin A1c, duration of treated diabetes, previous cancer, presence of inflammatory bowel disease, Charlson comorbidity score, neuropathy, renal disease, retinopathy, peripheral arteriopathy, aspirin, statins, the number of unique antidiabetic drugs and the total number of unique non-diabetic drugs in the year before cohort entry.

Figure