

CLINICAL—PANCREAS

Pancreatitis, Pancreatic, and Thyroid Cancer With Glucagon-Like Peptide-1–Based Therapies

MICHAEL ELASHOFF, ALEKSEY V. MATVEYENKO, BELINDA GIER, ROBERT ELASHOFF, and PETER C. BUTLER

Larry L. Hillblom Islet Research Center at David Geffen School of Medicine and Department of Biomathematics, University of California, Los Angeles, California

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BACKGROUND & AIMS: Glucagon-like peptide-1–based therapy is gaining widespread use for type 2 diabetes, although there are concerns about risks for pancreatitis and pancreatic and thyroid cancers. There are also concerns that dipeptidyl peptidase-4 inhibitors could cause cancer, given their effects on immune function. **METHODS:** We examined the US Food and Drug Administration's database of reported adverse events for those associated with the dipeptidyl peptidase-4 inhibitor sitagliptin and the glucagon-like peptide-1 mimetic exenatide, from 2004–2009; data on adverse events associated with 4 other medications were compared as controls. The primary outcomes measures were rates of reported pancreatitis, pancreatic and thyroid cancer, and all cancers associated with sitagliptin or exenatide, compared with other therapies. **RESULTS:** Use of sitagliptin or exenatide increased the odds ratio for reported pancreatitis 6-fold as compared with other therapies ($P < 2 \times 10^{-16}$). Pancreatic cancer was more commonly reported among patients who took sitagliptin or exenatide as compared with other therapies ($P < .008$, $P < 9 \times 10^{-5}$). All other cancers occurred similarly among patients who took sitagliptin compared with other therapies ($P = .20$). **CONCLUSIONS:** These data are consistent with case reports and animal studies indicating an increased risk for pancreatitis with glucagon-like peptide-1–based therapy. The findings also raise caution about the potential long-term actions of these drugs to promote pancreatic cancer.

Keywords: Side Effect; Toxicity; Tumor; Pancreas.

Hyperglycemia in type 2 diabetes is due to inadequate insulin secretion in the setting of insulin resistance. A new class of drugs has been introduced for treatment of type 2 diabetes that takes advantage of the properties of the gut hormone glucagon-like peptide-1 (GLP-1).¹ GLP-1 is secreted by L-type endocrine cells in the distal ileum in response to food ingestion and amplifies glucose-mediated insulin secretion.²

GLP-1 has a short half-life, degraded by the enzyme dipeptidyl peptidase-4 (DPP-4) in the circulation.³ To accomplish sustained GLP-1 receptor activation therapeutically, 2 strategies have been developed. In one, GLP-1 agonists that are resistant to DPP-4 degradation are administered by injection, including exenatide (Byetta; Amylin Pharmaceuticals, San Diego, CA) and liraglutide (Victoza; Novo Nordisk, Bagsvaerd, Denmark).^{4,5} The alternative strategy is use of inhibitors of DPP-4, such as sitagliptin (Januvia; Merck & Co, Inc, Whitehouse Station, NJ), when administered orally enhance levels of endogenously secreted GLP-1.^{4,5}

The attributes of GLP-1–based therapy for type 2 diabetes have been extensively reviewed.^{1,4–6} Interest has recently been focused on the potential adverse effects of these new therapies.^{7,8} Nausea is relatively common with the injected GLP-1 receptor agonists. Acute pancreatitis after administration of exenatide was originally reported in the form of case reports,^{9,10} but then followed by a cautionary letter from the US Food and Drug Administration (FDA).¹¹ Recently, a similar caution was made by the FDA with regard to pancreatitis associated with sitagliptin treatment.¹²

The manufacturers of exenatide and sitagliptin have suggested that the most likely reason for the apparent association between the use of these drugs and acute pancreatitis is the increased risk of pancreatitis in patients with type 2 diabetes.¹³ Recent animal studies showing pancreatitis as a consequence of GLP-1 mimetic therapy challenge that assumption and raise concerns about whether the asymptomatic chronic pancreatitis might be an as yet undetected adverse effect of GLP-1–based treatment.^{14,15} Moreover, because pancreatitis is a risk factor for pancreatic cancer, long-term GLP-1 receptor activation might lead to increased risk for pancreatic cancer.^{16,17} It has also been suggested that immunomodulatory effects of DPP-4 inhibition might increase risk for all cancers.^{18,19} Also, thyroid tumors were reported to be more common

Abbreviations used in this paper: AERS, adverse event reporting system; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; FDA, Food and Drug Administration; GLP-1, glucagon-like peptide-1; OR, odds ratio.

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in rodent toxicology studies with the GLP-1 agonist liraglutide, although the relevance of this in humans has been questioned.²⁰

Given the >20 million known patients with type 2 diabetes in the United States alone and the numerous GLP-1-based drugs either available now or in the final stages of development, the potential impact of adverse effects of this class of drugs is considerable. However, because this class of drugs is relatively newly available, there are limited data on adverse effects. In addition, available reports were sponsored by pharmaceutical companies and arguably have a limited capacity to detect adverse outcomes.^{21,22} The purpose of the present study was to gain the best possible insight into these potential adverse effects by examining the FDA adverse event reporting system (AERS) database.

Materials and Methods

Study Design

The primary goal of this analysis was to use the FDA AERS database to assess the association between treatment with exenatide (Byetta) or sitagliptin (Januvia) and an adverse event report of pancreatitis, where the drugs were listed as the primary suspect associated with a pancreatitis report in the database. A secondary goal was to examine the FDA AERS database for reported pancreatic or thyroid cancer associated with use of exenatide or sitagliptin. Third, we used the FDA AERS database to examine reports of all cancers in association with use of sitagliptin and exenatide. The FDA AERS database depends on spontaneous reporting and is subject to various reporting biases. For this reason, 2 levels of control were used for the analysis. First, 4 other diabetes medications, ie, rosiglitazone (Avandia; GlaxoSmithKline, London, UK), nateglinide (Starlix; Novartis, Basel, Switzerland), repaglinide (Prandin; Novo Nordisk, Bagsværd, Denmark), and glipizide, were selected as control drugs. Rosiglitazone has been reported to attenuate toxin-induced pancreatitis in rats²³ and to exacerbate pancreatic fat infiltration in high-fat-fed mice.²⁴ Rosiglitazone appears to be neutral with regard to cancer risk.¹³ It has been suggested that sulfonylurea therapy might increase risk for pancreatitis²⁵ and solid tumors,²⁶ so these drugs should be a conservative choice as controls. Second, control events were prospectively defined that were believed a priori to have no association with either of the test drugs, exenatide/sitagliptin, or the control drugs.

The predefined events of interest were pancreatitis, pancreatic cancer, thyroid cancer, and all cancers. We prospectively defined 5 types of control events, including back pain, urinary tract infection, chest pain, cough, and syncope. By this approach, we were able to address the issue that pancreatitis²⁷ and pancreatic cancer²⁸ are more common in type 2 diabetes because test and control drugs are used for treatment of type 2 diabetes.

Database inquiry. We downloaded the FDA AERS database for the period covering the first quarter of 2004

through third quarter of 2009. and applied the search terms listed below. As described in the study design, only primary suspect drugs were used in the analysis (ROLE_COD='PS'); cases with more than one primary suspect drug were counted for each drug. For pancreatitis, the search term "PANCREATITIS" was used. Control events used the search terms "BACK PAIN", "CHEST PAIN", "COUGH", "SYNCOPE", and "URINARY TRACT INFECTION". For pancreas cancer, the search terms "PANCREATIC MASS", "PANCREATIC NEOPLASM", "ADENOCARCINOMA PANCREAS" and "PANCREATIC CARCINOMA" were used. For thyroid cancer, the search terms "THYROID CANCER", "THYROID GLAND CANCER", "THYROID NEOPLASM" and "THYROID MASS" were used. For all other cancers, "THYROID" and "PANCREATIC" records were filtered out, and the search terms "LEUKAEMIA", "CANCER", "SARCOMA", "MYELO", "CARCINOM", "MALIGNAN", "NEOPLAS", "TUMOUR", "METASTASES", "MACROGLOBULINEMIA", "LYMPHOMA", "MELANOMA", "BLASTOMA", "CYTOMA", "MENINGIOMA", "MESOTHELIOMA", "HODGKIN", "GLIOMA", "ADENOMA", "BLADDER MASS", "BRAIN MASS", "BREAST MASS", "HEPATIC MASS", "RENAL MASS", "INTESTINAL MASS", "LARYNGEAL MASS", "OESOPHAGEAL MASS", "OVARIAN MASS", "PHARYNGEAL MASS", "PROSTATIC MASS", "PULMONARY MASS", "UTERINE MASS", "TESTICULAR MASS", "STOMACH MASS", "SCROTAL MASS", "SALIVARY GLAND MASS", "ABDOMINAL MASS", "LYMPHADENO" and "RHABDOMYO" were used. For the analysis that used only events reported to have occurred prior to 2007, the same database was filtered by EVENT_DT<2007 prior to querying for the above terms (if EVENT_DT was missing, FDA_DT<2007 was used). For drugs, the following search terms were used: exenatide: "BYETTA", "EXENATIDE"; sitagliptin: "JANUVIA", "SITAGLIPTIN"; control drugs: "AVANDIA", "ROSIGLITAZONE", "STARLIX", "NATEGLINIDE", "PRANDIN", "REPAGLINIDE", "NOVONORM", "GLIPIZIDE" and "GLUCOTROL". In all cases, search terms were applied with a wildcard character before and after the search term.

Statistical Analysis

Two levels of control were used for the comparative analysis of event rates. The count of events of interest (eg, pancreatitis) in a test drug (eg, exenatide) were compared to control drugs and to control events (events for which there was the presumption of no drug-event relationship) using 2 × 2 tables. The premise on which the 2-level control is based is that under the null hypothesis of no elevated event rate for the test drugs, the odds ratio (OR) in the 2 × 2 table should be 1. Fisher's exact test was used to test the null hypothesis that the OR was equal to 1. Two-sided 95% confidence intervals were also constructed for the estimated ORs. The Breslow-Day test was used to test for homogeneity of odds-ratios by gender, and the Mantel-Haenszel test was used to perform gender stratified analyses. All statistical analyses were conducted

Table 1. Test and Control Events for Exenatide and Sitagliptin vs Control Drugs

PANCREATITIS				
Drug	Pancreatitis events	Control events	Odds ratio vs control drugs	P-value vs control drugs
Exenatide	971	1433	10.68	2×10^{-16}
Sitagliptin	131	306	6.74	2×10^{-16}
Controls	43	678	—	—
PANCREATITIS (2006 AND PRIOR)				
Drug	Pancreatitis events	Control events	Odds ratio vs control drugs	P-value vs control drugs
Exenatide	152	748	2.57	8×10^{-7}
Sitagliptin	2	15	1.69	.37
Controls	32	405	—	—
PANCREAS CANCER				
Drug	Pancreas cancer events	Control events	Odds ratio vs control drugs	P-value vs control drugs
Exenatide	81	1433	2.95	9×10^{-5}
Sitagliptin	16	306	2.72	.008
Controls	13	678	—	—
THYROID CANCER				
Drug	Thyroid cancer events	Control events	Odds ratio vs control drugs	P-value vs control drugs
Exenatide	30	1433	4.73	4×10^{-3}
Sitagliptin	2	306	1.48	.65
Controls	3	678	—	—
ALL OTHER CANCERS				
Drug	All cancer events	Control events	Odds ratio vs control drugs	P-value vs control drugs
Exenatide	375	1433	1.08	.47
Sitagliptin	59	306	0.8	.2
Controls	164	678	—	—

using R version 2.9 (The R Foundation for Statistical Computing).

Results

Control Events

The validity of the analysis is predicated on a similar rate of reported control events for each drug in the analysis. For the 2 test drugs and 4 control drugs, this was found to be the case. However, one drug initially chosen for the analysis (pioglitazone) had an elevated control event reporting rate compared to the other drugs, which were otherwise similar in their control event rate. This was not driven by any one of the controls, but rather was an overall elevation in reported control events. This means that either pioglitazone truly has an increased frequency of these events, or some reporting bias exists with pioglitazone relative to the other drugs. In either case, its inclusion in the analysis would be suspect. As a practical issue, despite the higher control event rate (control reports/total reports), the actual number of control reports was relatively low, and dropping it from the analysis resulted in only a modest reduction in the power of the analysis. The similarity of the control event rates for the remaining drugs supported the validity of this 2-level control analysis approach.

Pancreatitis. Exenatide and sitagliptin had similar patterns of reported pancreatitis events relative to the controls events. Pancreatitis has been reported >6-fold more frequently as an adverse event for patients administered exenatide (OR = 10.68; 95% confidence interval [CI]: 7.75–15.1; $P < 10^{-16}$) or sitagliptin (OR = 6.74; 95% CI: 4.61–10.0; $P < 10^{-16}$) when compared with other therapies (Table 1, Figure 1). When the adverse reporting events of the GLP-1 class of drugs (exenatide and sitagliptin) were considered together, the reported event rate of pancreatitis was approximately 10-fold greater than that of other therapies (OR = 9.99; 95% CI: 7.26–14.1; $P < 10^{-16}$).

Because of recent attention to the potential link between use of GLP-1 mimetic drugs and pancreatitis after the FDA's first warning in 2007¹¹ that pancreatitis appeared to be an adverse effect of exenatide treatment, the analysis was repeated using only events reported to have occurred in 2006 or earlier. Because sitagliptin had only recently been made available at that time, there were insufficient reports to consider sitagliptin alone, so the event rates for the combined GLP-1 mimetic therapies of sitagliptin and exenatide were considered together. The reported event rate for pancreatitis for the GLP-1 mimetic drugs was still >2.5-fold increased compared to other therapies (OR = 2.55; 95% CI: 1.70–3.94; $P < 1 \times 10^{-6}$).

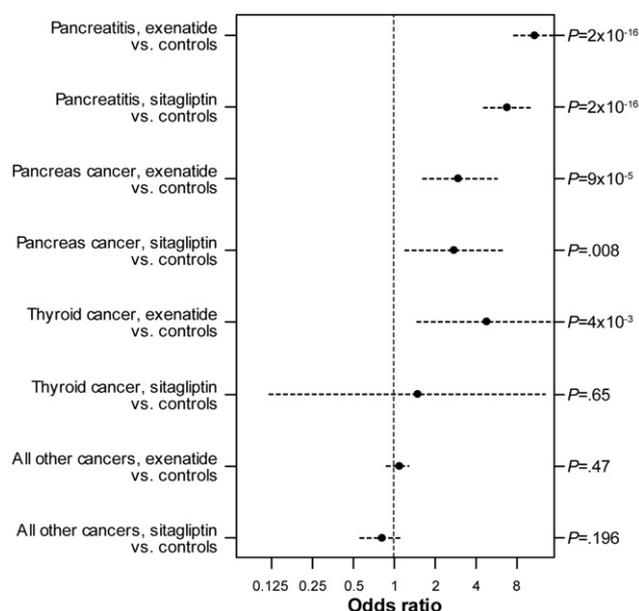


Figure 1. Odds ratio of test vs control events for exenatide, sitagliptin, and other therapies. The odds ratio of an adverse report of pancreatitis, pancreatic and thyroid cancer, or any cancer associated with exenatide and/or sitagliptin therapy vs other therapies.

Collectively, these data imply that there is an increased risk of pancreatitis in patients treated with either exenatide or sitagliptin vs the other therapies.

Pancreatic cancer. Because pancreatitis is a known risk factor for pancreatic cancer,¹⁷ we evaluated the reported rates of pancreatic cancer with exenatide and sitagliptin compared to control events relative to rosiglitazone.

The reported event rate for pancreatic cancer was 2.9-fold greater in patients treated with exenatide compared to other therapies ($P = 9 \times 10^{-5}$). The reported event rate for pancreatic cancer was 2.7-fold greater with sitagliptin than other therapies ($P = .008$).

Thyroid cancer. Because thyroid tumors were reported to be increased in rodents treated with liraglutide in a filing to the FDA,²⁰ we examined the frequency of reported adverse events of thyroid cancer with the GLP-1 mimetic therapies vs rosiglitazone. The reported event rate for thyroid cancer in patients treated with GLP-1 mimetic therapy was increased and reached statistical significance in the exenatide group (OR = 4.73; $P = 4 \times 10^{-3}$), but not in the sitagliptin group (OR = 1.48; $P = .65$).

All other cancers. There has been a suggestion that DPP-4 inhibition may lead to impaired immune function and increased risk for cancers.^{18,19} Therefore, we also examined the reported event rate for all other cancers (excluding pancreas and thyroid) associated with sitagliptin, exenatide, or the control therapies. Neither sitagliptin or exenatide were associated with a higher reported rate of other cancers. The risk for cancer increases with age but age was not different between the individuals in whom cancer (mean age, 61 years other therapies, 61 years exenatide, 64 years sitagliptin) or a control event (mean age, 62 years other therapies, 60 years exenatide, 63 years

sitagliptin) was reported for the drugs included in this analysis.

Discussion

We report a >6-fold increased reported adverse event rate for pancreatitis with either of the first two GLP-1-based drugs available on the market in the United States, exenatide and sitagliptin, in this analysis of the FDA AERS database.

Analysis of the FDA AERS database is not the ideal mechanism to compare adverse event rates between drugs. Limitations of the FDA AERS database, including incomplete data and reporting biases, are well-known.²⁹ However, AERS has proven effective in similar earlier evaluations at detecting unintended drug side effects.^{30–32} This analysis was undertaken notwithstanding these limitations, given the paucity of safety data available for this class of drugs, which is gaining a rapid increase in usage for a common disease. Randomized, controlled clinical trials remain the gold standard for such assessment. Those trials are typically powered for efficacy end points related to the relative attributes of the new drugs in accomplishing expected goals, such as glycemic control compared to previously available drugs. They do not necessarily accumulate sufficient data (in either patient numbers or follow-up) on infrequent or longer-term consequences of the drugs (eg, cancers). The primary goal of this study was to examine the FDA database as methodically as possible to establish whether there are sufficient grounds for concern that would indicate the need for studies that specifically examine the signals that arise in a prospective manner.

The approach we have taken should be robust against a range of potential reporting biases. In particular, if the test drugs have an overall increased reporting rate for events, the OR will be unaffected. Similarly, if the test events have an overall increased reporting rate, the OR will be unaffected. However, the approach has significant weaknesses. The analysis is retrospective. Potential confounders that influenced the choice of drug therapy for type 2 diabetes could introduce bias. For example if cigarette smokers were to be more likely treated with GLP-1 based therapy than other therapies for type 2 diabetes, a bias in favor of pancreatitis or pancreatic cancer would be introduced. Since cigarette smoking is not reported in the FDA data base we cannot exclude an unexpected bias in favor of diabetes treatment choice in this regard. More generally, the odds ratios reported here will be upwardly biased if patients who are at higher risk for pancreatitis, pancreatic and/or thyroid cancer received exenatide or sitagliptin, either as a first line therapy, or subsequent to a poor response to the therapy of first choice. There are plausible scenarios where this might happen, but we are unable to thoroughly determine the extent of this bias based on this retrospective study.

Also, although the controls (drugs and events) were prospectively defined, the analysis makes certain assump-

tions about these controls that cannot be easily tested. One assumption is that the control events are not causally related to either the test drugs or the control drug. The events were chosen based on a review of available reported adverse event data for these drugs, but proving a negative is difficult. A second assumption is that, conditional on control event counts, the test events are not subject to reporting bias. That is, the control event counts serve as a surrogate for any differential reporting bias between the drugs. It is possible that alternate control drugs and/or alternate choices for control events could lead to different conclusions. However, we believed that restricting the analysis to prospectively defined controls and limiting the number of possible analyses would avoid many of the biases of a data-mining approach, given the large scope of the AERS database. To directly address this potential concern, we repeated the analysis using an alternate set of control events identified from the top events in the database. In all cases where the original analysis was significant that significance was maintained in the analysis using the alternate control events.

A potential confounding factor for the present analysis is obesity. The FDA AERS database does not record obesity (eg, body mass index), which is associated with pancreatitis risk²⁵ and may be associated with a higher usage of exenatide prescription due to the reported weight-loss effect of that drug. However, Blomgren et al report that, although statistically significant, the magnitude of the effect of higher body mass index on pancreatitis risk is equivalent to a 1.2-fold increased risk per 5 units of body mass index.²⁵ Given the fact that the FDA AERS database yields a >6-fold increased frequency of pancreatitis with either exenatide or sitagliptin treatment compared to other therapies, the potential confounding effects of obesity on the observed results is likely to be minimal.

Another potential confounder is gender. We performed gender stratified analysis for all of the comparisons between test drugs and control drugs; in all cases where the original analysis was significant, that significance was maintained in the gender stratified analysis, with no evidence of a confounding effect by gender on the reported odds ratio.

In contrast to the findings here, several studies recently reported no increase in pancreatitis in patients treated with GLP-1 receptor mimetic therapy.^{22,33–35} These studies do not include any randomized controlled trials in which pancreatitis or pancreatic cancer were predefined end points, and that were adequately powered to address these questions. A retrospective study of pharmacy claims analysis found no increase in association between use of exenatide and pancreatitis compared to other antidiabetes drugs.³⁵

Recent animal studies that also showed pancreatitis after GLP-1–based treatment provided some insight into the potential mechanisms by which this adverse event may be mediated.^{14,15} GLP-1 receptors are abundantly expressed in the exocrine pancreas, and sitagliptin therapy has been shown to lead to increased pancreatic ductal

replication, acinar to ductal metaplasia, and, less commonly, acute pancreatitis in a rat model of type 2 diabetes.¹⁴ Increased ductal turnover and acinar to ductal metaplasia are both well-established characteristics of chronic pancreatitis in humans.³⁶ Low-grade chronic pancreatitis was noted in most rats treated with exenatide in one study,¹⁵ but not in a subsequent study.³⁷ In the absence of human pancreas from individuals treated with GLP-1 mimetic drugs, it remains unknown if GLP-1–based therapy can induce asymptomatic low-grade pancreatitis. This is of concern because chronic pancreatitis increases risk of pancreatic cancer.^{16,17,36}

For this reason, as a secondary analysis, we sought to address the question, does long-term GLP-1 therapy predispose to pancreatic cancer? At present there is no direct evidence to support an increase in pancreatic cancer with long-term GLP-1 therapy, but there are grounds for concern. Even though the drugs have only been available relatively recently, this analysis shows increased reported pancreatic cancer in association with either sitagliptin or exenatide treatment compared to other therapies. It might be argued that an apparent increase in pancreatic cancer with GLP-1 mimetic therapy is because pancreatic cancer is more frequent in type 2 diabetes,^{28,38} but in the present analysis, this was controlled for by comparison with adverse reporting in association with control antidiabetic drugs, so all cases included presumably had type 2 diabetes. The selected control drugs have been reported as either neutral¹³ or possibly even increasing the risk for pancreatic cancer.²⁷ We elected not to use metformin as a control because it has been reported to decrease the risk for pancreatic cancer.^{26,39} We elected not to use insulin as a control because this would likely include controls with type 1 diabetes.

Because pancreatitis presumably acts as a risk factor for subsequent pancreatic cancer through the mechanisms of chronic inflammation and increased cell turnover,³⁶ it is not surprising that there is a progressive increased risk with years of exposure. For example, in patients with inherited chronic pancreatitis, the risk increases progressively with years of exposure, eventually reaching almost 75%.¹⁷ The GLP-1–based drugs examined here have been on the market for no more than 6 years, raising the question of whether it is biologically plausible that there is already an increase in pancreatic cancer. Type 2 diabetes and obesity are known risk factors for chronic pancreatitis and pancreatic cancer, so it is reasonable to assume that in such individuals there is an increased incidence of the premalignant PanIN lesions in the pancreas. It has recently been proposed that these are derived from pancreatic duct glands that, in turn, might well be targets for GLP-1–induced proliferation.⁴⁰ It will be important to establish whether PanIN lesions and pancreatic duct glands express GLP-1 receptors and, if so, undergo proliferation in response to GLP-1 mimetic therapy. Such an effect could explain the relatively early signal for pancreatic cancer observed here.

Because of thyroid tumors in mice treated with liraglutide reported to the FDA by Novo Nordisk,²⁰ we also examined the FDA AERS database for thyroid cancer in association with exenatide or sitagliptin therapy. There was an increase in reported thyroid cancer as an adverse event related to exenatide or sitagliptin therapy (data combined) compared to other therapies, this increase was statistically significant for exenatide. GLP-1 therapy has been shown to lead to C-cell hyperplasia in rats, but it is unknown what, if any, effects GLP-1 therapy has on the human thyroid gland.²⁰ The adverse reporting in the FDA database is not sufficiently sophisticated to robustly distinguish between thyroid cancer subtypes. It is perhaps of concern that this signal has appeared in the relatively short duration the drugs have been available when there was little a priori concern that would be expected to bias reporting. The findings for pancreatic and thyroid cancer reported here imply that more detailed studies of the actions of GLP-1 on the thyroid gland and exocrine pancreas in humans are warranted.

Finally, we examined the relative frequency of all other reported cancers as adverse events related to each of the 2 study drugs. This analysis was prompted by the reported actions of DPP-4 inhibition on the immune system and concerns raised that these might promote cancer through decreased immunosurveillance.^{18,19}

Any action of DPP-4 inhibition to increase cancer risk might be expected to do so by permitting declaration of tumors previously held in check by an intact immune system.^{18,19,41} As such, the effect may manifest early. To date these data do not identify a signal of other cancers as searched with either drug. Given the multiple search terms required for this analysis and the numerous variations that might be introduced in such a search, we fully acknowledge that this is the least secure analysis. While the prior analyses remained unchanged through the various changes in search requested in review, the all other cancers outcome did change according to changes in search.

In conclusion, analysis of the FDA adverse event reporting database suggests that the GLP-1 class of drugs being widely promoted for treatment of type 2 diabetes could have serious unintended and unpredicted side effects. Pancreatitis is >6-fold more likely to be reported in association with sitagliptin or exenatide than other therapy in type 2 diabetes. Despite the fact that exenatide and sitagliptin have been available for a relatively short period, it is of concern that, when taken together, there is a significantly increased association of thyroid cancer and pancreatic cancer with these therapies. The most obvious conclusion from these studies is that careful long-term monitoring of patients treated with GLP-1 mimetics or DPP-4 inhibitors is required. Almost all clinical trials of these drugs include metformin, the unchallenged first-line therapy of choice for type 2 diabetes. In contrast, in clinical practice in the field, the new drugs are being used as early monotherapies. Because metformin likely suppresses the putative actions of GLP-1 based drugs to promote pancreatitis and pancreatic cancer, it will be

important to establish the impact of GLP-1 mimetic therapy in the absence of metformin in prospective clinical trials if this treatment is to be available for use in the absence of metformin. We agree with a recent proposal that such monitoring should be established independently of pharmaceutical companies.²⁹ For now this analysis of the FDA data base does not establish that pancreatitis, pancreatic and thyroid cancer are caused by GLP-1 based therapy. It simply raises the level of concern that they may be and that the appropriate prospective studies are required to rule them out.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: [10.1053/j.gastro.2011.02.018](https://doi.org/10.1053/j.gastro.2011.02.018).

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Reprint requests

Address requests for reprints to: Peter C. Butler MD, Larry L. Hillblom Islet Research Center, David Geffen School of Medicine at UCLA, 900 Veteran Avenue, 24-130 Warren Hall, Los Angeles, California 90095-7073. e-mail: pbutler@mednet.ucla.edu; fax: (310) 206-5368.

Conflicts of Interest

The authors disclose no conflicts.

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