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Thiazolidinedione Therapy Is Not Associated with Increased Colonic Neoplasia Risk in Patients with Diabetes Mellitus

James D. Lewis, MD, MSCE[1], **Angela M. Capra, MA**[2], **Ninah S. Achacoso, MS**[2], **Assiamira Ferrara, MD, PhD**[2], **Theodore R. Levin, MD**[2], **Charles P. Quesenberry Jr, PhD**[2], and **Laurel A. Habel, PhD**[2]

1 *Department of Medicine, Division of Gastroenterology, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine*

2 *Division of Research, Kaiser Permanente Northern California*

Abstract

Background & Aims—Diabetes mellitus is associated with an increased risk of colorectal cancer. Thiazolidinediones, which are ligands for PPARγ, are widely used to treat patients with diabetes. PPARγ is highly expressed in the colon and exposure to thiazolidinediones has been proposed to affect the risk for colorectal neoplasia. Studies using in vitro models suggest that thiazolidinediones have anti-neoplastic effects, whereas in vivo studies have produced mixed results--some indicate an increased risk for intestinal tumors. This study examined the association between PPARγ-targeted therapies and the risk of colonic neoplasia in patients with diabetes.

Methods—We conducted 3 retrospective case-control studies nested within the cohort of diabetic patients that were cared for within the Kaiser Permanente of Northern California system from 1994 to 2005. Case subjects were those with colonic neoplasia identified at the time of colonoscopy (study-1), sigmoidoscopy (study-2), or at follow-up lower endoscopy (study-3). Controls had no neoplasia identified at the endoscopic exam. A minimum of 1 year of therapy was used to define medication exposure.

Results—14,086 patients were included. Among patients undergoing colonoscopy, there was an inverse association between thiazolidinedione exposure and prevalence of neoplasia (adjusted OR=0.73, 95% CI 0.57–0.92); however, this was not evident among patients without anemia (adjusted OR= 0.97, 95% CI 0.64–1.49). Significant associations between any or long-term thiazolidinedione use and colonic neoplasia were not observed among patients undergoing sigmoidoscopy or serial lower endoscopies.

Conclusions—These results indicate that thiazolidinedione therapy is not associated with an increased risk for colonic neoplasia.

Introduction

Patients with type 2 diabetes mellitus have an increased risk for colorectal neoplasia.[1] One hypothesis for the relation between type 2 diabetes mellitus and colon neoplasia is that hyperinsulinemia promotes colon carcinogenesis. High fasting levels of insulin are associated

Contact information: James D. Lewis, MD, MSCE, 720 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021, Email: lewisjd@mail.med.upenn.edu, Tel: 215-573-5137, Fax 215-573-0813.

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with an increased risk of colon cancer.[2] Similarly, among patients with type 2 diabetes mellitus, those treated long-term with exogenous insulin may have a particularly high risk of colon cancer.[3] Elevated insulin levels and glucose have also been linked to the risk of colorectal adenomas, the precursor of most colorectal cancers.[4]

Peroxisome proliferator-activated receptor gamma (PPARγ) is expressed at high levels in both the colonic epithelium and in colon cancer cell lines.[5–8] Thiazolidinedione (TZD) ligands for PPARγ are used to treat type 2 diabetes mellitus. Unlike other commonly used therapies for diabetes mellitus, TZDs increase insulin sensitivity, thereby decreasing insulin and insulin-like growth factor levels.[9, 10] As such, if hyperinsulinemia directly leads to colonic neoplasia, one would anticipate that long-term therapy with TZDs might decrease the risk. Further, antiproliferative and proapoptotic effects of TZDs have been demonstrated in numerous cancer cell lines, including colorectal cancer.[11] However, animal models of colon carcinogenesis have provided mixed results.[11] In the azoxymethane model, TZDs have been shown to prevent aberrant crypt foci and tumor formation.[12, 13] In addition, partial deficiency of PPARγ receptor leads to increased susceptibility to tumors in this model.[14] In contrast, in two studies, C57BL/6J-APC^{Min}/+ mice treated with TZDs had higher rates of intestinal tumor formation[6, 7], while in a third study, pioglitazone decreased tumor formation in APC deficient mice.[15]

Data are limited on the effect of TZD therapy on colon carcinogenesis in humans.[16] [17] Two prior clinical studies were limited by short follow-up and exposure periods. Because it may take many years to decades to develop colon cancer and TZDs were only first marketed in 1997, studies that focused on cancer as an outcome may have lacked sufficient follow-up time to observe a biologically important effect. Therefore, we investigated whether there is an association between TZD use and development of adenomatous polyps, the precursor lesion to nearly all human colon cancers.

Methods

We conducted three retrospective case-control studies nested within the cohort of diabetic patients cared for within the Kaiser Permanente healthcare system in Northern California (KPNC) during the period 1994 to 1996 and who continue to receive care between 1999 and 2005.

Setting

Kaiser Permanente Northern California provides comprehensive healthcare services to approximately 3.2 million members, representing approximately 25% of the population of the geographic area. The KPNC pharmacy database includes information on each outpatient prescription dispensed at a KPNC pharmacy. Prior research has demonstrated that 80% to 85% of KPNC members fill all of their prescriptions at Kaiser pharmacies; it is approximately 95% for those with a pharmacy benefit[18].

Patients with diagnosed diabetes mellitus are identified from several sources (pharmacy data, glycosylated hemoglobin [HbA1c] level >=6.7%, and outpatient, emergency room, and hospitalization records) annually for inclusion in the KPNC Diabetes Registry. As of January 1, 1996, the identification method was estimated to be 96% sensitive[19].

Source cohort and selection of cases and controls

To be included in the study cohort, patients were required to have completed a survey of diabetic patients that was administered during the year 1994 to 1996 and to be identified as having type 2 diabetes mellitus. From approximately 85,000 patients with type 1 or type 2 diabetes enrolled

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in KPNC between 1994 and 1996, 62,465 completed the questionnaire and were identified as having type 2 diabetes mellitus. This cohort has been previously described.[20] Patients were excluded from the study cohort if they had a history of inflammatory bowel disease, familial adenomatous polyposis syndrome, or hereditary non-polyposis colon cancer syndrome (n= 237).

Three case-control studies were conducted within this cohort (Figure 1), one to examine neoplasia in the entire colon, one to focus primarily on patients undergoing colon cancer screening, and one to examine newly formed adenomas. To be included in the first case-control study, patients were required to have undergone at least one colonoscopy between January 1, 1999 and December 31, 2005 (the first colonoscopy being defined as the index endoscopy), to have been at least 50 years old at the time of the index colonoscopy and to have continuous pharmacy benefits from KPNC between January 1, 1997 and the date of the index colonoscopy. For the primary analyses, there could not have been a sigmoidoscopy in the 6 months preceding the colonoscopy. Inclusion criteria for the second case-control study were identical, except that patients must have undergone a sigmoidoscopy as their index endoscopy. Inclusion criteria for the third case-control study required the patient to have undergone two lower endoscopies (colonoscopy or sigmoidoscopy) between January 1, 1999 and December 31, 2005 with the second lower endoscopy being at least one year after the first, regardless of whether adenomatous neoplasia was present at the first exam. The second lower endoscopy was defined as the index endoscopy.

In the first case-control study, cases were defined as patients with one or more adenomatous lesions (adenomatous polyps or invasive colorectal cancer) at any location within the colon on the index endoscopy. For patients with a second lower endoscopy within six months of the index endoscopy (such as a colonoscopy to follow-up a polyp found on sigmoidoscopy), we included any adenomatous lesion identified at either procedure (i.e., this was treated as a single procedure). In the second case-control study, the adenomatous polyps or invasive cancer had to be located in the distal colon, defined as any lesion diagnosed at sigmoidoscopy or if diagnosed at follow-up colonoscopy that was located in the rectum or sigmoid colon or located in the distal 40cm if no anatomic segment was noted. Control subjects were defined as patients without adenomatous lesions on the index endoscopy (or follow-up lower endoscopy) using the same anatomic criteria. Similar criteria were used to define cases and controls for the third case-control study, except that the second lower endoscopy (more than 12 months after first endoscopy) was defined as the index exam.

All pathology reports were manually reviewed to determine the presence or absence of adenomatous lesions.

Identification of TZD exposure

Exposure was measured at any time prior to the index endoscopy. The primary exposure definition was cumulative exposure to TZDs for a minimum of one year prior to the date of the index endoscopy. Cumulative exposure was measured from prescription records. If the next prescription was filled within 30 days of the expected end date of the previous prescription, therapy was categorized as uninterrupted. However, if there were no refills within the 30 days after the expected end date of the previous prescription, we assumed a gap in therapy starting 30 days after the date that the previous prescription should have ended. Based on review of refill intervals, the following exception was made for prescriptions with 200 or more days supply. If there were no further refills (i.e. the last or only prescription) and the days supply was for 200 or more days, we assumed a duration of 100 days (the mode) for all oral medications and 30 days (the mode) for insulin. Only prescriptions from 1/1/97 to the index date were included when calculating cumulative exposure.

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In secondary analyses, we examined alternative definitions of TZD exposure, including cumulative duration of TZD therapy (categorized as none, less than 1 year, 1 to <2 years, 2 years or longer), time since most recent TZD therapy (categorized no use, current use, last use within the preceding year, last use 1 to less than 2 years prior, and at least 2 years prior), and average dose of TZD during the period of use. Because three different TZDs have been prescribed in the health plan, we standardized average daily dose by expressing it as a percentage of maximum recommended dose (45mg for pioglitazone, 8mg for rosiglitazone, and 600mg for troglitazone).

Confounder variables

Data on potential confounders were extracted from the diabetes survey (diabetes duration, body mass index, and race) and a variety of electronic databases. These databases included registration files (age, sex, and location of residence), laboratory data (baseline HbA1C concentration), pharmacy data (other diabetes medications, acid suppression medications, statins, and nonsteroidal anti-inflammatory drugs [NSAIDs]), and medical encounters (lower endoscopy between January 1, 1995 and January 1, 1999, and diabetic retinopathy). Household income was estimated based on the median income of the census block of residency. For diabetes medications other than TZDs, we used the same definition of exposure (i.e. at least one year of cumulative exposure at any time prior to the index date). However, for other concomitant medications such as aspirin and NSAIDs, we required at least one year of cumulative exposure and use within the year preceding the index endoscopy to be considered exposed.[21]

To adjust for confounding as a result of prior colon cancer screening with lower endoscopy, we included a variable for the most recent prior lower endoscopy during the period from January 1, 1995 to the index date. We elected to categorize this variable into five levels: no prior lower endoscopy, prior colonoscopy (with or without sigmoidoscopy) in the preceding 3 years, prior sigmoidoscopy without colonoscopy in the preceding 3 years, prior colonoscopy (with or without sigmoidoscopy) more than 3 years prior to the index endoscopy, and prior sigmoidoscopy without colonoscopy more than 3 years prior to the index endoscopy. This categorization was based on the concept that the likelihood of developing new polyps increases with increasing duration from the most recent colonoscopy, that the subclinical period for colonic polyps is likely more than seven years, and that sigmoidoscopy examines only part of the colon[22].

Statistical analyses

In each of the case-control studies, the association between TZD exposure and colonic polyps was assessed using logistic regression. We included age, sex, other categories of diabetes medications and calendar year in all models. A separate indicator variable was created for each of the different classes of diabetes medications. We then added other confounders separately to determine whether inclusion of the variable altered the baseline estimate of the odds ratio by 10% or more. Variables that met this criterion were included in the final multivariable model. Time between lower endoscopies and the presence or absence of adenomatous neoplasia on the first lower endoscopy were tested for confounding and effect modification in the third case-control study using multivariable models and stratified models. For analyses of dose and duration, we repeated this process of confounder selection.

Secondary analyses were performed defining case subjects as having advanced adenomas or early adenomas. We defined advanced adenoma according to the histology and did not include the polyp size since we did not have access to endoscopy reports. Advanced neoplasia was defined as any adenoma with villous feature, high-grade dysplasia or invasive cancer. Separate logistic regression models were used to calculate odds ratios for early adenoma and advanced

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adenoma relative to no adenoma. In these analyses, patients were categorized according to their most advanced lesion.

In order to assure that we were not including patients with glucose intolerance rather than diabetes mellitus, a sensitivity analysis was conducted in the first case-control study excluding patients without a minimum of one year of cumulative exposure to at least one category of diabetes medications. A set of sensitivity analyses was conducted in the first two case-control studies including all patients who had a sigmoidoscopy prior to their index colonoscopy in the first study and including patients who had a colonoscopy or sigmoidoscopy as their index lower endoscopy in the second study. Another sensitivity analysis included large (>9mm) tubular adenomas based on the size noted on the pathology report as advanced adenomas. An additional sensitivity analysis in the third case-control study only defined exposure based solely on prescriptions filled between the first and second lower endoscopy. Finally, because TZD use can cause anemia that might prompt a lower endoscopy, a final sensitivity analysis excluded patients with a diagnosis of anemia (hemoglobin less than 13.5g/dl in males, 11.5g/dl in females) within the 6 months preceding the index date.

Results

Among the 62,465 patients with type 2 diabetes mellitus, 14,086 had undergone at least one lower endoscopy during the study period and met the other inclusion criteria. Cases and controls were relatively similar in all baseline characteristics and across the three case-control studies (Table 1). In each case-control study, there were slightly lower percentages of case subjects that were women (e.g. 41% cases vs. 49% controls in study-1) or users of prescription NSAIDs (e.g. 12% cases vs. 17% controls in study-1). The median duration of TZD use was 769.5 days (IQR 545 – 1108 days) in study-1, 760.5 days (IQR 545.5 – 1114.5 days) in study-2, and 850.5 days (IQR 590.0 – 1296.0 days) in study-3.

Study 1 – Adenoma in Any Region of the Colon

During the study period, 4248 patients underwent at least one colonoscopy, of whom 1296 (31%) had at least one adenoma. TZDs were used by 104 (8%) patients with adenomas and 318 (11%) patients without adenomas (unadjusted OR 0.72, 95% CI 0.57–0.91). After adjusting for age, sex, year of the endoscopy and use of diabetes medications other than TZDs, case subjects were less likely to have been exposed to TZDs (adjusted OR 0.73, 95% CI 0.57–0.92). No other variables met our definition of a confounder. We observed stronger associations between TZD use and absence of adenomas with current use than with former use and with use for at least one year than with less than 1 year in duration (Table 2). When we categorized adenomas as early or advanced, the results were similar, although the confidence intervals were wider because of the smaller number of case subjects.

Sensitivity analyses for study 1 provided similar results with one exception. Among the 554 case subjects and 1095 control subjects without a history of anemia, there was no evidence of an inverse association between TZD exposure and adenomatous neoplasia at colonoscopy. In this subgroup, TZD exposure for 1 year or longer [39 cases (7%) and 84 controls (8%)] had an adjusted odds ratio of 0.97 (95% CI 0.64–1.46). Similarly, the inverse associations for current use and longer term therapy observed in the overall cohort were not observed after excluding patients with anemia (Table 2). When we examined the subjects who had a history of anemia, the results were similar to the overall analyses. In this subgroup, TZD exposure was less common among patients with adenomas, particularly among patients who had taken TZDs for at least 1 year and who were currently being treated with a TZD (Table 2). A test for statistical interaction based on the presence or absence of anemia was not significant (p=0.39).

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Post hoc stratified analyses on selected clinical characteristics (HBA1c, diabetes duration, insulin therapy, and race) are included in supplemental Table 1 available at www.gastrojournal.org. These analyses generally provided similar results to the primary analyses.

Study 2 – Adenoma in the Distal Colon

During the study period, 9813 patients underwent at least one lower endoscopy, of whom 951 (10%) had at least one distal adenoma. TZDs were used by 60 (6%) patients with distal adenomas and by 656 (7%) of patients without distal adenomas. After adjusting for age, sex, year of the endoscopy and use of diabetes medications other than TZDs, use of TZDs was not associated with the presence of distal adenomas (adjusted OR 0.86, 95% CI 0.65–1.14) (Table 3). Likewise, there was little evidence of strengthening the association with more recent use (current use adjusted OR 0.86, 95% CI 0.61–1.20), increased duration of use (≥2 years adjusted OR 1.08, 95% CI 0.76–1.54), or higher average daily dose (≥0.65 units adjusted OR 0.96, 95% CI 0.67–1.38) (Table 3). When we categorized distal adenomas as early or advanced, the results were similar. Exposure to TZDs was not associated with early adenoma (adjusted OR 0.83, 95% CI 0.59–1.17) or advanced adenomas (adjusted OR 0.93, 95% CI 0.58–1.50). The sensitivity and stratified analyses produced nearly identical results to the primary analyses (sensitivity analyses data not shown, stratified analyses available in supplemental Table 2 at www.gastrojournal.org).

Study 3 – New or Missed Lesions in the Distal Colon

During the study period, 1825 patients underwent two lower endoscopies at least 1 year apart, of whom 159 (9%) had at least one distal adenoma on the second endoscopy. TZDs were used by 11% of these patients and 14% of patients without distal adenomas on the second endoscopy. After adjusting for age, sex, year of the endoscopy and use of diabetes medications other than TZDs, use of TZDs was not significantly associated with the presence of adenomatous polyps on the second lower endoscopy (adjusted OR 0.75, 95% CI 0.44, 1.28). There was little evidence of a dose or duration relationship (Table 4). Because only two patients with 1 year or longer exposure to TZDs had advanced adenomas on repeat colonoscopy, subgroup analyses of advanced adenomas were not informative. Sensitivity analyses, including an analysis where exposure definition was limited to the time period between the two endoscopies, provide similar results to the primary analyses (data not shown).

Neoplasia in the Proximal Colon

To explore the differences in results between studies-1, -2 and -3, a post hoc exploratory analysis of neoplasia in the proximal colon was conducted using data from patients in study-1. This analysis included 964 case subjects (82 exposed to TZDs) and 3284 controls (340 exposed to TZDs) and demonstrated results similar to the primary analysis, with an inverse association between TZD exposure and the prevalence of colonic neoplasia that was nearly statistically significant (adjusted OR 0.78, 95% CI 0.60–1.01). Interestingly, stratification based on the presence or absence of anemia did not influence these results as it did in the analysis of the entire colon, albeit the confidence intervals were wider due to the reduced sample size (with anemia adjusted OR 0.78, 95% CI 0.57–1.07; without anemia adjusted OR 0.79, 95% CI 0.50–1.27).

Discussion

Previous animal studies have suggested that exposure to TZDs can increase or decrease the risk of colonic neoplasia. Because patients with type 2 diabetes mellitus have an increased risk of colorectal cancer, it is important to determine whether the phenomena in observed animal models apply to humans. Two prior studies addressed this question in patients with diabetes.

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Koro et al. did not observe an association between TZD therapy and colon cancer risk, but lacked sufficient data to conduct a duration response analysis.[16] Govindarajan et al. observed a decreased incidence of colon cancer among African American, but not among white patients.[17] Both studies had only short-term follow-up periods (median 18 months of total follow-up in the Koro study[16] and 12 months of TZD exposure in the Govindarajan study[17]). As a result, the follow-up and exposure periods were potentially too short to observe a biological effect, particularly if the TZD exposure increases the risk of colon cancer. Because it will take decades to sufficiently follow large cohorts to address the risk of colon cancer following TZD exposure, we studied development of adenomatous polyps. We did not obtain evidence to indicate that exposure to TZDs increases the risk of colonic neoplasia. Although in our primary analysis for neoplasia throughout the colon we observed an inverse association between TZD exposure and colonic neoplasia, this was not observed when we limited the analysis to patients without a history of anemia. Furthermore, when we examined patients undergoing sigmoidoscopy or serial lower endoscopies, we did not observe a significant association between TZD use and adenomatous polyps in the distal colon. However, there was evidence of a reduced prevalence of polyps in the proximal colon among users of TZDs, regardless of presence or absence of anemia. Thus, we conclude that treatment of type 2 diabetes mellitus with TZDs does not increase the risk of colonic neoplasia; whether TZD use decreases the risk of proximal colon neoplasia is less clear.

Like Govindarajan et al. [17], who observed a decreased incidence of colon cancer among African Americans treated with TZDs, we observed a decreased incidence of colonic neoplasia among patients treated with TZDs in study-1 (patients who underwent colonoscopy). However, these findings might have been artifacts of the indication for colonoscopy. Specifically, patients who are treated with TZDs are more likely to develop anemia, a symptom of colorectal cancer. However, the anemia that accompanies TZD therapy is not a consequence of gastrointestinal bleeding, or more specifically bleeding from colonic neoplasia. As a result, among those patients who underwent colonoscopy to evaluate anemia, patients treated with TZDs would be less likely to have experienced anemia as a consequence of colonic neoplasia. This would bias the observed association between TZD exposure and colonic neoplasia toward an inverse association. Govindarajan et al. did not analyze data excluding patients with anemia. However, when we restricted our analyses to African Americans without anemia, we did not observe an inverse association between TZD exposure and colonic neoplasia (data not shown).

The subgroup analysis of patients with anemia who underwent sigmoidoscopy (study-2) or serial lower endoscopies (study-3) yielded similar results to the primary analysis (data not shown). So why didn't the presence or absence of anemia have the same effects in the case-control studies focusing on the distal colon? One possibility is that sigmoidoscopy is less sensitive than colonoscopy and resulting misclassifications could have masked a true association. Alternatively, because anemia is a sign of possible colon cancer, patients with anemia are generally referred for colonoscopy rather than sigmoidoscopy. In fact, we designed study-2 to primarily capture patients undergoing the lower endoscopy (sigmoidoscopy) for colon cancer screening rather than to evaluate symptoms. Curiously however, when we examined the relationship between TZD exposure and the prevalence of neoplasia in the proximal colon, the results were similar regardless of the presence of anemia, suggesting an inverse relationship between TZD exposure and prevalence of proximal colon neoplasia.

Taken together, these observations indicate that despite conflicting clinical data[16, 17] and data from animal models, there is no evidence that TZDs increase the risk of colonic neoplasia. It is possible that that TZD exposure decreases the risk of neoplasia in the proximal colon, compared with the distal colon. However, our study was not designed to test this hypothesis directly, and had limited power for this analysis as only a small number of adenomas were detected in the proximal colon Also, although some studies have reported a differential effect

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of insulin, insulin like growth factor 1 (IGF-1), and insulin like growth factor binding protein 1 (IGFBP-1) on proximal and distal colon neoplasia (a potential mechanism for this observation), this has not been confirmed in other studies[23–26]. Future studies should evaluate the differential effects of TZDs in the colon and rectum or the proximal and distal colon.

This study had a longer follow-up period than previous clinical studies, allowing us to examine cumulative dose and duration of TZD exposure. Approximately 30% of the patients treated with TZDs had more than 2 years of exposure. If a positive association between TZD exposure and colonic neoplasia exists, we would have expected to observe a higher incidence of polyp formation among patients with the longest duration of TZD exposure. We did not observe a duration-response or dose-response relationship between TZDs and colon neoplasia in our data sets.

It is possible that our follow-up periods were still too short to observe effects of TZDs on polyp incidence or prevalence. In our longest duration category (at least 2 years), the median durations of exposure were 2.9 years (IQR 2.4 – 4.0 years) and 3.0 years (IQR 2.4 – 3.9 years) in studies-1 and -2, respectively (data not shown). Previous studies have demonstrated that aspirin, COX-2 inhibitors and calcium can reduce the recurrence and/or lead to regression of adenomatous polyps within one year of therapy initiation[27–29], presumably by initiating apoptosis and decreasing proliferation, which are proposed mechanisms of PPARγ ligands. Because many of the patients in studies-1 and -2 would have had prevalent polyps at the time that TZD therapy was initiated, were TZDs to have a pro- or anti-carcinogenic effect late in the process of tumor progression, we anticipated seeing an increased or decreased prevalence of advanced polyps among TZD users following even relatively short durations of therapy. If TZDs have a pro- or anti-carcinogenic effect in the early phase of colon tumor progression, these would have been observed in study-3.

Studies-1 and -2 probably included some patients whose polyps formed before TZD therapy was initiated. Study-3 was designed specifically to address this issue. By focusing on the second exam, we minimized the risk of bias from prevalent colonic neoplasia.

In designing the study, concerns were raised about differential patterns of use of lower endoscopies in patients treated with different diabetes therapies. However, we previously demonstrated in this same population that rates of lower endoscopy were generally similar among patients treated with different diabetes medications, but that patients treated with metformin were slightly more likely to undergo lower endoscopy, perhaps because this drug often induces diarrhea.[30] However, diarrhea is not a typical symptom of colonic neoplasia, and would therefore not bias the results. Furthermore, all analyses were all adjusted for metformin use.

Our study lacked data on family histories of colon cancer, although it is unlikely that these differed between TZD-exposed and unexposed patients. It should be noted that patients in study-2 were more likely to have undergone screening and may be less likely to have a family history of colon cancer.

This study also had incomplete data on use of aspirin and over-the-counter NSAIDs. Prescription NSAID use was more common among patients without colonic neoplasia, although it did not prove to be a confounding factor in statistical models. Furthermore, although over-the-counter NSAID use is more common than prescription use, among frequent NSAID consumers, prescription use is more common.[28]; misclassification of NSAID use due to missing over-the-counter data has been demonstrated to have only a minimal effect on the observed relationship between NSAIDs and colonic neoplasia.[32]

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In focusing on adenomatous polyps, the precursor to colon cancer, and including dose and duration analyses, this study provides strong evidence against a clinically significant increase in risk of colonic neoplasia among patients with diabetes mellitus treated for up to several years with TZDs.

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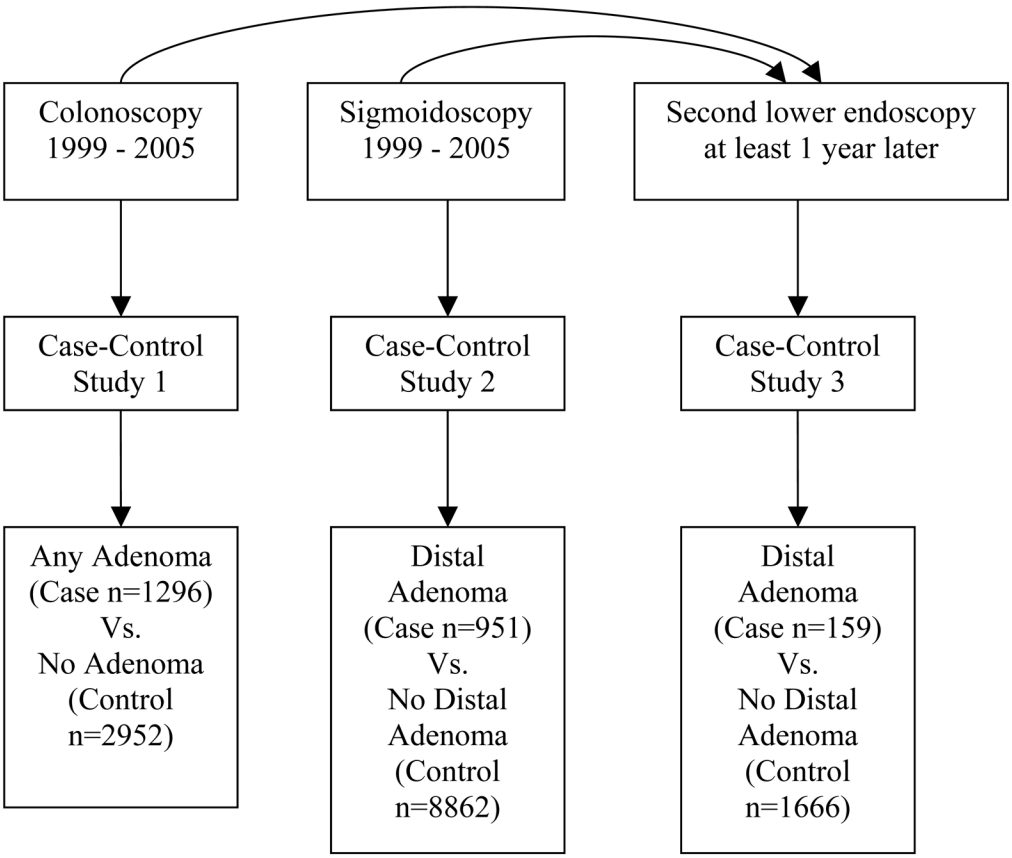

Figure 1.
Schematic representation of the three case-control studies. From the 62,465 Kaiser Permanente members who completed the diabetes survey in 1994–1996, 14,061 were eligible and underwent a colonoscopy or sigmoidoscopy during the study period. Among these, 1,825 underwent a second lower endoscopy that qualified for inclusion in the third case-control study, with case and control status based on the findings at the second lower endoscopy.

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Table 1

Characteristics of TZD Users and Non-Users

	Study-1 Neoplasia anywhere in the colon		Study-2 Distal colon neoplasia		Study-3 Distal colon neoplasia on repeat exam	
	Cases n=1296	**Controls n=2952**	**Cases n=951**	**Controls n=8862**	**Cases n=159**	**Controls n=1666**
Female (%)	41	49	37	46	46	47
Age (median years, IQR)	71 (65–77)	71 (64–77)	67 (60–74)	66 (60–73)	71 (65–76)	71 (65–76)
Race (%)						
White	60	59	57	52	62	55
Black	14	12	12	16	11	16
Hispanic	12	12	12	13	13	13
Asian	10	11	14	14	10	12
Other	2	3	2	3	1	2
Missing	2	3	2	3	3	2
BMI (%)						
25 or less	17	17	16	17	18	17
>25 to 30	36	34	38	34	36	33
>30	36	38	36	37	32	39
Missing	10	11	10	12	13	12
Socioeconomic status (%)						
< median	49	47	42	45	48	45
≥ the median	49	50	55	52	48	53
Missing	3	3	2	3	4	3
Education (%)						
<12 years	19	18	14	14	13	15
12 years	26	28	23	25	33	27
> 12 years	51	49	57	55	45	52
Missing	5	5	6	6	9	6
Diabetes duration (%)						
Less than 5 years	26	30	34	33	31	31
5 to <10 years	25	23	25	24	22	23
10 or more years	39	40	32	35	36	38
Missing	10	8	9	9	11	8
Diabetic retinopathy (%)	12	11	11	10	10	10
Hemoglobin A1c percentage* (%)						
<7	26	28	23	26	20	28
7 to <8	21	20	21	21	17	21
8 to <9	14	15	16	14	20	15
9 to <10	9	9	10	9	9	9
10 or greater	15	14	15	16	18	14
Missing	14	14	15	14	16	13
Diabetes medications** (%)						
TZD	8	11	6	7	11	14
Sulfonylurea	64	67	63	66	68	70
Metformin	32	38	37	38	45	50
Insulin	35	33	29	29	38	33
Other	0	<1	<1	<1	0	<1
Concomitant medications† (%)						
NSAID‡	12	17	11	15	10	17
Aspirin‡	2	2	1	1	6	2
Proton pump inhibitor	4	6	2	3	6	6
Statin	38	38	32	34	47	53
Most recent lower endoscopy during 1995–1998 (%)						
Colonoscopy ≤ 3 years prior††	5	5	1	1	6	6

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	Study-1 Neoplasia anywhere in the colon		Study-2 Distal colon neoplasia		Study-3 Distal colon neoplasia on repeat exam	
	Cases n=1296	Controls n=2952	Cases n=951	Controls n=8862	Cases n=159	Controls n=1666
Sigmoidoscopy ≤ 3 years prior††	5	5	1	3	6	7
Colonoscopy > 3 years prior††	19	19	3	3	11	9
Sigmoidoscopy >3 years prior††	19	22	11	16	11	14
None	53	49	84	78	67	64
Lower endoscopy with polypectomy 1995–1998 (%)	18	16	5	4	13	12
Index endoscopy (%)						
Colonoscopy	N/A	N/A	N/A	N/A	65	62
Sigmoidoscopy	N/A	N/A	N/A	N/A	16	35
Sigmoidoscopy followed by colonoscopy	N/A	N/A	N/A	N/A	19	3
Time between lower endoscopies (median years, IQR)	N/A	N/A	N/A	N/A	2.8 (1.6–4.4)	3.0 (1.9–4.3)

* HbA1c was measured at baseline entry into the cohort

** At least one year of cumulative use prior to the index date

† At least one year of cumulative use and use within 1 year of the index date

‡ Based on prescription data. Excludes over-the-counter purchases.

†† Prior to index date

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Table 2

Association Between TZD Use and the Prevalence of Adenomatous Polyps in the Colon (Study-1)

	All Patients							Without Anemia	With Anemia
	Controls	Any adenoma		Early adenoma		Advanced adenoma		Any adenoma	Any adenoma
	n	n	Adjusted OR* (95% CI)	n	Adjusted OR* (95% CI)	n	Adjusted OR* (95% CI)	Adjusted OR* (95% CI)	Adjusted OR* (95% CI)
Ever exposed									
No (no TZD use or <1 year of use)	2634	1192	1.00	753	1.00	439	1.00	1.00	1.00
Yes (1 year or longer)	318	104	0.73 (0.57, 0.92)	65	0.72 (0.54, 0.95)	39	0.74 (0.52, 1.07)	0.97 (0.64, 1.46)	0.65 (0.48,0.87)
Time since most recent TZD use									
No TZD use or <1 year of use	2634	1192	1.00	753	1.00	439	1.00	1.00	1.00
Current user	206	61	0.66 (0.49, 0.89)	39	0.66 (0.46, 0.95)	22	0.65 (0.41, 1.03)	0.73 (0.43, 1.22)	0.64 (0.44,0.93)
Less than 1 year	65	21	0.72 (0.44, 1.19)	12	0.65 (0.35, 1.22)	9	0.85 (0.41, 1.73)	1.33 (0.54, 3.30)	0.58 (0.31,1.08)
1 to <2 years	21	8	0.85 (0.37, 1.95)	7	1.14 (0.48, 2.73)	1	0.30 (0.04, 2.26)	0.91 (0.17, 4.84)	0.87 (0.33,2.25)
2 years or longer	26	14	1.21 (0.62, 2.35)	7	0.98 (0.42, 2.29)	7	1.58 (0.67, 3.73)	2.85 (0.95, 8.48)	0.69 (0.27,1.73)
Duration of therapy**									
No TZD use	2398	1098	1.00	694	1.00	404	1.00	1.00	1.00
Less than 1year	236	94	0.90 (0.69, 1.16)	59	0.91 (0.67, 1.23)	35	0.89 (0.61, 1.30)	0.84 (0.53, 1.33)	0.95 (0.70,1.30)
1 to <2 years	149	46	0.70 (0.49, 0.98)	26	0.62 (0.40, 0.95)	20	0.83 (0.51, 1.36)	0.89 (0.51, 1.56)	0.62 (0.40,0.97)
2 years or longer	169	58	0.73 (0.54, 1.01)	39	0.78 (0.54, 1.14)	19	0.65 (0.40, 1.07)	1.02 (0.58, 1.80)	0.66 (0.45,0.97)
Average daily dose									
No or <1 year of use	2634	1192	1.00	753	1.00	439	1.00	1.00	1.00
<0.65 units per day	156	48	0.69 (0.49, 0.96)	30	0.69 (0.46, 1.03)	18	0.69 (0.41, 1.15)	0.99 (0.55, 1.77)	0.60 (0.39,0.91)
0.65 or greater units per day	162	56	0.77 (0.56, 1.05)	35	0.74 (0.51, 1.09)	21	0.80 (0.50, 1.28)	0.95 (0.55, 1.64)	0.70 (0.47,1.03)

* Adjusted only for age, sex, calendar year of index date, and use of other diabetes medications. Addition of other variables did not change any of the odds ratios by 10% of more.

** Duration of therapy with TZDs prior to the index date.

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Table 3

Association Between TZD Use and Prevalence of Distal Adenomatous Polyps in the Colon (Study-2)

	Controls	Any adenoma		Early adenoma		Advanced adenoma	
	n	n	Adjusted OR* (95% CI)	n	Adjusted OR* (95% CI	n	Adjusted OR* (95% CI)
Ever exposed							
No (no TZD use or <1 year of use)	8206	891	1.00	622	1.00	269	1.00
Yes (1 year or longer)	656	60	0.86 (0.65, 1.14)	40	0.83 (0.59, 1.17)	20	0.93 (0.58, 1.50)
Time since most recent TZD use							
No TZD use or <1 year of use	8206	891	1.00	622	1.00	269	1.00
Current user	437	40	0.86 (0.61, 1.20)	30	0.92 (0.62, 1.35)	10	0.70 (0.37, 1.34)
Less than 1 year	107	10	0.86 (0.45, 1.66)†	6	0.75 (0.33, 1.73)	4	1.1 2 (0.41, 3.08)
1 to <2 years	40	5	1.22 (0.48, 3.13)	2	0.69 (0.16, 2.87)	3	2.58 (0.78, 8.51)
2 years or longer	72	5	0.70 (0.28, 1.74)	2	0.42 (0.10, 1.73)	3	1.22 (0.37, 3.99)
Duration of therapy**							
No TZD use	7650	826	1.00	575	1.00	251	1.00
Less than 1year	556	65	1.12 (0.86, 1.48)	47	1.17 (0.85, 1.60)	18	1.02 (0.62, 1.67)
1 to <2 years	316	22	0.66 (0.42, 1.03)	13	0.57 (0.32, 1.01)	9	0.85 (0.43, 1.68)
2 years or longer	340	38	1.08 (0.76, 1.54)	27	1.11 (0.73, 1.67)	11	1.02 (0.54, 1.92)
Average daily dose							
No or <1 year of use	8206	891	1.00	622	1.00	269	1.00
<0.65 units per day	328	26	0.76 (0.50, 1.15)	17	0.72 (0.44, 1.20)	9	0.83 (0.42, 1.66)
0.65 or greater units per day	328	34	0.96 (0.67, 1.38)	23	0.93 (0.60, 1.44)	11	1.03 (0.55, 1.91)

* Adjusted only for age, sex, calendar year of index date, and use of other diabetes medications.

† Adjusting for race, this OR = 0.78. None of the other odds ratios changed by 10% or more with the addition of race or any other variable to the model.

** Duration of therapy with TZDs prior to the index date

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Table 4

Association Between TZD Use and Prevalence of New or Missed Adenomatous Polyps in the Distal Colon (Study-3)

	Controls	Any adenoma		Early adenoma	
	n	n	Adjusted OR* (95% CI)	n	Adjusted OR*† (95% CI)
Ever exposed					
No (no TZD use or <1 year of use)	1431	142	1.00	100	1.00
Yes (1 year or longer)	235	17	0.75 (0.44, 1.28)	15	0.87 (0.49, 1.54)
Time since most recent TZD use					
No TZD use or <1 year of use	1431	142	1.00	100	1.00
Current user	145	10	0.75 (0.38, 1.47)	9	0.87 (0.43, 1.78)
Less than 1 year	37	3	0.85 (0.26, 2.82)	3	1.14 (0.34, 3.78)
1 to <2 years	29	2	0.65 (0.15, 2.77)	1	0.44 (0.06, 3.29)
2 years or longer	24	2	0.79 (0.18, 3.43)	2	1.01 (0.23, 4.45)
Duration of therapy**					
No TZD use	1287	126	1.00	93	1.00
Less than 1year	144	16	1.16 (0.66, 2.03)	7	0.64 (0.29, 1.44)
1 to <2 years	95	8	0.92 (0.43, 1.97)	6	0.84 (0.35, 2.01)
2 years or longer	140	9	0.67 (0.33, 1.36)	9	0.82 (0.40, 1.68)
Average daily dose					
No or <1 year of use	1431	142	1.00	100	1.00
<0.65 units per day	115	9	0.87 (0.43, 1.77)	8	0.97 (0.46, 2.07)
0.65 or greater units per day	120	8	0.66 (0.31, 1.39)	7	0.78 (0.35, 1.73)

*Adjusted only for age, sex, calendar year of index date, and use of other diabetes medications.

†Analyses for advanced adenomas were not performed since only two patients with 1 year or longer TZD exposure had advanced adenomas at follow-up lower endoscopy.

**Duration of therapy with TZDs prior to the index date