

Insulin Therapy and Colorectal Adenomas in Patients with Diabetes Mellitus

Patricia Wong^{1,2}, Mark G. Weiner³, Wei-Ting Hwang², and Yu-Xiao Yang^{1,2}

Abstract

Background: Patients with type 2 diabetes mellitus (DM) are at increased risk for colorectal adenomas and cancer because of endogenous hyperinsulinemia. Exogenous insulin therapy has been associated with higher colorectal cancer incidence. The aim of this study was to evaluate the association between exogenous insulin therapy and adenoma formation, accounting for duration of therapy and location and stage of the adenoma.

Methods: We conducted a cross-sectional study of patients with type 2 diabetes between the ages of 50 and 80 years who completed full colonoscopies. Cases were patients with any adenoma on index colonoscopy. Patients without any adenoma composed the control group. Multivariable logistic regression was used to calculate odds ratios (OR) and associated confidence intervals (CI).

Results: Compared with the controls, case patients ($n = 196$) did not have a significantly increased odds of insulin exposure, when exposure was defined as 12 months or more of insulin use compared with no insulin. However, the odds of insulin exposure among the cases was significantly increased when exposure was defined as 18 months or more (OR 1.6, 95% CI 1.1–2.5), 24 months or more (OR 1.7, CI 1.1–2.6), and 36 months or more (OR 2.0, 95% CI 1.2–3.4) of insulin use (test for trend $P = 0.05$). A similar trend in insulin exposure was seen among type 2 diabetics with advanced adenomas. Adenoma location was not significantly affected by insulin therapy.

Conclusions: Chronic insulin therapy is associated with increased risk of colorectal adenomas in patients with type 2 diabetes.

Impact: Diabetes patients receiving insulin may need more stringent colon cancer screening. *Cancer Epidemiol Biomarkers Prev*; 21(10); 1833–40. ©2012 AACR.

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States (1). Nearly all sporadic CRC's are thought to arise from adenomas (2). Detection and removal of adenomatous polyps significantly decrease the risk of CRC and are currently the primary means of CRC prevention (3).

The appropriate approach to screening depends on an individual's level of risk on the basis of personal, family, and medical history (4). Early initiation of screening and shorter intervals between colonoscopies is recommended for patients with an increased risk for CRC. Current guidelines do not identify patients with type 2 DM or insulin-users as individuals of increased risk. However, there is growing evidence that type 2 DM is associated

with an increased risk for CRC (5). Endogenous hyperinsulinemia is one possible mechanism behind the increased risk of CRC among patients with type 2 diabetes (6). It has been postulated that insulin induces cell proliferation and reduces apoptosis by increasing the bioavailability of IGF-1 (7). There has been substantial support for the "hyperinsulinemia-colorectal cancer" theory, including experimental and epidemiologic evidence (8–10). High levels of serum insulin have also been independently associated with increased CRC risk (11, 12).

Exogenous insulin use leads to substantially higher augmentation of the systemic hyperinsulinemic state compared with endogenous hyperinsulinemia associated with insulin resistance (13). Based on these observations, recent studies have examined the effect of exogenous insulin therapy on the risk of CRC in patients with type 2 DM and have reported a significant increase in risk of CRC and colorectal adenomas, respectively, among patients with type 2 diabetes on insulin therapy compared with noninsulin users (14, 15).

We sought to further investigate the association between exogenous insulin use and colorectal adenoma formation in a US-based population. Specifically, we were interested in the effect of varying durations of insulin therapy as well as adenoma characteristics, such as

Authors' Affiliations: ¹Division of Gastroenterology, Hospital of the University of Pennsylvania; ²Center for Clinical Epidemiology and Biostatistics; and ³Division of General Internal Medicine, University of Pennsylvania, Philadelphia

Corresponding Author: Yu-Xiao Yang, 423 Guardian Drive, 722 Blockley Hall, Philadelphia, PA 19104. Phone: 1-215-573-5027; Fax: 1-215-349-5915; E-mail: yangy@mail.med.upenn.edu

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histology and location. With the rapidly increasing prevalence of type 2 DM world-wide and the recognition that the vast majority of these patients will eventually require chronic exogenous insulin to achieve adequate glucose control (16), this association could have a substantial impact on CRC screening practices.

Materials and Methods

Study design

We conducted a cross-sectional study using 2 electronic medical records systems within the University of Pennsylvania Health System (UPHS), USA. This study was approved by the University of Pennsylvania Institutional Review Board.

Source of data

Two UPHS patient databases were used for this study: (i) EPIC, the UPHS ambulatory electronic medical record system and (ii) Olympus endoscopy database. EPIC has been in place since 1998 and is in use at approximately 60 UPHS-affiliated ambulatory care sites, including 8 primary care and 3 endocrine practices. Over 180,000 patients have been seen since its implementation. Data include patient demographics, medical diagnoses, social and family history, and medications. Medical diagnoses are identified by International Classification of Disease-9 (ICD-9) codes. All orders for pharmacy are written through EPIC and contain information on start date, dosage, dispense amount, and refills. Daily data extracts are written to a fully documented relational database that can be queried using Microsoft Access.

The Olympus endoscopy database is used by the 3 UPHS-affiliated gastroenterology practices (Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, and Penn Medicine at Radnor). It has been in place since 1993 and contains information on over 80,000 conducted colonoscopies. Data include indication for procedure, findings, completeness of exam, and interventions conducted such as polypectomies.

Study population

We first identified all patients with more than one ICD-9 diagnosis of diabetes from a primary care or endocrine practice in the EPIC database from October 1998 to May 2007 ($n = 14,753$). By selecting patients with at least 2 separate ICD-9 diagnoses we hoped to decrease the number of patients with glucose intolerance or who were being evaluated for the possible diagnosis of diabetes, without actually meeting the criteria for diabetes. We also limited our study to patients followed by a primary care or endocrine practice to minimize misclassification of prescription and confounder data. From among those subjects who met our criteria for the diagnosis of diabetes, we conducted a second query for patients who had undergone a full colonoscopy within our Olympus endoscopy database ($n = 5,844$). Eligible subjects had to have an ICD-9 diagnosis of diabetes at least 12 months before the

index date of colonoscopy ($n = 3,279$). We then included only those patients between the ages of 50 and 80 years ($n = 2,776$), as patients undergoing colonoscopies before age 50 were likely to have additional risk factors for CRC. For patients who had undergone multiple colonoscopies, only the first colonoscopy results were reviewed ($n = 2,044$). We excluded patients with prior colonoscopies based on information contained in the Olympus endoscopy database and the EPIC database. We also limited our subjects to those who were in the EPIC database for equal to or greater than 1 year before their colonoscopy ($n = 1,168$). Additional exclusion criteria included factors that placed subjects at above-average risk for colorectal adenoma formation, specifically having a diagnosis of inflammatory bowel disease (IBD; $n = 11$), hereditary colon cancer syndromes ($n = 1$), personal history of adenoma or CRC ($n = 94$), or prior colon surgery ($n = 19$).

All colonoscopy and pathology reports were manually reviewed by a gastroenterologist (PW). We then applied additional exclusion criteria including an incomplete colonoscopy ($n = 44$); poor bowel preparation ($n = 92$); missing colonoscopy report ($n = 38$); missing pathology information ($n = 36$); or CRC on biopsy ($n = 5$). Cancer was defined as invasion of malignant cells beyond the muscularis mucosa. The remaining 869 patients with type 2 diabetes and complete colonoscopies made up the study cohort.

Case definitions

From the study cohort, those who had at least 1 adenoma on index colonoscopy were defined as cases ($n = 196$). In our secondary analyses, cases were redefined as advanced adenomas if the adenoma was 1 cm or more (based on the endoscopy report) or contained villous features or high grade dysplasia ($n = 59$). Intramucosal carcinoma or carcinoma *in situ* was classified as high-grade dysplasia. Polyp location was determined as left versus right colon if the polyp was located in the sigmoid colon, rectum, or less than 45 cm from the anal verge. Right-sided polyps were defined as proximal to the sigmoid colon or 45 cm or more from the anal verge.

To test the hypothesis that insulin therapy leads to larger polyps by inducing cell proliferation, adenomatous polyps were also categorized according to size (≤ 5 mm or < 10 mm).

Control definition

Controls were defined as patients with either no polyps or only nonadenomatous polyps on index colonoscopy ($n = 673$) for all analyses. Nonadenomatous polyps included hyperplastic and inflammatory polyps, benign tumors, and normal mucosa on pathology. The same control group was used in the secondary analysis where the case group only included those with advanced adenoma.

Exposure definitions

The primary exposure of interest was 12 months or more of insulin exposure observed in EPIC medical

records system. Insulin duration was defined as date of index colonoscopy minus date of first insulin prescription. Because the minimal amount of insulin exposure needed to warrant an effect on adenoma formation is not known, this amount of exposure was based on a prior study by Yang and colleagues, where an increase in risk of CRC was seen after 1 year or more of insulin therapy.¹⁴

In a secondary analysis, we examined the effect of longer durations of insulin exposure on adenoma formation. Duration of insulin exposure was defined as non-mutually exclusive 6 months or more, 12 months or more, 18 months or more, 2 years or more, and 3 years or more.

Statistical analysis

Among the patients with type 2 diabetes in our EPIC patient database, approximately 35% were insulin-users. Previous studies involving non-VA populations presenting for initial colonoscopy at large academic centers report prevalence rates of adenoma of at least 27% (17). Under these assumptions, we required 119 cases to detect an OR of 2.0 (detectable difference 0.17) with $\alpha = .05$ and power of 90% (PS Power and Sample Size Program, Version 2.1.31).

Characteristics of cases and controls were expressed as means (standard deviation) and differences in values were determined using *t*-test for continuous variables and chi-square for categorical variables. ORs for the association between colorectal adenomas and insulin exposure were determined using univariable and multivariable logistic regression analysis. Potential confounders determined a priori were age, sex, race, body mass index (BMI; categorized as <25, 25–29, ≥ 30), any history of tobacco use, family history of CRC, history of anemia (defined as having any recorded hemoglobin of <12.5 for men, <11.7 for women), indication for colonoscopy, and exposure to NSAIDs or aspirin, metformin, sulfonyleurea, and/or thiazolidinediones.

For patients with missing height information (14%), BMI was imputed by plotting receiver operating curves (ROC) for males and females who had complete recordings of both height and weight. The ROC curves were then used to define weight thresholds for BMI 25 or more and BMI 30 or more with high sensitivity and specificity, using previously described methodology developed in the same EPIC patient population (18). Cut points were selected that provided at least 90% specificity and approximately 80% sensitivity. For women, cut points were less than 73.2 kg for BMI less than 25; 73.2–82.7 kg for BMI 25–29; and more than 82.7 kg for BMI 30 or more. For men, cut points were less than 81.5 kg for BMI less than 25; 81.5–97.7 kg for BMI 25–29; and more than 97.7 kg for BMI 30 or more.

Indication for colonoscopy was categorized into 3 categories, based on the associated likelihood of having a positive finding on colonoscopy (17). Because patients often had more than one indication for procedure, categories were defined as follows: Low-association (category 1) included patients with average risk or with any family history of CRC and no indications from category 2 or 3

medium-association (category 2) included changes in bowel habits, pain, or weight loss, and no indications from category 3; high-association (category 3) included anemia, guaiac-positive stools, or rectal bleeding.

All medication exposures were defined as exposed if the subject had 1 year or more duration, determined from date of last prescription minus date of first prescription before index colonoscopy, to allow for adequate exposure time to have a potential effect on polyp formation. Left-sided polyps were defined as sigmoid, rectum, or less than 45 cm from the anal verge. Right-sided polyps were defined as proximal to the sigmoid colon or 45 cm or more from the anal verge.

Only those variables that resulted in a more than 10% change in the crude OR when added to the crude model were included in the final regression model; this confounder selection approach was found to be superior to other methods in etiologic modeling in observational studies (19). Interactions between variables insulin use for 12 months or more and NSAID/aspirin use and between insulin use for 12 months or more and anemia were also determined by using the likelihood-ratio test. An interaction was considered significant if $P < 0.05$. We also conducted a test for trend with escalating duration categories of insulin use to look for potential duration–response, using a nonparametric test for trend as executed with the *nptrend* command in STATA. All statistical analyses were conducted with STATA 9 (STATA Corp.).

Results

The final study cohort consisted of 869 patients with type 2 DM (Table 1). Of these, 196 had at least one adenoma (23%) on index colonoscopy. Compared with those without adenomas, patients with any adenoma were older and more likely to be male, to have had a history of tobacco use and to be referred for a colonoscopy because of a category 1 indication.

No significant difference in odds of insulin exposure was found among the patients with type 2 diabetes with any adenoma compared with patients with no adenomatous polyp on index colonoscopy, when insulin exposure was defined as 12 months or more (OR 1.2, 95% CI 0.8–1.8, $P = 0.3$; Table 2). ORs were adjusted for age and sex only because no other variables met criteria for inclusion in the final model using our a priori specified confounder selection criterion. No significant interaction terms were determined. This association was unchanged in the adjusted analysis (Table 2).

In our secondary analysis, we identified 59 patients (7%) with type 2 DM who had an advanced adenoma on index colonoscopy. Study cohort characteristics were similar to those using any adenoma as the case definition (Table 1). No significant difference in odds of insulin exposure was found among patients with advanced adenomas when insulin exposure was defined as 12 months (OR 0.9, 95% CI 0.5–2.0, $P = 0.9$; Table 2).

Table 1. Study cohort characteristics. Patients with type 2 diabetes with any adenoma or advanced adenoma on index colonoscopy (cases) compared with controls

	Cases		Controls	P value	
	Any adenoma (n = 196)	Advanced adenoma (n = 59)	No adenoma (n = 673)	Any adenoma	Advanced adenoma ^c
Age at time of colonoscopy					
Mean (SD)	64.4 (8.5)	65.2 (8.7)	63.1(8.0)	0.05	0.06
50–59, n(%)	65 (33.2)	18 (30.5)	257 (38.2)	0.10	0.03
60–69, n(%)	76 (38.8)	20 (33.9)	275 (40.9)		
70–80, n(%)	55 (28.1)	21 (35.6)	141 (21.0)		
Sex, n (%)					
Female	99 (50.5)	25 (42.4)	396 (58.8)	0.04	0.01
Male	97 (49.5)	34 (57.6)	277 (41.2)		
Race, n(%)					
White	58 (29.6)	18 (30.5)	217 (32.2)	0.4	1.0
Black	119 (60.71)	37 (62.7)	414 (61.5)		
Asian	4 (2.0)	1 (1.69)	11 (1.6)		
Unknown	15 (7.6)	3 (5.1)	31 (4.6)		
BMI categories, n(%)					
<25	26 (13.3)	7 (11.9)	111 (16.5)	0.2	0.4
25–29	59 (30.1)	18 (30.5)	160 (23.8)		
≥ 30	111 (59.0)	34 (57.6)	402 (59.7)		
Any tobacco history, n(%)					
Yes	108 (55.1)	14 (23.7)	277 (41.2)	0.002	0.001
No	66 (33.7)	39 (66.1)	316 (47.0)		
Unknown	22 (11.2)	6 (10.2)	80 (11.2)		
Any family history of CRC, n(%)	17 (8.7)	6 (10.2)	45 (6.7)	0.3	0.3
History of anemia ^a n(%)	96 (49.0)	25 (42.4)	334 (49.6)	0.9	0.3
Indication for procedure ^b , n(%)					
Category 1	138 (70.4)	43 (72.9)	405 (60.2)	0.01	0.1
Category 2	17 (3.7)	4 (6.8)	109 (16.2)		
Category 3	41 (21.0)	12 (20.3)	159 (23.6)		
Exposure to NSAID/aspirin for ≥ 1 yr, n(%)	81 (41.3)	24 (40.7)	231 (34.3)	0.07	0.3
Exposure to metformin for ≥ 1 yr, n(%)	80 (40.8)	20 (33.9)	256 (38.0)	0.5	0.5
Exposure to thiazolidinedione for ≥ 1 yr, n(%)	24 (12.2)	5 (8.5)	108 (16.0)	0.2	0.1
Exposure to sulfonylurea for ≥ 1 yr, n(%)	49 (25)	19 (32.2)	155 (23.0)	0.6	0.1

^aAnemia defined as hgb less than 12.5 for men, less than 11.7 for women.

^bIndication for procedure categorized according to the level of association with having an adenoma on colonoscopy. Category 1 (low) includes average risk or family history and no indications from category 2 or 3. Category 2 (medium) includes change in bowel habits, pain, or weight loss and no indications from category 3. Category 3 (high) includes anemia, guaiac-positive stools, or rectal bleeding.

^cAdvanced adenoma defined as 1 cm or more, villous features, or high-grade dysplasia.

Duration of therapy

There was evidence of a significant association between insulin use and adenoma formation when duration of insulin therapy exceeded 18 months (Table 3). There was evidence of a duration–response effect (test for trend $P = 0.049$). We also observed a positive association between any adenoma and insulin exposure when insulin therapy was defined as a continuous variable (multivariable OR 1.2; 95% CI 1.0–1.3, $P = 0.08$ for each incremental year of insulin therapy on average up to 4 years of therapy). A similar trend was

observed among our smaller cohort of patients with advanced adenomas, though not statistically significant (Table 3).

Location and size of polyps

In a subgroup analysis examining location and size of polyps, we used at least 2 years of insulin exposure to define exposure, given that our primary analysis showed a positive association between adenoma formation and insulin use at this duration of exposure. Results were generally similar for left-sided and right-sided polyps

Table 2. Association between any adenoma or any advanced adenoma and at least 1 year of insulin exposure^a

	Any adenoma				Advanced adenoma			
	Case n(%)	Control n(%)	Crude OR (95% CI)	Adjusted OR (95% CI)	Case n(%)	Control n(%)	Crude OR (95% CI)	Adjusted OR ^b (95% CI)
No insulin (reference)	141 (77.5)	518 (80.7)	Reference	Reference	44 (81.5)	518 (80.7)	Reference	Reference
≥1 yr insulin	41 (22.5)	124 (19.3)	1.2 (0.8–1.8)	1.2 (0.8–1.8)	10 (18.5)	124 (19.3)	0.9 (0.5–1.9)	0.9 (0.5–2.0)

^aCases and controls who had insulin exposure less than 1 year in duration were excluded from this analysis.

^bAdjusted for sex and age only as none of the other variables met the a priori confounder selection criteria.

and for polyps less than 5 mm in diameter as in the overall analysis (Table 4).

Discussion

In this cross-sectional study within a US-based health care system, we found that chronic insulin therapy in patients with type 2 DM was associated with an increased risk of colorectal adenomas. This effect was seen after at least 18 months of insulin exposure, where we saw a 60% increase in the odds of insulin exposure among patients with any colorectal adenoma. There was evidence of a duration–response effect, with a 20% incremental increase in odds of colorectal adenoma for each additional year of insulin use on average (up to 4 years). A similar positive association was observed between advanced colorectal adenomas and insulin use, although not statistically significant. These data support the hypothesis that chronic insulin therapy is positively associated with an increased risk of colorectal neoplasia in patients with type 2 DM.

Many observational studies have examined the association between type 2 DM and the risk of CRC, and most

studies have shown a positive association between type 2 DM and CRC (5). The leading hypothesis for the observed positive association between DM and CRC risk is hyperinsulinemia (7, 20). During the early stages of DM, increased levels of insulin are produced by β -pancreatic cells in response to peripheral insulin resistance. Insulin raises serum IGF-1 levels by inhibiting IGF-binding proteins and by binding insulin or insulin-like growth factor receptors on the liver (7). The IGF signaling system regulates growth and development of many tissues and plays an important role in carcinogenesis through regulating cell proliferation, adhesion, migration, and apoptosis (21). Conditions where there are high circulating levels of IGF-1, such as acromegaly, have been associated with an increased risk of CRC (22). The association between insulin and insulin-like growth factor and adenomatous polyps is also supported by other observational studies (23–26).

Nearly all patients with type 2 DM will eventually need exogenous insulin therapy for adequate glycemic control as β -pancreatic cell function deteriorates. In the UKPDS,

Table 3. Association between any or advanced adenomas and varying definitions of exposure according to the durations of observed insulin exposure^a

Exposure definitions Duration of insulin exposure	Any adenoma				Advanced adenoma			
	Case	Control	Crude OR	Adjusted OR ^b	Case	Control	Crude OR	Adjusted OR ^b
No insulin	141 (71.9)	51 (77.0)	Reference	Reference	44 (74.6)	51 (77.0)	Reference	Reference
≥6 months	49 (26%)	144 (22%)	1.2 (0.9–1.8)	1.3 (0.9–1.8)	14 (24%)	144 (22%)	1.1 (0.6–2.1)	1.2 (0.6–2.2)
≥12 months	41 (23%)	124 (19%)	1.2 (0.8–1.8)	1.2 (0.8–1.8)	10 (19%)	124 (19%)	0.9 (0.5–1.9)	0.9 (0.5–2.0)
≥18 months	40 (22%)	92 (15%)	1.6 (1.1–2.4)	1.6 (1.1–2.5)	9 (17%)	92 (15%)	1.2 (0.5–2.4)	1.2 (0.6–2.5)
≥2 years	34 (19%)	77 (13%)	1.6 (1.0–2.5)	1.7 (1.1–2.6)	8 (15%)	77 (13%)	1.2 (0.6–2.7)	1.3 (0.6–2.9)
≥3 years	23 (14%)	43 (8%)	2.0 (1.1–3.4)	2.0 (1.2–3.4)	6 (12%)	43 (8%)	1.6 (0.7–4.1)	1.7 (0.7–4.3)
Each incremental year of insulin therapy	n/a	n/a	1.2 (1.0–1.3)	1.2 (1.0–1.3)	n/a	n/a	1.0 (0.8–1.3)	1.0 (0.8–1.3)

^aCases and controls who had insulin exposure less than 6 months in duration were excluded from this analysis.

^bAdjusted for sex and age only as none of the other variables met the a priori confounder selection criteria.

Table 4. Localization and characterization of adenomas in type 2 diabetics exposed to at least 2 years of insulin

Case definition	Case N (%)	Control N (%)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)
Left and right-sided adenoma	11 (13%)	77 (13%)	1.6 (0.8–3.2)	1.7 (0.8–3.4)
Any left-sided adenoma	18 (19%)	77 (13%)	1.5 (0.9–2.7)	1.6 (0.9–2.8)
Any right-sided adenoma	27 (20%)	77 (13%)	1.7 (1.0–2.7)	1.8 (1.1–2.9)
Adenoma <10mm	28 (21%)	77 (13%)	1.7 (1.1–2.8)	1.8 (1.1–2.9)
Adenoma <5 mm	21 (20%)	77 (13%)	1.7 (1.0–2.9)	1.7 (1.0–2.9)

^aAdjusted for sex and age only as none of the other variables met the a priori confounder selection criteria.

53% of patients with type 2 DM required insulin therapy 6 years after their initial diagnosis, and almost 80% required insulin by 9 years (16, 27). With increasingly stringent guidelines for glycemic control put forth by the American Diabetes Association (28) and growing evidence for reduction in microvascular complications with earlier introduction of insulin therapy in the disease course (29, 30), insulin-users represent a substantial and growing proportion of the entire type 2 DM population. Among patients with DM, systemic insulin levels are further augmented by exogenous insulin therapy, despite the reduction of endogenous insulin production, as shown by 24-hour plasma insulin levels (31). This is because of the inefficiency of exogenous insulin in maintaining glucose homeostasis (13).

Such further increase in hyperinsulinemia could lead to higher risk of colorectal neoplasia among DM patients using insulin compared with those not using insulin. Only 2 studies to date were specifically designed to investigate the effect of exogenous insulin therapy on colorectal adenomas or cancers in patients with type 2 DM. Consistent with the finding of the current study, Yang and colleagues observed a significantly increased risk of CRC after 3–5 years of observed insulin use (OR 2.9, 95% CI 1.1–7.7) compared with no insulin use (14). There was a 20% increase in the risk of CRC (OR of 1.2, 95% CI 1.0–1.4) associated with each incremental year of insulin therapy on average. Because colorectal adenoma is the target of CRC cancer screening programs, it is important to elucidate the effect of insulin therapy on adenoma development. To that end, Chung and colleagues reported a 3-fold increase in risk of colorectal adenomas in patients with at least 1 year of insulin therapy (OR 3.0, 95% CI 1.1–8.9) in a Korean-based population (15). However, that Korean study was limited by its small sample size as evidenced by the wide CI as well as potential bias from self-referral for colonoscopy. Our study significantly extends these previous works by achieving a more precise effect estimate and by elucidating for the first time the presence of a duration–response effect and the effect of insulin therapy on advanced adenoma. Progression of normal mucosa to adenomatous polyp to invasive cancer occurs through a "multihit" process of mutational activation of oncogenes and inactivation of tumor suppressor

genes which takes place over many years (32). Our findings of a clinically meaningful increase in the association between adenomas and insulin exposure after at least 3 years of insulin therapy (OR 2.0, 95% CI 1.2–3.4) are consistent with this model.

Schoen and colleagues, reported that the association between insulin and IGF-1 levels and colorectal adenomas appears to be more pronounced among advanced adenomas compared with nonadvanced adenomas (26). These findings may suggest that insulin and IGF-1 play a role in the progression of nonadvanced adenomas to advanced adenomas. While the association seemed to increase with longer durations of insulin exposure in our study, we did not find a statistically significant positive association between insulin therapy and advanced adenomas. However, our analysis was limited by small sample size, with less than 10 cases of advanced adenomas within each category of insulin duration.

Subsite-specific effect of DM on CRC risk has been described in previous observational studies with inconsistent results, with some (33–36), but not all (37, 38) the studies showing a preferential effect toward proximal colon cancer. Our study is the first, to our knowledge, to look at the distribution of adenomas in patients with type 2 DM on chronic insulin therapy. We found comparable increased rates of adenomas in both the proximal and distal colon in patients on chronic insulin therapy compared with patients not on insulin. Given that proximal and distal colorectal neoplasia may have different morphology and patterns of progression, this information would have an influence on the choice of CRC screening modality (e.g., colonoscopy vs. flexible sigmoidoscopy) among patients with type 2 DM. Further studies are necessary to confirm this site-specific effect of exogenous insulin.

There were several strengths to our study. Our sample size allowed us to not only evaluate the association between insulin therapy and adenomas in patients with type 2 DM, but also to explore different durations of insulin exposure and adenoma location with adequate power. We were also able to obtain clinical and demographic information allowing us to adjustment for potential confounders.

A few potential limitations need to be considered. We did not have information on several potential

confounders including measures of central obesity, exercise, and diet. In addition, our analyses regarding the risk of advanced adenomas may be underpowered because of the relatively small number of patients who had advanced adenomas. In addition, to the extent that diabetes itself increases the risk for adenomas, the effect of insulin therapy might have been underestimated by comparing insulin-using diabetics to other diabetics.

Because of the cross-sectional design of our study, a temporal relationship between insulin use and adenoma formation cannot be established. Because we used the first colonoscopy as the index colonoscopy in our study, we cannot be certain that adenomas did not develop before the initiation of insulin therapy. However, this misclassification would be expected to be nondifferential by adenoma status, resulting in bias toward the null. We were also unable to determine the exact start date of insulin therapy in those subjects who initiated insulin therapy before entering the EPIC database. This could lead to misclassification of duration of insulin therapy, or left-censoring, such that the estimated duration of insulin therapy required before seeing an effect on adenoma risk may be underestimated. Prescription dates within the database were used to determine duration of exposure, by subtracting the last prescription date from the first. However, if the last prescription date included multiple refills, the true duration of medication exposure in these patients could have been underestimated. This would lead to misclassification of exposed patients as nonexposed patients. Also, we assumed 100% compliance with insulin therapy, but this assumption may not be true. However, any misclassification of our exposure definition would tend to lead to an underestimate of the effect of exogenous insulin on the risk of adenoma formation. Furthermore, a dose-response association between insulin use and risk of adenoma would strengthen the causal relationship between the 2. However, insulin usage in each individual patient was widely variable depending on factors such as patient diet and compliance with insulin use. We were unable to accurately capture such usage data using information contained in our electronic medical records to meaningfully assess this effect. However, our duration-response analysis should at least capture the cumulative insulin dose exposure to some extent.

Because initiation of insulin use is associated with longer duration of and more severe type 2 DM, one could postulate that these factors may affect the observed risk association. We were unable to obtain accurate data on the duration of type 2 DM from our patient database to adjust for this variable. Because of the cross-sectional design of our study, we were unable to measure levels of hemoglobin A1c levels or C-peptide, both potential surrogate markers for extent of glycemic control and pancreatic beta-cell function. However, previous studies have reported that duration of DM was not associated with CRC risk (14, 15). More recently, Yang and colleagues investigated the association between serial hemoglobin

A1c levels as a longitudinal marker of glycemic control and CRC risk and found no significant association (39). Based on these findings, neither DM duration nor chronic glycemic control would appear to be relevant confounders for the association between insulin therapy and colorectal neoplasia.

We could not reliably exclude patients with type 1 DM from our cohort. However, patients with type 1 DM comprise only 5% of the entire DM population and probably lower prevalence in an older population. Thus, it is unlikely that the observed association is because of inclusion of patients with type 1 DM.

Finally, patients receiving insulin may receive closer medical care, including CRC screening. However, because our outcome of interest (i.e., adenoma) is almost always asymptomatic, such closer medical contact is unlikely to be related to the presence of adenoma. Furthermore, a recent retrospective cohort study showed that insulin users did not have a higher rate of low endoscopy use (HR 0.98, CI .91–1.05) compared with sulfonylurea only users (40).

In summary, these data show that long-term use of insulin therapy is associated with an increased prevalence of colorectal adenoma including right-sided adenomas in patients with type 2 DM. Our data support the role of insulin in the pathogenesis of adenoma and CRC formation. Given the potential for bias in this cross-sectional single-center study, further studies are needed to replicate this association and determine whether more intensive CRC screening is warranted and whether colonoscopy screening is preferred among the growing population of insulin-using type DM patients. In the meantime, these results reinforce the importance of adherence to existing colorectal screening guidelines in patients with type 2 DM on insulin therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P. Wong, Y. Yang
Development of methodology: P. Wong, W.T. Hwang, Y. Yang
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P. Wong, M.G. Weiner, Y. Yang
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P. Wong, M.G. Weiner, W.T. Hwang, Y. Yang
Writing, review, and/or revision of the manuscript: P. Wong, M.G. Weiner, W.T. Hwang, Y. Yang
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P. Wong, M.G. Weiner, Y. Yang
Study supervision: Y. Yang

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