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# Metformin for Primary Colorectal Cancer Prevention in Diabetic Patients: A Case-Control Study in a US Population

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## Abstract

**Background—**Emerging evidence from observational studies suggests that metformin may be beneficial in the primary prevention of colorectal cancer (CRC). However, none of these were conducted in a US population. Since environmental factors, such as Western diet and obesity, are implicated in the causation of CRC, we conducted a large case control study to assess the effects of metformin on CRC incidence in a US population.

**Methods—**MarketScan® databases were used to identify diabetic patients with CRC. A case was defined as having an incident diagnosis of CRC. Up to two controls matched for age, sex and geographical region, were selected for each case. Metformin exposure was assessed by prescription tracking in the 12 months period prior to the index date. Conditional logistic regression was used to adjust for multiple potential confounders and to calculate adjusted odds ratios (AOR).

**Results—**The mean age of participants was 55 and 57 years in the control and case group, respectively (p=1.0). Sixty percent of the study participants were males and 40% were females in each group. In the multivariable model, any metformin use was associated with 15% reduced odds

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of CRC (AOR, 0.85, 95% confidence interval (CI), 0.76–0.95, p<0.007). After adjusting for health-care utilization the beneficial effect of metformin was reduced to 12% (AOR, 0.88, 95% CI, 0.77–1.00, p=0.05). The dose-response analyses showed no significant association with metformin dose, duration or total exposure.

**Conclusions—**Metformin use is associated with reduced risk of developing CRC among diabetic patients in the US population.

### Keywords

Metformin; colorectal cancer; chemoprevention; diabetes and MarketScan® database

## INTRODUCTION

Cancer and diabetes are extremely prevalent diseases worldwide and are associated with substantial adverse health effects. Colorectal cancer (CRC) is the second most commonly diagnosed cancer in females and third most commonly diagnosed cancer in males. Over 1.2 million incident cases and 608,700 deaths were recorded globally in 2008[1]. At least six case-control studies and 9 cohort studies suggest that the relative risk of CRC is higher in diabetic patients (predominantly type 2)[2]. A recent consensus statement by the American Diabetes Association and the American Cancer Society concluded that there is higher risk of CRC in type 2 diabetics[3]. Diabetes is thought to promote the development of carcinogenesis through a complex processes. These include hyperinsulinemia, hyperglycemia and chronic inflammation[3]. Metformin is the most commonly prescribed drug for treatment of type 2 diabetes mellitus. An important clue to metformin's actions was the discovery that metformin up-regulates AMP-activated protein kinase (AMPK)[4] which is a central regulator of cellular energy metabolism. Subsequent epidemiological studies linked metformin use to an anti-cancer effect[5] which has lead to great interest in repurposing metformin for cancer treatment and prevention.

Metformin is a generic, inexpensive, easily available drug that belongs to the biguanide class of agents. Metformin's excellent safety profile makes it an attractive anti-cancer drug. Metformin is mainly used for treatment of type 2 diabetes mellitus but is also used in polycystic ovarian disease and morbid obesity. Metformin causes its anti-hyperglycemic action by suppressing hepatic glucose output (inhibition of gluconeogenesis and glycogenolysis), increasing peripheral tissue (skeletal muscle and adipocytes) insulin sensitivity and decreasing intestinal absorption of glucose[6]. Metformin is usually well tolerated with infrequent gastrointestinal adverse effects, such as diarrhea, flatulence, and abdominal discomfort, as the major side effects[7]. Hypoglycemia is rare[8] and lactic acidosis is extremely rare (0.03 cases per 1000 patient-years)[6].

There have been several observational studies from Europe and Asia suggesting a reduced incidence of CRC as well as other cancers including breast, lung, prostate, ovarian and pancreatic cancer in diabetic patients on metformin[9–13]. Supporting these human observations, metformin has been shown to inhibit growth and induce apoptosis in cell lines and animal models for various cancers including colorectal cancer[14, 15]. A recent prospective randomized clinical trial showed decrease in the mean number of aberrant

cryptic foci (a putative precursor lesion for CRC) in non-diabetic patients after 30 days metformin treatment as compared to placebo[16]. There is a growing body of evidence that metformin's anti-cancer activity is mediated by both its cellular and systemic effects[17]. The systemic effects of metformin are mainly reductions in hyperglycemia that can potentially counteract the Warburg effect (dependence of cancer cells on glucose as predominant source of energy). The cellular or direct effects are believed to involve activation of the AMPK pathway[18–20], which can potentially counteract the effects of hyperinsulinemia by systemic inhibition of growth factors including glucose, insulin, insulin-like growth factor 1 (IGF-1), insulin-like growth factor 1 receptor (IGF-1R), insulin-like growth factor binding protein (IGF-BP) and leptin (but an increase in adiponectin), eventually leading to inhibition of protein synthesis, and reductions in cell growth and proliferation.

Despite these observational studies and rationale, we know of no large, retrospective, nation wide studies in the US population that examined metformin's potential effectiveness in reducing the incidence of CRC. Furthermore, because environmental factors, especially Western diet and obesity, are believed to play important causal roles in the genesis of sporadic colon cancer, such a study in a US population is warranted to address the potential efficacy of metformin in this country[21]. We, therefore, conducted a case control study using MarketScan database to address this question in a US population.

## MATERIALS AND METHODS

### Patients and eligibility criteria

The study was conducted using MarketScan® Commercial Claims and Encounters Database (Truven Health Analytics, Ann Arbor, MI, USA). MarketScan® is a longitudinal database that contains individual-level, de-identified health insurance claims data of nearly 150 million individuals from all geographic areas of the United States. All diabetic (DM) patients above the age of 18 years diagnosed with CRC from 2005 to 2010 were identified in the MarketScan® database using the International Classification of Disease (9th revision, clinical modification; ICD9-CM) codes (DM; ICD-9 codes 250.0 to 250.9; CRC; ICD-9 codes 153.0 to 153.9, 154.0, 154.1 and 154.8). To reduce the false positive rate of CRC cases, only patients with at least two or more claims of ICD-9 codes indicating CRC on different dates within a period of 3 months were included. Additionally, only patients with continuous enrollment in the 12 months period prior to the earliest CRC diagnosis date were included in the study to ensure completeness of claims data. The primary objective was to assess the odds of developing of CRC in metformin users and nonusers. The study was approved by the Institutional Review Board of the University of Chicago, IL, USA.

### Cases and controls

A case was defined as a diabetic patient having an incident diagnosis of CRC. For the purpose of this study, a CRC case was considered incident if there were no claims indicative of CRC in the previous year so as to ensure metformin use prior to the development of CRC. A control was defined as a diabetic patient without a diagnosis of CRC. The controls were identified by first matching patients by age, sex, and geographical region (*i.e.*, Northeast, North Central, South, West and unknown) to a case, then by ascertaining those that were

enrolled in the same month as the month of diagnosis of matching case and finally keeping only patients with twelve month continuous enrollment as controls. Therefore, up to two controls individually matched for age, sex and geographical region were selected *per* case.

### Exposure ascertainment

The exposure to metformin was estimated by tracking the prescriptions in the 12 months prior to the index date. The index date for cases was defined as the earliest date of CRC diagnosis. Similarly, the index date for controls was defined as the date of diagnosis of the case that was used to find the matched controls. We gathered the dose and duration of metformin use for each study participant. The exposure assessment in the year prior to CRC diagnosis ensured inclusion of only incident cases of CRC to the best extent possible for this study.

### Potential confounders

We collected data on multiple potential confounders of patient-related variables and concurrent medications 12 months prior to the index date. The patient-related variables for this purpose included obesity (ICD-9 codes 278.00 and 278.01), polycystic ovary disease (PCOD; ICD-9 code 256.4), inflammatory bowel disease (IBD; ICD-9 codes 556.0 to 556.9, 555.0 to 555.2 and 555.9), coronary artery disease (CAD; ICD-9 codes 410.0 to 410.9, 414.0 to 414.4, 414.8, 414.9, and 429.2), age, sex, geographic region and comorbidity scores. The comorbidity scores were calculated using the modified Charlson algorithm available from the SEER-Medicare website[22] and revised to fit the data structure in MarketScan®. Medications being used concurrently in the last 1-year (including the index date), for which statistical model adjustments were made, included prescribed nonsteroidal anti-inflammatory drugs but excluding over the counter aspirin (NSAIDs; Ibuprofen, Naproxen, Indomethacin, Diclofenac, Piroxicam, Etodolac, Fenoprofen, Flurbiprofen, Ketoprofen, Meclofenamate, Meloxicam, Nabumetone, Oxaprozin, Sulindac, Tolmetin, Celecoxib), statins, sulfonylureas (SU), thiazolidinediones (TZD) and insulin. We also gathered data on healthcare utilization by counting the number of outpatient visits and number of hospitalizations during the 12 months prior to the index date.

### Statistical analyses

The differences between the case and control group for covariates was determined by chi-square or t-test. In the primary analyses, the odds of developing CRC for diabetic patients exposed to metformin and those not exposed to metformin was calculated. Conditional logistic regression was used to estimate the AOR and 95% CI, adjusting for patient-related variables, concomitant medications and health care utilization. In the secondary analyses, we calculated the magnitude of effect of metformin's dose, duration and total exposure on CRC risk. To study dose response relationships, we collected data on dose and duration of metformin for the study participants with at least one prescription claim for metformin in the past year. We divided the duration of use into four quartiles (≤123, 124–240, 241–313 and ≥314 days) for statistical analyses. Similarly, the daily dose of metformin was divided into four quartiles (≤1000, 1001–1500, 1501–2000 and ≥2001 mg) for statistical analyses. We also calculated the total metformin exposure by multiplying the metformin dose with duration of use. A p-value was considered statistically significant if the two-sided p-value

was ≤ 0.05. The data management was done using SAS®, Enterprise Guide version 5.1 (SAS Institute Inc., Cary, NC, USA) and all statistical analyses were done using STATA®, version 12.0 (StataCorp LP, College Station, TX, USA).

## RESULTS

### Study participants

The total number of study participants was 8,046 with 2,682 in the case group and 5,364 in the control group. The mean age was 55 and 57 years in the case and control group, respectively (p=1.0). There were 60% males and 40% females in each group. Any metformin exposure was seen in 36.6% of patients in the case group and 38.4% of patients in the control group, respectively. On univariate analysis, there were no significant differences in terms of age, sex, geographical region, year of diagnosis, obesity, PCOD, statins, metformin, SU, TZD and insulin use. However, comorbidies, including IBD, CAD and NSAIDs use were significantly different between the two groups with higher percentages in the case group compared to the control group except for NSAIDs use (Table I). The Charlson comorbidity score was significantly higher in the control group but the number of hospital admissions and the number of outpatient visits were significantly higher in the case group as compared to controls (Table I).

### Metformin and odds of developing colorectal cancer

In a multivariate model, any metformin use was associated with 15% reduced odds of CRC (AOR 0.85, 95% CI, 0.76–0.95, $p$=0.007) while controlling for all the patient-related variables, concomitant medications and Charlson comorbidity score (Table II). We found that PCOD, obesity, statins and TZD showed no significant association with the odds of developing CRC whereas Charlson comorbidity index and prescribed NSAIDs were associated with significantly decreased odds of developing CRC. Inflammatory bowel disease, sulfonylurea, CAD, insulin, number of hospital admissions and number of outpatient visits were associated with significantly increased odds of developing CRC. (Table II). Adjustment for healthcare utilization in the multivariate model (besides all other covariates) resulted in 12% reduced odds of CRC with any metformin use (AOR 0.88, 95% CI, 0.77–1.00, $p$=0.05) as compared to no metformin use (Table III).

### Dose response analysis with metformin

The mean and median duration of metformin intake was 218 and 240 days, respectively. The mean and median metformin daily dose taken by study participants was 1,500 mg whereas the mean and median metformin total dose taken by study participants was 3,29,300 and 3,02,000 mg. However, no significant dose response relationship was found between metformin dose, duration or total exposure (dose × duration) and odds of developing CRC (Table IV).

## DISCUSSION

There is growing interest to explore the role of metformin as a chemopreventive agent given the experimental evidence in support of metformin as an anti-cancer drug[15, 23]. In a large

case control study of patients with diabetes, we found a 12–15% statistically significant reduced risk of developing CRC with any metformin use. However, the dose-response analyses did not show any significant relationship between dose, duration or total exposure of metformin and CRC. Although a clear dose-response effect would have strengthen our findings the lack of a dose-response effect might be due to a threshold effect achieved at the lowest dose. In this regard, Lee et al in another epidemiological study found a significantly reduced CRC risk at all dose levels of metformin (500, 500–1000 and 1000 mg) in female metformin users (but not in male users)[9]. Similarly, Tseng et al. reported that the beneficial effect of metformin becomes significant only after 3 years of use[24].

Our study is unique in that there are no prior studies addressing the effectiveness of metformin in reducing the risk of CRC among diabetic patients in a US population. This population, moreover, has relatively distinct environmental risk factors, especially Western diet and obesity. Additionally, our study population is relatively younger (mean age ~57 years; range 18–64 years) as compared to median age of CRC diagnosis in the United States (~68 years)[25]. Our study population is also relatively younger compared to previously published studies[9–11, 24].

There has been a consistent association between diabetes and many cancers including colon cancer. As noted above, the key mechanisms linked to cancer in diabetic population are hyperglycemia, hyperinsulinemia and chronic inflammation[3]. In our analyses insulin use was associated with significantly increased risk of developing CRC (AOR 1.45, 95% CI, 1.27–1.65, $p<0.001$), which supports the hypothesis that insulin may be increasing CRC risk by promoting signaling through insulin-like growth factor (IGF) receptors resulting in increased cell growth, proliferation, survival and migration. Similarly, sulfonylureas, which act by promoting insulin secretion, were also associated with increased CRC risk (AOR 1.15, 95% CI, 1.02–1.31, $p<0.02$).

Besides diabetes, other chronic diseases associated with higher incidence of CRC were IBD (AOR 1.95, 95% CI, 1.14–3.34, $p=0.01$) and CAD (AOR 1.66, 95% CI, 1.43–1.93, $p<0.001$). This might be related to common risk factors as well as common pathological changes seen in these diseases (such as, chronic inflammation in the colon in IBD and systemic inflammation in CAD). Although we expected to find a higher incidence of CRC in individuals with obesity and PCOD we did not find any significant association, which might be due to unexpected underreporting of obesity (about 4% prevalence) and PCOD (less than 1% prevalence) in our dataset. The influence of these comorbidities should be considered in future studies using datasets with adequate representation of individuals affected with obesity and PCOD. Lastly, an enormous body of evidence suggests that aspirin/NSAIDs use is associated with reduced risk of developing CRC[26–28]. We evaluated the effect of prescribed NSAIDs and found a 16% decreased odds of developing CRC (AOR 0.84, 95% CI, 0.73–0.96, $p=0.01$). Only two other studies in the current metformin literature controlled for aspirin/NSAIDs use but found no statistically significant association[24, 29]. Similarly, statins are believed to decrease the CRC incidence due to several of their pleiotropic effects (most importantly anti-inflammatory properties)[30]. While not statistically significant, we found that the use of statins was associated with 9% lower odds of developing CRC (AOR 0.91, 95% CI, 0.82–1.01, $p=0.10$).

Our results are similar to the results of several other observational studies that were conducted using either Health Information Network database of United Kingdom or Taiwanese National Health Insurance database. In these studies, metformin was associated with a statistically significant reduction of 27% to 44% in the incidence of CRC[10, 11, 24] (except one study reporting 64% reduction[9]; Table V). Despite these positive studies, two nested case control studies using the General Practice Research Database, United Kingdom found no effect of metformin on CRC risk (Table V)[29, 31]. However, three large meta-analyses, including case control and cohort studies, have shown a statistically significant reduction in the risk (approximately 32–37%) of developing CRC in individuals on metformin as compared to those not on metformin with mild to moderate heterogeneity ($I^2$ = 24–44%)[32–34]. Collectively, these numerous positive observational studies and metaanalyses suggest that metformin use is associated with reduction in the incidence of CRC. However, the magnitude of beneficial effect seen in our study is much smaller than the metaanalyses. There are at least two possible factors that might have contributed to this. First, our study had a relatively younger population, which may have resulted in missing some CRC cases as the cancer incidence increases with age. Second, our study was comprised of a relatively healthier population as evidenced by the lower Charlson comorbidity Index (mean of 1.1 in cases and 1.47 in controls) which could also have resulted in under-diagnosis of CRC.

We emphasize that our study has many strengths. First, the large sample size of our study provided sufficient power to address the impact of metformin use on the risk of developing CRC. Second, a computerized prescription database was used for assessing the exposure to drugs of interest, thereby minimizing the recall bias. Third, several steps were taken to avoid misclassification bias, such as, using a stringent case definition (as described in methods) and using only patients with at least 12 months of continuous enrollment prior to the date of diagnosis. Forth, we controlled for many potential confounders including diseases and concomitant medications during the 12 months prior to the date of diagnosis. Fifth, we adjusted for health care utilization by estimating the number of outpatient visits and hospital admissions. Disparities in health-care utilization can induce a potential bias in a case control study. For example, if patients in the case group are using more health-care resources compared to the control group this can erroneously result in better outcomes in the case group. This was true in our study as the case group used more health care resources. Thus, the beneficial effect of metformin was reduced when we adjusted for health-care utilization (see Table III).

The major limitation of our study is its retrospective study design, which limits the ability to control for unknown potential confounders and sometimes known confounders when the data is not available (such as race and body mass index data is not available in MarketScan® database). It is possible that such confounders have affected our results. First, we were unable to control for aspirin usage, as this is mainly available an over the counter drug in the United States and this information is not available in the MarketScan® database. It is theoretically possible that the beneficial effect of metformin observed in our study is partially driven by higher over the counter use of aspirin in the case group. Individuals with CAD are more likely to take over the counter aspirin. The univariate analysis of our data does show a higher rate of CAD in the case group, which could suggest that a higher proportion of individuals in the case group might be taking aspirin. Since we adjusted for

CAD in our multivariate model, however, it is unlikely that the results of our study merely reflect potential confounding by aspirin. Second, it is possible that a higher health conscious behavior such as screening colonoscopy is associated with increased metformin usage. Therefore, it is possible that the reduced incidence of CRC in the case group is due to a greater likelihood of adhering to cancer screening guidelines among metformin users. We could not adjust for screening colonoscopy in our study, however, because the guideline-recommended screening interval for colonoscopy is every 5–10 years, and given our study duration of only 1 year, we would have missed many screening colonoscopies outside of our observation period. However, we did adjust for overall health care utilization, which showed a higher utilization of healthcare resources in the case group compared to control, which reduced the beneficial effect of metformin (AOR 0.88, 95% CI, 0.77–1.00, p=0.05). Therefore, it is possible that our results of beneficial effect of metformin are in part due to greater health conscious behavior in the case group as compared to control group. Third, we could not adjust for lifestyle (diet and exercise) and socioeconomic factors in our analysis. We do not expect, however, that these variables would be significantly different between the two groups to explain the findings of our study. Additionally, we matched for age, sex, geographical region and year of diagnosis that would have balanced these factors between the case and control groups. Fourth, we could not adjust for smoking and alcohol consumption as this information is not available in MarketScan database. Lastly, our data was not linked to cancer registries and therefore, there could be ascertainment bias in the incident cohort as identified from claims using ICD-9 codes.

In conclusion, the results of our study suggest that metformin may have beneficial effect in reducing the risk of CRC among diabetic patients in the US population. The magnitude of the effect we measured is smaller than prior reports in studies from Asia and Europe. This may reflect the relatively younger population in our study and differences in adjustments for potential confounders among different studies. Furthermore, due to inherent nature of our study design, a causal relationship cannot be established. Further, prospective controlled studies are needed to rigorously test metformin's efficacy as a colon cancer chemopreventive agent.

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## Abbreviations

| | |
|---|---|
| **CRC** | colorectal cancer |
| **AOR** | adjusted odds ratio |
| **CI** | confidence interval |
| **IBD** | inflammatory bowel disease |
| **CAD** | coronary artery disease |

| | |
|---|---|
| **PCOD** | polycystic ovary disease |
| **SU** | sulfonylurea |
| **TZD** | thiazolidinediones |
| **NSAID** | non-steroidal anti-inflammatory drugs |

## References


1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: A Cancer Journal for Clinicians. 2011; 61:69–90. [PubMed: 21296855]
2. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. Endocr Relat Cancer. 2009; 16:1103–1123. [PubMed: 19620249]
3. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010; 33:1674–1685. [PubMed: 20587728]
4. Zhou G, Myers R, Li Y, et al. Role of AMP-activated protein kinase in mechanism of metformin action. J Clin Invest. 2001; 108:1167–1174. [PubMed: 11602624]
5. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ. 2005; 330:1304–1305. [PubMed: 15849206]
6. Bailey CJ, Turner RC. Metformin. N Engl J Med. 1996; 334:574–579. [PubMed: 8569826]
7. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med. 1999; 131:281–303. [PubMed: 10454950]
8. DeFronzo RA. Pathogenesis of type 2 diabetes: implications for metformin. Drugs. 1999; 58(Suppl 1):29–30. discussion 75–82. [PubMed: 10576522]
9. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC. Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC Cancer. 2011; 11:20. [PubMed: 21241523]
10. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care. 2009; 32:1620–1625. [PubMed: 19564453]
11. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia. 2009; 52:1766–1777. [PubMed: 19572116]
12. Garrett CR, Hassabo HM, Bhadkamkar NA, et al. Survival advantage observed with the use of metformin in patients with type II diabetes and colorectal cancer. Br J Cancer. 2012; 106:1374–1378. [PubMed: 22421948]
13. Jiralerspong S, Palla SL, Giordano SH, et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol. 2009; 27:3297–3302. [PubMed: 19487376]
14. Korsse SE, Peppelenbosch MP, van Veelen W. Targeting LKB1 signaling in cancer. Biochim Biophys Acta. 2012; 1835:194–210. [PubMed: 23287572]
15. Hosono K, Endo H, Takahashi H, et al. Metformin suppresses azoxymethane-induced colorectal aberrant crypt foci by activating AMP-activated protein kinase. Mol Carcinog. 2010; 49:662–671. [PubMed: 20564343]
16. Hosono K, Endo H, Takahashi H, et al. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. Cancer Prev Res (Phila). 2010; 3:1077–1083. [PubMed: 20810669]
17. Pollak MN. Investigating metformin for cancer prevention and treatment: the end of the beginning. Cancer Discov. 2012; 2:778–790. [PubMed: 22926251]
18. Jalving M, Gietema JA, Lefrandt JD, et al. Metformin: taking away the candy for cancer? Eur J Cancer. 2010; 46:2369–2380. [PubMed: 20656475]
19. Pierotti MA, Berrino F, Gariboldi M, et al. Targeting metabolism for cancer treatment and prevention: metformin, an old drug with multi-faceted effects. Oncogene. 2012

20. Rattan R, Ali Fehmi R, Munkarah A. Metformin: an emerging new therapeutic option for targeting cancer stem cells and metastasis. J Oncol. 2012; 2012:928127. [PubMed: 22701483]
21. Lipkin M, Reddy B, Newmark H, Lamprecht SA. Dietary factors in human colorectal cancer. Annu Rev Nutr. 1999; 19:545–586. [PubMed: 10448536]
22. National Cancer Institute NIoH. SEER-Medicare: Calculation of Comorbidity Weights. Available from URL: (http://healthservices.cancer.gov/seermedicare/program/comorbidity.html) [accessed June 15, 2013, 2013]
23. Tomimoto A, Endo H, Sugiyama M, et al. Metformin suppresses intestinal polyp growth in ApcMin/+ mice. Cancer Sci. 2008; 99:2136–2141. [PubMed: 18803638]
24. Tseng CH. Diabetes, metformin use, and colon cancer: a population-based cohort study in Taiwan. Eur J Endocrinol. 2012; 167:409–416. [PubMed: 22778198]
25. SEER Cancer Statistics Factsheets: Colon and Rectum Cancer. National Cancer Institute; Bethesda, MD: http://seer.cancer.gov/statfacts/html/colorect.html. Available from URL: SEER Cancer Statistics Factsheets: Colon and Rectum Cancer. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/colorect.html
26. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA. 2005; 294:914–923. [PubMed: 16118381]
27. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Wu K, Fuchs CS. Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterology. 2008; 134:21–28. [PubMed: 18005960]
28. Rothwell PM, Wilson M, Elwin CE, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010; 376:1741–1750. [PubMed: 20970847]
29. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology. 2004; 127:1044–1050. [PubMed: 15480982]
30. Sehdev A, Shih YC, Huo D, Vekhter B, Lyttle C, Polite B. The Role of Statins for Primary Prevention in Non-elderly Colorectal Cancer Patients. Anticancer Res. 2014; 34:5043–5050. [PubMed: 25202089]
31. Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin is not associated with a decreased risk of colorectal cancer: a case-control analysis. Cancer Epidemiol Biomarkers Prev. 2012; 21:280–286. [PubMed: 22178569]
32. Decensi A, Puntoni M, Goodwin P, et al. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2010; 3:1451–1461. [PubMed: 20947488]
33. Zhang ZJ, Zheng ZJ, Kan H, et al. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis. Diabetes Care. 2011; 34:2323–2328. [PubMed: 21949223]
34. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One. 2012; 7:e33411. [PubMed: 22448244]

## Table I

Characteristics of study population in case and control groups.

| Variable Name | | Cases N (%) = 2,682 (33.33) | Controls N (%) = 5,364 (66.67) | P-value* (Chi-Square) |
|---|---|---|---|---|
| **Mean Age (SD, range)** | | 57.37 (±5.51; 26–64) | 55.23 (±5.69; 23–64) | 1.0 (t-test) |
| **Male**<br>**Female** | | 1,603 (59.77)<br>1,079 (40.23) | 3,203 (59.77)<br>2,158 (40.23) | 1.0 |
| **Region/zip code** | **Northeast** | 191 (7.12) | 383 (7.14) | 0.92 |
| | **North Central** | 731 (27.26) | 1,477 (27.54) | |
| | **South** | 1,404 (52.35) | 2,790 (52.01) | |
| | **West** | 345 (12.86) | 684 (12.75) | |
| | **Unknown** | 11 (0.41) | 30 (0.56) | |
| **Year of Diagnosis** | **2005** | 310 (11.56) | 620 (11.56) | 1 |
| | **2006** | 282 (10.51) | 564 (10.51) | |
| | **2007** | 570 (21.25) | 1,140 (21.25) | |
| | **2008** | 536 (19.99) | 1,072 (19.99) | |
| | **2009** | 593 (22.11) | 1,186 (22.11) | |
| | **2010** | 391 (14.58) | 782 (14.58) | |
| **Obesity** | | 112 (4.18) | 193 (3.6) | 0.20 |
| **Inflammatory Bowel Disease** | | 29 (1.08) | 29 (0.54) | 0.007 |
| **Coronary Artery Disease** | | 389 (14.5) | 641 (11.95) | 0.001 |
| **Polycystic Ovary Disease** | | 1 (0.04) | 6 (0.1) | 0.28 |
| **Statins** | | 992 (36.99) | 2,091 (38.98) | 0.083 |
| **Metformin** | | 983 (36.65) | 2,059 (38.39) | 0.13 |
| **NSAIDs** | | 372 (13.87) | 865 (16.13) | 0.008 |
| **Sulfonylurea** | | 683 (25.47) | 1,359 (25.34) | 0.89 |
| **Insulin** | | 502 (18.72) | 913 (17.02) | 0.06 |
| **Thiazolidinedione** | | 488 (18.22) | 1,069 (19.93) | 0.06 |
| **Charlson Comorbidity Score** | | 1.10 ± 1.04 | 1.47 ± 0.87 | <0.001 (t-test) |
| **Admissions (Mean ± SD)** | | 0.58 ± 0.96 | 0.19 ± 0.62 | <0.001 (t-test) |
| **Outpatient Visits (Mean ± SD)** | | 19.99 ± 19.42 | 15.91 ± 16.81 | <0.001 (t-test) |

*Univariate p-value calculated with chi-square unless specified.

## Table II

Results of metformin exposure and odds of developing colorectal cancer in multivariate regression model.

| Variable | COR (95% CI) | P-value | AOR (95% CI) | P-value |
|---|---|---|---|---|
| **Associated with Increased Odds** | | | | |
| Insulin use | 1.12 (0.99–1.27) | 0.05 | 1.45 (1.27–1.65) | <0.001 |
| Coronary artery disease | 1.25 (1.09–1.43) | 0.001 | 1.66 (1.43–1.93) | <0.001 |
| Inflammatory bowel disease | 2 (1.19–3.34) | 0.008 | 1.95 (1.14–3.34) | 0.01 |
| Sulfonylurea use | 1.00 (0.90–1.12) | 0.89 | 1.15 (1.02–1.31) | 0.02 |
| Hospital admissions | 1.95 (1.81–2.10) | <0.001 | 2.55 (2.32–2.81) | <0.001 |
| Number of outpatient visits | 1.012 (1.010–1.015) | <0.001 | 1.01 (1.011–1.019) | <0.001 |
| **Associated with Decreased Odds** | | | | |
| Metformin | 0.92 (0.84–1.02) | 0.12 | 0.85 (0.76–0.95) | 0.007 |
| Prescribed NSAIDs | 0.83 (0.72–0.95) | 0.007 | 0.84 (0.73–0.96) | 0.01 |
| Charlson comorbidity Index | 0.58 (0.55–0.62) | <0.001 | 0.54 (0.50–0.58) | <0.001 |
| **No significant Association** | | | | |
| Obesity | 1.16 (0.92–1.47) | 0.20 | 1.19 (0.93–1.52) | 0.16 |
| Polycystic ovary disease | 0.33 (0.04–2.76) | 0.30 | 0.32 (0.03–2.75) | 0.30 |
| Statins | 0.91 (0.83–1.01) | 0.07 | 0.91 (0.82–1.01) | 0.10 |
| Thiazolidinedione | 0.89 (0.79–1.00) | 0.06 | 0.92 (0.81–1.06) | 0.28 |

Abbreviations: COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval.

*Adjusted for obesity, polycystic ovary disease, inflammatory bowel disease, sulfonylurea use, coronary artery disease, prescribed NSAIDs, insulin, metformin, Thiazolidinedione, Charlson comorbidity index, number of hospital admission and number of outpatient visits.

## Table III

Results of metformin exposure and odds of developing colorectal cancer in multivariate regression model that included healthcare utilization.

| Variable | AOR* | P-value* |
|---|---|---|
| **Metformin** | **0.88 (0.77–1.00)** | **0.05** |
| Hospital admissions | 2.55 (2.32–2.81) | <0.001 |
| Number of outpatient visits | 1.01 (1.011–1.019) | <0.001 |

* Model adjusted for obesity, inflammatory bowel disease, polycystic ovary disease, coronary artery disease, Charlson comorbidity index, NSAIDs, sulfonylureas, thiazolidinediones, statins and insulin.

**Table IV**

Stratified analysis by metformin dose, duration and total exposure (dose × duration).

| Variable Name | Quartiles | N (%) | AOR (95% CI) | P-value | P-value for Trend |
|---|---|---|---|---|---|
| **Metformin Duration (days) (days)** | ≤123 | 755 (25.07) | 1.00 | | 0.33 |
| | 124–240 | 754 (25.04) | 1.12 (0.81–1.55) | 0.48 | |
| | 241–313 | 760 (25.24) | 1.04 (0.75–1.44) | 0.79 | |
| | >314 | 742 (24.64) | 0.89 (0.63–1.26) | 0.54 | |
| **Metformin Dose (mg)** | ≤1,000 | 1,231 (40.88) | 1.00 | | 0.97 |
| | 1,001–1,500 | 326 (10.83) | 1.09 (0.73–1.62) | 0.64 | |
| | 1,501–2,000 | 1,313 (43.81) | 1.04 (0.79–1.36) | 0.77 | |
| | >2001 | 141 (4.68) | 0.89 (0.51–1.55) | 0.69 | |
| **Total Metformin Exposure (dose × duration)** | ≤150,000 | 785 (26.07) | 1.00 | | 0.40 |
| | 150,001–306,000 | 730 (24.24) | 1.12 (0.81–1.55) | 0.48 | |
| | 306,001–522,000 | 747 (24.81) | 1.04 (0.75–1.44) | 0.79 | |
| | >522,001 | 749 (24.88) | 0.89 (0.63–1.26) | 0.54 | |

*Model adjusted for obesity, inflammatory bowel disease, polycystic ovary disease, coronary artery disease, Charlson comorbidity index, NSAIDs, sulfonylureas, thiazolidinediones, statins and insulin

**Table V**

Studies evaluating the role of metformin in reducing the incidence of colorectal cancer.

| Study | Design | Sample Size | Mean Age | Data Source/Collection Period | Outcome | HR/OR (P< 0.05 for all studies) |
|---|---|---|---|---|---|---|
| **Positive Observational Studies** | | | | | | |
| Currie et al. 2009[11] | Retrospective cohort | 62,809 | 64 | Health Information Network database of UK/2000–2005 | Incidence | HR 0.56<br>95% CI, 0.40–0.76 (M vs. SU) |
| Libby et al. 2009[10] | Retrospective cohort | 8,170 | 66 | Health Informatics Centre (HIC), Scotland, UK/1994–2003 | Incidence | HR, 0.6<br>95% CI, 0.38–0.94 |
| Lee et al. 2011[9] | Retrospective cohort | 480,984 | NR (20 or older) | Taiwanese National Health Insurance database/2000–2007 | Incidence | HR 0.36<br>95% CI, 0.13–0.98 |
| Tseng et al. 2012[24] | Retrospective cohort | 114,562 | NR (all ages) | Taiwanese National Health Insurance database/1996–2005 | Incidence | HR 0.73<br>95% CI, 0.58–0.92 |
| **Negative Observational Studies** | | | | | | |
| Bodmer et al. 2012[31] | Case Control | 6,440 | 70 | UK–based General Practice Research Database (GPRD)/1995–2009 | Incidence | OR 1.43<br>95% CI, 1.08–1.90 |
| Yang et al. 2004[29] | Nested Case Control | 24,918 | 75 | UK–based General Practice Research Database (GPRD)/1987–2002 | Incidence | OR 1.0<br>95% CI, 0.6–1.7 |

Abbreviations: NR, not reported; HR, hazard ratio; OR, odds ratio; CI, confidence interval