Anti-Diabetic Medications and the Risk of Colorectal Cancer in Patients with Diabetes Mellitus: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Anti-diabetic medications (ADM) may modify colorectal cancer (CRC) risk in patients with diabetes mellitus (DM). We performed a systematic review and meta-analysis, evaluating the effect of metformin, thiazolidinediones (TZD), sulfonylureas and insulin on CRC risk in diabetic patients.

Methods: We conducted a systematic search of multiple bibliographic databases, up to September 2012, for articles which evaluated exposure to metformin, TZD, sulfonylureas and insulin, reported CRC risk in patients with DM, and reported odds ratio (OR) or provided data for their estimation. Summary OR estimates with 95% confidence intervals (CI) were estimated using random-effects model.

Results: Fifteen studies reporting 13,871 cases of CRC in 840,787 patients with DM were included. Meta-analysis of observational studies showed an 11% reduction in CRC risk associated with metformin use (n=9 studies; OR, 0.89; 95% CI, 0.81-0.99), whereas TZD use was not associated with CRC risk (n=5 studies; OR, 0.96; 95% CI, 0.87-1.05). Conversely, a trend towards higher CRC risk was observed with sulfonylurea (n=7 studies; OR, 1.11; 95% CI, 0.97-1.26) and insulin (n=9 studies; OR, 1.33; 95% CI, 0.91-1.94) use, although these associations were not statistically significant. There was considerable heterogeneity across studies, partly explained by study location and adjustment for concomitant use of other ADM. Post-hoc analysis of randomized controlled trials did not reveal any significant association between ADM and CRC risk.

Conclusions: Meta-analysis of published studies supports a protective association between metformin use and CRC risk in patients with DM,

Impact: Clinical trials of chemopreventive effect of metformin against CRC are warranted.
INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy worldwide, with a 6% lifetime risk of developing this cancer; half the patients diagnosed with this cancer die from it. Most cases of sporadic CRC are thought to arise from dysplastic adenomas. Regular screening with colonoscopic resection of premalignant polyps is the preferred approach to preventing sporadic CRCs, and has been associated with decreased mortality. Unfortunately, suboptimal adherence, access and expense, limit population-wide adoption of screening colonoscopy. Given limitations of screening tests and poor prognosis associated with CRC, there is great emphasis on identifying high risk patients and exploring chemopreventive strategies to reduce the burden of CRC.

Diabetes mellitus (DM) is an established, independent risk factor for CRC, with a reported 30%-40% higher risk as compared to non-diabetic patients. The putative carcinogenic effects of DM may be attributable to insulin- and insulin-like growth factors and/or an obesity-associated chronic inflammatory state. Encouragingly, several preclinical studies have shown that conventional anti-diabetic medications (ADM) may modify the risk of some cancers, including CRC. For example, metformin has been shown to have anti-neoplastic effects through both insulin-dependent and insulin-independent mechanisms. Thiazolidinediones (TZD) have been postulated to trigger cell growth arrest, induce apoptosis and prevent cancer cell invasion. In contrast, sulfonylureas, which stimulate insulin secretion, and insulin itself may increase cell proliferation and inhibit apoptosis, thereby promoting oncogenesis. To date, epidemiological studies have shown that metformin use in diabetic patients may be associated with lower risk of CRC whereas insulin and insulin secretagogues may be associated with higher CRC risk. However, existing data remain inconsistent. Previous meta-analyses are limited in evaluating the risk modification with metformin alone.
(failing to account for the concomitant cancer-modifying effects of other ADM)(20, 21) or have included a very small number of studies.(22)

To better understand the association between commonly prescribed ADM and CRC risk, we performed a systematic review and meta-analyses of observational studies and randomized controlled trials (RCT) that investigated the effect of metformin, TZD, sulfonylureas and insulin on the risk of developing CRC in patients with DM.
MATERIALS AND METHODS

This systematic review was conducted following guidance provided by the Cochrane Handbook(23) and is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.(24) The process followed a priori established protocol.

Search strategy

First, a systematic literature search of Medline (1966 through September 30, 2012), Embase (1988 through September 30, 2012) and Web of Science (1993 through September 30, 2012) databases was conducted by two study investigators (S.S. and H.S.) for all relevant articles on the association between ADM use and risk of CRC in patients with DM. Medical subject headings terms used in the search included "hypoglycemic agents", "metformin", "sulfonylurea compounds", "thiazolidinediones", "insulin" combined with "neoplasms". The title and abstract of studies identified in the search were reviewed by two authors independently (S.S. and P.S) to exclude studies that did not answer the research question of interest. The full text of the remaining articles was examined to determine whether it contained relevant information. Next, bibliographies of the selected articles, as well as review articles on the topic were manually searched for additional articles. Thirdly, manual search of abstracts from major gastroenterology and oncology conferences (2005-2012) was performed for additional abstracts on the topic.

Selection criteria

Studies considered in this meta-analysis were either observational studies or RCTs that met the following inclusion criteria: (1) evaluated and clearly defined exposure to ADM, (2) reported CRC risk in patients with DM and (3) reported relative risk or odds ratio (OR), or provided data
for their calculation. Inclusion was not otherwise restricted by study size, language or publication type. When there were multiple publications from the same population, only data from the most comprehensive report were included. We excluded studies that compared one form of insulin (like long-acting insulin glargine) with other forms of insulin, and studies that reported the risk of colorectal adenomas with ADM. The flow diagram summarizing study identification and selection is shown in Figure 1.

The methodologic quality of observational studies was assessed by two authors independently (S.S and H.S.) using the Newcastle-Ottawa scale.(25) In this scale, studies were scored across three categories: selection (4 questions) and comparability (2 questions) of study groups, and ascertainment of the outcome of interest (3 questions), with all questions with a score of one, except for comparability of study groups, where separate points were awarded for controlling age and/or sex (maximum two points). The methodological quality of RCTs was assessed using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials.(26) This tool focuses on adequacy of randomization and allocation concealment procedures, blinding and loss to follow up. Any discrepancies were addressed by a joint re-evaluation of the original article.

**Data abstraction**

Data were independently abstracted onto a standardized form by two reviewers (S.S. and P.S.). The following data were collected from each study: study design, time period of study/year of publication, country of the population studied, primary outcome reported, type of ADM, dose and duration of use (if reported), information source of exposure ascertainment and outcome assessment, total number of persons in each group (exposed v. not exposed), OR and 95% confidence intervals (CI) with and without adjustment for confounding factors. When data on
males and females was reported separately, we pooled this to derive a summary estimate for the study. For all analysis, referent group was composed of patients with DM, not exposed to medication of interest. Data on the following risk factors for CRC were extracted from each study, where available: age, sex, ethnicity, body mass index (BMI), family history of CRC, smoking, alcohol, physical activity, dietary factors (red meat, fat intake, fruits and vegetables), DM severity and duration, use of aspirin and/or non-steroidal anti-inflammatory drugs, use of statins or hormone replacement therapy, as well as frequency of screening colonoscopy in study participants. Conflicts in data abstraction were resolved by consensus, referring back to the original article.

**Outcomes assessed**

The primary analysis focused on assessing the risk of CRC in patients with DM based on type of ADM use. *A priori* hypotheses to explain potential heterogeneity in the direction and magnitude of effect among different observational studies included location of study (Western population v. Asian population), study design (case-control v. cohort) and whether the study adjusted for the concomitant use of other ADM besides the index medication. Due to significant differences in the design of observational studies and post-hoc analysis of RCTs, data from these RCTs were analyzed and presented separately.

**Statistical analysis**

We used the random-effects model described by DerSimonian and Laird to calculate meta-analytic OR and 95% CI.(27) Since outcomes were relatively rare, OR were considered approximations of relative risk. Adjusted OR reported in studies was used for analysis to account for confounding variables. We assessed heterogeneity between study-specific estimates
using 2 methods. (28, 29) First, the Cochran’s Q statistical test for heterogeneity, which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect, was measured. Because this test is underpowered to detect moderate degrees of heterogeneity, a p-value of <0.10 was considered suggestive of significant heterogeneity. Second, to estimate what proportion of total variation across studies was due to heterogeneity rather than chance, $I^2$ statistic was calculated. In this, a value of <30%, 30%-60%, 61%-75% and >75% were suggestive of low, moderate, substantial and considerable heterogeneity, respectively. (29) Once heterogeneity was noted, between-study sources of heterogeneity were investigated using subgroup analyses by grouping original estimates according to study characteristics (as described above). In this analysis, a test of interaction comparing the two sub-groups was performed; (30) if the p-value for difference between subgroups was <0.10, it was considered statistically significant (i.e., p<0.10 suggested that stratifying based on that particular study characteristic partly explained the heterogeneity observed in the analysis). We assessed for publication bias quantitatively using Egger’s regression test (publication bias present if p≤0.10), (31) and qualitatively, by visual inspection of funnel plots of the logarithmic OR versus their standard errors. (32) All p values were two tailed. For all tests (except for heterogeneity and publication bias), p<0.05 was considered statistically significant. All calculations and graphs were performed using Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, NJ). (33)
RESULTS

From a total of 3118 unique studies identified using the search strategy, 15 studies fulfilled the inclusion criteria and were included in meta-analysis (5 case-control, 8 cohort, 2 RCTs).(13, 14, 16-19, 34-42) These studies cumulatively reported 13,871 CRC cases in 840,787 patients with DM. There were 4 Taiwanese studies from the same cohort,(15, 34, 43, 44) and hence, only one report was included in the main analysis.(34) There were 3 studies that compared the association between insulin glargine (as compared with non-glargine insulin) and the risk of cancer, and these were excluded from analysis.(45-47)

Characteristics of included studies

The characteristics of the included studies are shown in Table 1. All studies were population-based. Thirteen studies represented Western populations (7 based in U.S.A., 5 based in Europe, 1 multi-center RCT),(13, 14, 16-19, 35, 36, 38-42) one study was performed in an Asian population (Taiwan)(34) and one study was a multi-center RCT across U.S.A, Europe and Asia.(37) The earliest study period began in 1987, and the latest ended in 2011. There was a small overlap of time period in two studies performed using the UK General Practice Research Database.(16, 17)

Most patients in the included studies were on multiple ADM for management of DM, and the comparator group for estimation of OR was based on exposure to medication of interest and non-exposure to the same medication. Three studies included only patients on monotherapy for DM, in which follow-up was censored when a second ADM was added.(13, 40, 41) In six studies, the adjusted OR for the drug of interest accounted for the simultaneous use of other ADM.(14, 17, 19, 34, 35, 37)
Quality of included studies

The overall methodologic quality of this body of evidence was moderate to high. Supplemental Table 1 and 2 depict the performance of studies on the Newcastle-Ottawa scale. For most studies, exposure was ascertained from prescription pharmacy database; outcome assessment was based on standard medical diagnostic codes with independent validation of a random sample. The duration and adequacy of follow-up in cohort and non-response rate in case-control studies was inconsistently reported. Most studies adjusted for the following confounders: age (15/15), sex (15/15), BMI (7/15), DM duration and/or severity (10/15), smoking (7/15), family history of CRC (2/15), use of aspirin and/or non-steroidal anti-inflammatory drugs (7/15) or use of statins and/or hormone replacement therapy (3/15). Colonoscopy rates were reported and adjusted for in only one study (Table 1).(18) The quality of the randomized trials was moderate.

Metformin and risk of colorectal cancer

Of the 10 studies (9 observational and 1 RCT) that reported on the association between metformin use and CRC risk, 4 demonstrated an apparent chemoprotective association,(13, 14, 40, 41) and 6 reported no significant relationship.(16, 17, 19, 34, 36, 39) Meta-analysis of observational studies demonstrated that metformin use (as compared to non-use) was associated with a statistically significant 22% reduction in CRC incidence (n=9 studies; unadjusted OR, 0.78; 95% CI, 0.63-0.96). When only the adjusted OR estimates from each study were analyzed, the summary estimate decreased to 11% reduction in CRC risk (Supplementary Figure 1). There was substantial heterogeneity between studies (Cochran's Q test p <0.01, I²=62%), which could be explained partly by study location (Western v. Asian) and study design (case-control v. cohort) (Table 2).
The chemopreventive association was stable and significant on restricting analysis to studies that adjusted for concomitant ADM use (n=7 studies; adjusted OR, 0.88; 95% CI, 0.78-0.99) and studies that compared metformin monotherapy with other ADM use (n=3 studies; adjusted OR, 0.72; 95% CI, 0.53-0.98). This association between metformin use and CRC risk was most prominent in the Western populations (n=8 studies; adjusted OR, 0.86; 95% CI, 0.76-0.97). Post-hoc analysis of RCT (7 cases of CRC, 1454 patients on metformin) revealed no significant chemopreventive or oncogenic effect of metformin (n=1 study; adjusted OR, 1.00; 95% CI, 0.40-2.47).(36)

**Thiazolidinediones and risk of colorectal cancer**

Six studies (5 observational and 1 RCT) reported on the association between TZD use and CRC risk, and none demonstrated a significant protective or harmful relationship.(19, 34-36, 38, 40) On meta-analysis of five observational studies, TZD appeared to have a neutral effect on CRC risk in DM patients (unadjusted OR, 0.97; 95% CI, 0.92-1.03; adjusted OR, 0.96; 95% CI, 0.87-1.05) (Supplemental Figure 2). The results were consistent across all studies with low heterogeneity (Cochran's Q test p=0.75, I²=0%). No significant difference was noted in subgroup analysis based on study design, location or adjustment for concomitant use of other ADM (Table 3). Post-hoc analysis of the ADOPT trial (4 cases of CRC, 1456 patients on rosiglitazone) revealed no significant chemopreventive or oncogenic association between TZD and CRC risk (n=1 study; adjusted OR, 0.47; 95% CI, 0.16-1.39).(36)

**Sulfonylureas and risk of colorectal cancer**

Of 8 studies (7 observational and 1 RCT) that reported on the association between sulfonylurea use and CRC risk, 3 found an increased risk of CRC with sulfonylurea use (as compared to non-
use), (13, 34, 41) and 5 showed no significant association. (16, 17, 19, 36, 40) Meta-analysis of 7 observational studies demonstrated there was a statistically insignificant increased CRC risk with sulfonylurea use among diabetic patients (unadjusted OR, 1.20; 95% CI, 0.98-1.46). This association was persistent, albeit less prominent after adjusting for potential confounders (adjusted OR, 1.11; 95% CI, 0.97-1.26) (Supplementary Figure 3). This summary estimate was also stable on meta-analysis of sulfonylurea monotherapy studies (n=3 studies; adjusted OR, 1.18; 95% CI, 0.92-1.51), but on analysis restricted to studies which adjusted for concomitant effects of other ADM, there was 13% increased risk of CRC (n=7 studies; adjusted OR, 1.13; 95% CI, 1.00-1.29). There was considerable heterogeneity across studies (Cochran's Q test p <0.01, $I^2=79\%$), which could be explained based on study location (Western v. Asian) and concomitant effect of other ADM (Table 4). Unlike metformin, the association between sulfonylurea use and CRC risk was not statistically significant in the Western population studies (n=6 studies; adjusted OR, 1.06; 95% CI, 0.94-1.19) but more prominent in Asian subjects. Post-hoc analysis of the ADOPT trial (10 cases of CRC, 1441 patients on glibenclamide) on oral anti-diabetic monotherapy revealed no significant chemopreventive or oncogenic effect of sulfonylureas (n=1 study; adjusted OR, 1.84; 95% CI, 0.78-4.35). (36)

**Insulin and risk of colorectal cancer**

Ten studies (9 observational and 1 RCT) reported on the association between insulin use (long and/or short-acting) and CRC risk in patients with DM. Three studies demonstrated an increased risk of CRC, (13, 16, 34) whereas 7 studies reported null association, (17-19, 37, 38, 40, 42) On meta-analysis of 9 observational studies, there was a trend towards increased CRC risk associated with insulin use (as compared to non-use), both on unadjusted (unadjusted OR, 1.28; 95% CI, 0.88-1.86) and adjusted analysis (adjusted OR, 1.33; 95% CI, 0.91-1.94), though this
was not statistically significant (Supplementary Figure 4). The results were considerably heterogeneous (Cochran's Q test $p < 0.01$, $I^2 = 96\%$), which was explained by location where the study was performed (Table 5). On exclusion of the one outlier Asian study, the heterogeneity decreased (Cochran's Q test $p = 0.02$, $I^2 = 57\%$). Post-hoc analysis of the ORIGIN trial (76 cases of CRC, 6264 patients on insulin glargine) did not show a significant difference in CRC risk with insulin glargine use (as compared to ‘standard of care’) (n=1 study; adjusted OR, 1.09; 95% CI, 0.79-1.51).(37)

On further subgroup analysis, this apparent oncogenic association was less prominent in the Western population studies (n=8 studies; adjusted OR, 1.18; 95% CI, 0.99-1.40) and most prominent in the Taiwanese study (adjusted OR, 2.56; 95% CI, 2.40-2.72). The results were stable across study design, and whether or not analysis was adjusted for concomitant use of other ADM.

**Stratified analysis**

Based on data from 4 studies, duration-response relation between insulin use and CRC risk was not observed (short duration insulin use [0-2 yrs]: adjusted OR, 1.27; 95% CI, 0.98-1.63; long duration insulin use [2-5 yrs]: adjusted OR, 1.37; 95% CI, 0.93-2.01).(16-18, 42) On subgroup analysis, there was no appreciable difference in the effects of insulin on CRC risk, based on sex [n= 2 studies; males v. females – adjusted OR (95% CI): 0.93 (0.62-1.41) v. 0.97 (0.70-1.34)](17, 18) or tumor location (colon cancer: n=2 studies; adjusted OR, 1.10; 95% CI, 0.93-1.29; rectal cancer: n=3 studies; adjusted OR, 1.07; 95% CI, 0.83-1.37).(18, 19, 42) Sufficient information was not available to perform a similar stratified analysis based on sex, tumor location or duration-response relationship, for other ADM (metformin, TZD or sulfonylureas) and risk of CRC.
Sensitivity Analysis and Publication Bias

To assess whether any one study had a dominant effect on the meta-analytic OR, each study was excluded and its effect on the main summary estimate and Cochran’s Q-test p-value for heterogeneity was evaluated; the results were unchanged. When we excluded the studies with the most weight for each individual analysis (Ruiter et al for metformin and sulfonylureas, Chang et al for TZD and insulin), (34, 41) the conclusions of the main analysis did not change significantly for metformin (adjusted OR, 0.87; 95% CI, 0.76-1.00), TZD (adjusted OR, 0.99; 95% CI, 0.91-1.08), sulfonylureas (adjusted OR, 1.11; 95% CI, 0.92-1.33), or insulin (adjusted OR, 1.15; 95% CI, 0.99-1.34). On replacing one Taiwanese study (34) with other similar population-based cohort studies from the same Taiwanese population, (15, 43) there was no significant change in overall association of CRC with metformin (adjusted OR, 0.85; 95% CI, 0.76-0.96), sulfonylureas (adjusted OR, 1.06; 95% CI, 0.96-1.17) or insulin (adjusted OR, 1.27; 95% CI, 0.94-1.69). Due to significant heterogeneity between studies, a single summary estimate for number needed to treat with metformin to prevent one case of CRC (or number needed to treat with sulfonylureas or insulin to cause one case of CRC) could not inferred.

There was no evidence of publication bias, both quantitatively (p=0.56 for metformin, p=0.23 for TZD, p=0.94 for sulfonylureas, p=0.15 for insulin), and qualitatively, on visual inspection of the funnel plot for studies (figures not shown).
DISCUSSION

In this comprehensive meta-analysis of 15 studies analyzing the association between conventional ADM and CRC risk in over 840,000 patients with primarily type 2 DM, we found that metformin use was associated with a modest, yet statistically significant, protective association (11% risk reduction), whereas TZD, sulfonylurea and insulin use were associated with neutral or possibly slightly increased risks (compared to non-use of the ADM of interest). The observed benefits associated with metformin use were evident even after accounting for the simultaneous cancer-modifying effects of multiple ADM, and was stable across observational study designs and on replacing studies with similar studies from the same cohorts. However, the reported meta-analysis was limited by substantial heterogeneity across studies that could be explained by differences in study design and/or location. Based on the data from our study, we speculate that the variable effects of different ADM on cancer risk modification may at least partially explain why intensive glucose lowering through combination therapy is not always associated with lower cancer risk.(48, 49)

The anti-neoplastic effect of metformin is postulated to be mediated by activation of adenosine monophosphate-activated protein kinase (AMPK) and consequent inhibition of the mammalian target of rapamycin (mTOR) pathway, a downstream effector of growth factor signaling which is frequently activated in malignant cells.(50) In addition, metformin may also inhibit cell growth and promote cell senescence by inhibiting cyclin D1 expression and pRb phosphorylation.(51) The direct chemopreventive effect of metformin has been demonstrated in non-diabetic, animal models of CRC. In the adenomatous polyposis coli (APC\textsuperscript{Min+/+}) mice, a murine model of familial adenomatous polyposis, metformin has been shown to suppress intestinal polyposis.(52) Metformin also suppresses azoxymethane-induced formation of
colorectal aberrant crypt foci (ACF), a reliable surrogate biomarker of CRC, by activating AMPK.\(^{(53, 54)}\). This suppression of ACF was also demonstrated in a pilot study on chemopreventive effects of low dose oral metformin in non-diabetic human subjects.\(^{(55)}\) Besides a tumor-cell specific effect, metformin has a systemic effect, improving insulin sensitivity and promoting weight loss.\(^{(10)}\) On the other hand, sulfonylureas, by increasing insulin secretion, and exogenous insulin itself, can promote oncogenesis either directly or indirectly by increasing insulin-like growth factor 1 activity, resulting in abnormal stimulation of multiple cellular signaling cascades, enhancing growth factor-dependent cell proliferation and affecting cell metabolism.\(^{(12)}\) Previous observations support a functional, albeit limited, role of hyperinsulinemia and aberrant glucose homeostasis due to insulin resistance, in the pathogenesis of colorectal neoplasia.\(^{(56-58)}\)

Differences observed in the Western and Asian population in our analysis should be interpreted with caution since only one of the included studies represented an Asian population. The differential association may be due to differences in dietary habits and/or other cultural behaviors. *In vivo* studies have shown that metformin has greatest anti-neoplastic activity in mice receiving a high-energy diet associated with hyperinsulinemia as compared to mice receiving a control diet.\(^{(59)}\) The oncogenic association between insulin use and CRC risk was more pronounced in the Asian population for unclear reasons. This increased susceptibility of Asians to the oncogenic effect of insulin has also been observed in patients with hepatocellular cancer.\(^{(60)}\)

The strengths of our study include the comprehensive and simultaneous assessment of the effects of all conventional ADM on risk modification of CRC; performance of unadjusted analysis and meta-analysis of adjusted risk estimates reported in the studies to account for the impact of potential confounders as well as multiple sub-group analysis to ensure stability of the
association and identify factors responsible for heterogeneity. While Zhang et al recently performed a meta-analysis of metformin and CRC risk,(21) they did not account for the potential cancer-modifying effects of other ADM. In their analysis of 4 studies, they observed a 37% lower CRC risk with metformin use; further, subgroup analyses were not reported. In our study, the inclusion of more studies and simultaneous assessment of cancer-modifying effect of other ADM resulted in a lower risk estimate associated with metformin than has been reported in other meta-analyses.(20-22) Soranna et al estimated the association between metformin and sulfonylureas and risk of all-cause cancer; however, they were unable to estimate the impact of sulfonylureas, TZD and insulin on CRC risk separately.(22)

**Limitations**

There were several limitations to our meta-analysis that merit consideration. First, the cancer-modifying association between ADM and CRC risk were based on data from observational studies, which accounted for nearly all of the included CRC cases (n=13,704 cases; 98.9%); no statistically significant association were apparent based on the RCT cases (167 cases, 1.1%). These RCTs were not adequately powered to detect a significant difference between classes of ADM with respect to CRC risk reduction and subjects included in these studies were not systematically screened for CRC, which might conceivably have introduced some degree of detection bias. Observational studies of ADM on cancer risk are prone to immortal time bias and inherent time-lagging issues, when comparing first line treatment with metformin with second and third line treatments with other agents.(61) This may potentially over-estimate the apparent chemopreventive effect of metformin, as well as the oncogenic effect of insulin. Second, despite adjusting for potential covariates when such data were available, the possibility of residual confounding from obesity or other factors, such as confounding by indication and severity cannot
be excluded.\textsuperscript{[62, 63]} Moreover, the included studies could not account for ‘healthy user effect’, wherein the diagnosis of DM may potentially modify dietary consumption and physical activity of patients as well as influence uptake of preventive health measures like screening colonoscopy. Third, the nature of the comparator group for each individual ADM was composed of other ADM, which may have inherent cancer-modifying effects. We tried to account for this by performing a subgroup analysis restricted to those studies which reported OR after adjusting for the effect of other ADM, and observed stable results. Finally, the individual studies were limited in reporting an association between classes of ADM and site-specific CRC risk modification. Hence, we could not establish whether different ADM are differentially associated with risk of proximal or distal CRC.

**Conclusion**

Based on the results of this meta-analysis, it appears that metformin use may be associated with a lower risk of CRC in diabetic patients, while sulfonylureas and insulin do not significantly increase CRC risk. These data support the hypothesis that in diabetic patients at high-risk for CRC (due to their metabolic condition with or without other risk factors) who are candidates for pharmacologic therapy, may be best served by metformin. Our data also suggests that the treatment of DM with metformin, in combination with other ADMs, is not associated with an increased risk for CRC; however, this observation needs further investigation. Since the observed magnitude of CRC risk reduction associated with metformin was relatively modest, the number needed to treat to prevent one case of CRC would be large. A definitive, randomized chemoprevention trial is needed to rigorously assess the effects of metformin on incident CRC in diabetic patients, but would be lengthy, logistically challenging, and resource intensive. To
facilitate further clarification of metformin’s CRC chemopreventive potential, clinical evaluation in an enriched patient population (i.e., history of sporadic colorectal neoplasia) is ongoing.(64)
REFERENCES:


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<td>U.S.A.; Population-based</td>
<td>2000-2004; 3.9y</td>
<td>Pharmacy prescription database</td>
<td>ICD-9 codes and medical record review</td>
<td>191,223</td>
<td>383</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1,2,16</td>
</tr>
<tr>
<td>Ruiter(41) 2012</td>
<td>Cohort</td>
<td>Netherlands; Population-based</td>
<td>1998-2008; 2.8-4.6y</td>
<td>Pharmacy prescription database</td>
<td>ICD-9 diagnostic codes on hospital discharge</td>
<td>85,289</td>
<td>527</td>
<td>61.8</td>
<td>0</td>
<td>38.2</td>
<td>0</td>
<td>1,2</td>
</tr>
</tbody>
</table>

**Observational Studies – Case-Control Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Location/ Setting</th>
<th>Time Period; Mean F/U (y)</th>
<th>Exposure ascertainment</th>
<th>Outcome assessment</th>
<th>Total subjects†</th>
<th>CRC cases†</th>
<th>Metformin (%)</th>
<th>TZD (%)</th>
<th>SU (%)</th>
<th>Insulin (%)</th>
<th>Confounding variables adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodmer(17) 2012</td>
<td>C-C</td>
<td>U.K.; Population-based</td>
<td>1995-2009; NR</td>
<td>Pharmacy prescription database</td>
<td>Read Diagnostic codes</td>
<td>6439</td>
<td>920</td>
<td>43.1</td>
<td>-</td>
<td>49.6</td>
<td>16.8</td>
<td>1-3,6,10-12,14-16</td>
</tr>
<tr>
<td>Chang(34) 2012</td>
<td>C-C</td>
<td>Taiwan; Population-based</td>
<td>2000-2008; 7.9y</td>
<td>Pharmacy prescription database</td>
<td>ICD-9 diagnostic codes with record linkage with National Cancer Register</td>
<td>35912</td>
<td>7200</td>
<td>79.7</td>
<td>17.8</td>
<td>90.5</td>
<td>31.8</td>
<td>1,2,11,15,16</td>
</tr>
<tr>
<td>Koro(38) 2007</td>
<td>C-C</td>
<td>U.S.A.; Population-based</td>
<td>1997-2004; 1.5y</td>
<td>Pharmacy prescription database</td>
<td>ICD-9 diagnostic codes</td>
<td>2435</td>
<td>408</td>
<td>-</td>
<td>20.2</td>
<td>-</td>
<td>5.6</td>
<td>1,2,15</td>
</tr>
<tr>
<td>Vinikoor(42)</td>
<td>C-C</td>
<td>U.S.A.;</td>
<td>2001-2006</td>
<td>Self-report</td>
<td>Histologically</td>
<td>1995</td>
<td>1007</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>29.3</td>
<td>1,2,5,11,13,17</td>
</tr>
</tbody>
</table>
### Characteristics of included studies assessing the risk of colorectal cancer in patients with diabetes mellitus treated with antidiabetic medications

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Study Period</th>
<th>Data Source</th>
<th>Diagnosing Method</th>
<th>Number of Included Patients</th>
<th>Number of CRC Cases</th>
<th>CRC Incidence Rate (Per 100,000 Person-Years)</th>
<th>OR/RR (95% CI)</th>
<th>Variables Adjusted</th>
<th>Number of Patients with DM</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Randomized Controlled Trials**

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Study Design</th>
<th>Setting</th>
<th>Study Period</th>
<th>Data Source</th>
<th>Diagnosing Method</th>
<th>Number of Included Patients</th>
<th>Number of CRC Cases</th>
<th>CRC Incidence Rate (Per 100,000 Person-Years)</th>
<th>OR/RR (95% CI)</th>
<th>Variables Adjusted</th>
<th>Number of Patients with DM</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADOPT(36) 2006</td>
<td>RCT</td>
<td>U.S.A., Europe; Hospital-based</td>
<td>2000-2006; 4.0y</td>
<td>RCT</td>
<td>Adverse event review</td>
<td>4351</td>
<td>21</td>
<td>33.4</td>
<td>33.1</td>
<td>33.5</td>
<td>-</td>
<td>1-4, 6,10,11,16,17</td>
</tr>
<tr>
<td>ORIGIN(37) 2012</td>
<td>RCT</td>
<td>Americas, Europe, Asia; Hospital-based</td>
<td>2003-2011; 6.2y</td>
<td>RCT</td>
<td>Adverse event review</td>
<td>12537</td>
<td>146</td>
<td>27.4</td>
<td>-</td>
<td>29.6</td>
<td>50.0</td>
<td>1-3,6,10-12,15,16</td>
</tr>
</tbody>
</table>

*unclear if represents only patients with DM; †- where required, number in brackets represents number of CRC patients with preceding diagnosis of DM; Variables adjusted for: 1=Age, 2=sex, 3=BMI, 4=ethnicity, 5=family H/O CRC, 6=smoking, 7=alcohol, 8=physical activity, 9=dietary factors (red meat, fat intake, fruits and vegetables), 10=duration of diabetes mellitus or severity, 11=aspirin/NSAID, 12=statin use, 13=Vitamin D/Calcium intake, 14=hormone replacement therapy, 15=other ADM, 16=other comorbidities (coronary artery disease, chronic kidney disease etc.), 17=Socioeconomic status, 18=GI procedures (lower gastrointestinal endoscopy, colonic surgery) [C-C=Case-control; CRC=Colorectal cancer; NR=Not reported; RCT=Randomized Controlled Trial; SU=Sulfonylureas; TZD=Thiazolidinediones]
<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Metformin</th>
<th>p-value for difference between sub-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>3</td>
<td>1.04</td>
</tr>
<tr>
<td>Cohort</td>
<td>6</td>
<td>0.82</td>
</tr>
<tr>
<td>Study location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>8</td>
<td>0.86</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1.04</td>
</tr>
<tr>
<td>Adjusted for other ADM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>0.88</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Table 2. Subgroup analysis of studies comparing the association between metformin and CRC risk. For each anti-diabetic medication, sub-group analyses were performed by grouping studies on the basis of study design, geographical location of study sample and whether the studies adjusted for concomitant use of other anti-diabetic medications. $P_{interaction}$ refers to p-value for a test of interaction to assess for (statistically significant) differences in summary estimates based on sub-groups; a value of <0.10 was considered statistically significant.
Table 3. Subgroup analysis of studies comparing the association between thiazolidinediones and CRC risk. For each anti-diabetic medication, sub-group analyses were performed by grouping studies on the basis of study design, geographical location of study sample and whether the studies adjusted for concomitant use of other anti-diabetic medications. $P_{\text{interaction}}$ refers to p-value for a test of interaction to assess for (statistically significant) differences in summary estimates based on sub-groups; a value of <0.10 was considered statistically significant.

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Thiazolidinediones</th>
<th>p-value for difference between sub-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>2</td>
<td>0.98</td>
</tr>
<tr>
<td>Cohort</td>
<td>3</td>
<td>0.95</td>
</tr>
<tr>
<td>Study location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>4</td>
<td>0.97</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0.94</td>
</tr>
<tr>
<td>Adjusted for other ADM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>0.92</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>1.04</td>
</tr>
</tbody>
</table>
Table 4. Subgroup analysis of studies comparing the association between sulfonylureas and CRC risk. For each anti-diabetic medication, sub-group analyses were performed by grouping studies on the basis of study design, geographical location of study sample and whether the studies adjusted for concomitant use of other anti-diabetic medications. $P_{interaction}$ refers to p-value for a test of interaction to assess for (statistically significant) differences in summary estimates based on sub-groups; a value of $<0.10$ was considered statistically significant.

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Sulfonylureas</th>
<th></th>
<th></th>
<th>p-value for difference between sub-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>3</td>
<td>1.04</td>
<td>0.73-1.48</td>
<td>0.72</td>
</tr>
<tr>
<td>Cohort</td>
<td>4</td>
<td>1.11</td>
<td>0.97-1.28</td>
<td></td>
</tr>
<tr>
<td>Study location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>6</td>
<td>1.05</td>
<td>0.93-1.19</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>1.39</td>
<td>1.22-1.58</td>
<td></td>
</tr>
<tr>
<td>Adjusted for other ADM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>1.13</td>
<td>1.00-1.29</td>
<td>0.09</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td>0.80</td>
<td>0.55-1.17</td>
<td></td>
</tr>
</tbody>
</table>
Table 5. Subgroup analysis of studies comparing the association between insulin and CRC risk. For each anti-diabetic medication, sub-group analyses were performed by grouping studies on the basis of study design, geographical location of study sample and whether the studies adjusted for concomitant use of other anti-diabetic medications. $P_{\text{interaction}}$ refers to $p$-value for a test of interaction to assess for (statistically significant) differences in summary estimates based on sub-groups; a value of $<0.10$ was considered statistically significant.
FIGURE LEGENDS:

Figure 1. Flowsheet summarizing study identification and selection.
4834 records identified through database searching

29 additional records identified through other sources

3118 records after duplicates removed

3118 records screened

3048 Excluded
1342 Preclinical Studies
1063 Unrelated to Cancer
435 Review and case reports
208 CRC not reported,
Cancer treatment/survival studies

70 full-text articles assessed for eligibility

55 Excluded
46 CRC not reported/cancer treatment or survival studies
3 Inappropriate comparator group
3 Incomplete information
3 Studies from overlapping populations

15 studies included in quantitative synthesis (meta-analysis)
Anti-Diabetic Medications and the Risk of Colorectal Cancer in Patients with Diabetes Mellitus: A Systematic Review and Meta-Analysis


Cancer Epidemiol Biomarkers Prev  Published OnlineFirst September 16, 2013.

Updated version  Access the most recent version of this article at: doi:10.1158/1055-9965.EPI-13-0429

Supplementary Material  Access the most recent supplemental material at: http://cebp.aacrjournals.org/content/suppl/2013/09/16/1055-9965.EPI-13-0429.DC1

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