Antidiabetic Medications and the Risk of Colorectal Cancer in Patients with Diabetes Mellitus: A Systematic Review and Meta-analysis

Siddharth Singh, Harkirat Singh, Preet Paul Singh, M. Hassan Murad, and Paul J. Limburg

Abstract

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

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

Results: Fifteen studies reporting 13,871 cases of colorectal cancer in 840,787 patients with diabetes mellitus were included. Meta-analysis of observational studies showed an 11% reduction in colorectal cancer risk associated with metformin use (n = 9 studies; OR, 0.89; 95% CI, 0.81–0.99), whereas TZD use was not associated with colorectal cancer risk (n = 5 studies; OR, 0.96; 95% CI, 0.87–1.05). Conversely, a trend toward higher colorectal cancer 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 ADMs. Post-hoc analysis of randomized controlled trials did not reveal any significant association between ADM and colorectal cancer risk.

Conclusions: Meta-analysis of published studies supports a protective association between metformin use and colorectal cancer risk in patients with diabetes mellitus.

Impact: Clinical trials on the chemopreventive effect of metformin against colorectal cancer are warranted.

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metformin use in diabetic patients may be associated with lower risk of colorectal cancer (13, 14), whereas insulin and insulin secretagogues may be associated with higher colorectal cancer risk (15, 16). However, existing data remain inconsistent (17–19). Previous meta-analyses are limited in evaluating the risk modification with metformin alone (failing to account for the concomitant cancer-modifying effects of other ADMs; refs. 20, 21) or have included a very small number of studies (22).

To better understand the association between commonly prescribed ADMs and colorectal cancer 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 colorectal cancer in patients with diabetes mellitus.

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. Singh and H. Singh) for all relevant articles on the association between ADM use and risk of colorectal cancer in patients with diabetes mellitus. Medical subject heading terms used in the search included "hypoglycemic agents," "metformin," "sulfonylurea compounds," "thiazolidinediones," and "insulin" combined with "neoplasms." The title and abstract of studies identified in the search were reviewed by two authors independently (S. Singh and P. Singh) 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. Third, 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: (i) evaluated and clearly defined exposure to ADMs, (ii) reported colorectal cancer risk in patients with diabetes mellitus, and (iii) reported relative risk or 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 ADMs. The flow diagram summarizing study identification and selection is shown in Fig. 1.

Figure 1. Flowsheet summarizing study identification and selection. CRC, colorectal cancer.
The methodologic quality of observational studies was assessed by two authors independently (S. Singh and H. Singh) 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, in which separate points were awarded for controlling age and/or sex (maximum two points). The methodologic quality of RCTs was assessed using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials (26). This tool focuses on the adequacy of randomization and allocation concealment procedures, blinding, and loss to follow-up. Any discrepancies were addressed by a joint reevaluation of the original article.

Data abstraction

Data were independently abstracted onto a standardized form by two reviewers (S. Singh and P. Singh). 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 vs. not exposed), OR, and 95% confidence intervals (CI) with and without adjustment for confounding factors. When data on males and females were reported separately, we pooled these to derive a summary estimate for the study. For all analysis, referent group was composed of patients with diabetes mellitus not exposed to medication of interest. Data on the following risk factors for colorectal cancer were extracted from each study, where available: age, sex, ethnicity, body mass index (BMI), family history of colorectal cancer, smoking, alcohol, physical activity, dietary factors (red meat, fat intake, fruits, and vegetables), diabetes mellitus severity and duration, use of aspirin and/or nonsteroidal 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 colorectal cancer in patients with diabetes mellitus based on the type of ADM used. A priori hypotheses to explain potential heterogeneity in the direction and magnitude of effect among different observational studies included location of study (Western population vs. Asian population), study design (case–control vs. cohort), and whether the study adjusted for the concomitant use of other ADMs besides the index medication. Because of 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). Because outcomes were relatively rare, ORs were considered approximations of relative risk. Adjusted ORs reported in studies were used for analysis to account for confounding variables. We assessed heterogeneity between study-specific estimates using two methods (28, 29). First, the Cochran 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 carried out. Because this test is underpowered to detect moderate degrees of heterogeneity, a P value of less than 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, I² statistic was calculated. In this, a value of less than 30%, 30%–60%, 61%–75%, and more than 75% was 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 subgroups was performed (30); if the P value for difference between subgroups was less than 0.10, it was considered statistically significant (i.e., P < 0.10 suggested that stratifying on the basis of that particular study characteristic partly explained the heterogeneity observed in the analysis). We assessed for publication bias quantitatively using the Egger regression test (publication bias present if P < 0.10; ref. 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), a P value of less than 0.05 was considered statistically significant. All calculations and graphs were performed using Comprehensive Meta-Analysis (CMA) version 2 (Biostat; ref. 33).

Results

From a total of 3,118 unique studies identified using the search strategy, 15 studies fulfilled the inclusion criteria and were included in meta-analysis (5 case–control, 8 cohort, and 2 RCTs; refs. 13, 14, 16–19, 34–42). These studies cumulatively reported 13,871 colorectal cancer cases in 840,787 patients with diabetes mellitus. There were four Taiwanese studies from the same cohort (15, 34, 43, 44), and hence, only one report was included in the main analysis (34). There were three studies that compared the association between insulin glargine (as compared with nonlarginine 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 the
Table 1. Characteristics of included studies assessing the risk of colorectal cancer in patients with diabetes mellitus treated with ADMs

<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><strong>Observational studies: cohort studies</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Campbell and colleagues (18) 2010</td>
<td>Cohort</td>
<td>USA; population-based</td>
<td>1992-2007; NR</td>
<td>Self-report</td>
<td>Self-reported with independent validation</td>
<td>15,4975 (11,335)</td>
<td>2,909 (335)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1-11, 14, 17, 18</td>
</tr>
<tr>
<td>Currie and colleagues (13) 2009</td>
<td>Cohort</td>
<td>UK; population-based</td>
<td>NR; 2.4</td>
<td>Pharmacy prescription database</td>
<td>Read diagnostic codes</td>
<td>59,609</td>
<td>292</td>
<td>72.1</td>
<td>—</td>
<td>33.9</td>
<td>16.0</td>
<td>1, 2, 6, 10, 15</td>
</tr>
<tr>
<td>Ferrara and colleagues (19) 2011</td>
<td>Cohort</td>
<td>USA; population-based</td>
<td>1997-2005; 2.5-3.7</td>
<td>Pharmacy prescription database</td>
<td>Cancer Registry</td>
<td>252,467</td>
<td>1,650</td>
<td>43.5</td>
<td>12.6</td>
<td>52.8</td>
<td>20.4</td>
<td>1, 2, 4, 10, 15</td>
</tr>
<tr>
<td>Govindarajan and colleagues (3) 2007</td>
<td>Cohort</td>
<td>USA; population-based</td>
<td>1997-2004; NR</td>
<td>Medical record review</td>
<td>ICD-9 diagnostic codes</td>
<td>87,678</td>
<td>1,137</td>
<td>—</td>
<td>12.9</td>
<td>—</td>
<td>—</td>
<td>1-4, 10, 15</td>
</tr>
<tr>
<td>Libby and colleagues (14) 2009</td>
<td>Cohort</td>
<td>USA; population-based</td>
<td>1997-2004; NR</td>
<td>Medical record review</td>
<td>ICD-9 diagnostic codes, with record linkage</td>
<td>81,207</td>
<td>1,650</td>
<td>43.5</td>
<td>12.6</td>
<td>52.8</td>
<td>20.4</td>
<td>1, 2, 4, 10, 15</td>
</tr>
<tr>
<td>Morden and colleagues (9) 2011</td>
<td>Cohort</td>
<td>USA; population-based</td>
<td>2003-2008; ~2</td>
<td>Pharmacy prescription database</td>
<td>ICD-9 diagnostic codes</td>
<td>81,207</td>
<td>1,650</td>
<td>43.5</td>
<td>12.6</td>
<td>52.8</td>
<td>20.4</td>
<td>1, 2, 4, 10, 15</td>
</tr>
<tr>
<td>Oliveria and colleagues (6) 2007</td>
<td>Cohort</td>
<td>USA; population-based</td>
<td>2000-2004; 3.9</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>Rimer and colleagues (6) 2012</td>
<td>Cohort</td>
<td>Netherlands; population-based</td>
<td>1998-2008; 2.8-4.6</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>
<tr>
<td><strong>Observational studies: case-control studies</strong></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodmer and colleagues (17) 2012</td>
<td>C-C</td>
<td>UK; population-based</td>
<td>1995-2009; NR</td>
<td>Pharmacy prescription database</td>
<td>Read diagnostic codes</td>
<td>6,439</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 and colleagues (34) 2012</td>
<td>C-C</td>
<td>Taiwan; population-based</td>
<td>2000-2008; 7.9</td>
<td>Pharmacy prescription database</td>
<td>ICD-9 diagnostic codes with record linkage with the National Cancer Register</td>
<td>35,912</td>
<td>7,200</td>
<td>79.7</td>
<td>17.8</td>
<td>90.5</td>
<td>31.8</td>
<td>1-3, 6, 10-12, 14-16</td>
</tr>
<tr>
<td>Koro and colleagues (8) 2007</td>
<td>C-C</td>
<td>USA; population-based</td>
<td>1997-2004; 1.5</td>
<td>Pharmacy prescription database</td>
<td>ICD-9 diagnostic codes</td>
<td>2,435</td>
<td>408</td>
<td>—</td>
<td>20.2</td>
<td>5</td>
<td>6.2</td>
<td>1, 2, 15</td>
</tr>
<tr>
<td>Vinikoor and colleagues (42) 2009</td>
<td>C-C</td>
<td>USA; population-based</td>
<td>2001-2006</td>
<td>Self-report</td>
<td>Histologically confirmed CRC</td>
<td>1,935 (341)</td>
<td>1,007 (183)</td>
<td>—</td>
<td>—</td>
<td>29.3</td>
<td>—</td>
<td>1, 2, 5, 6, 11, 13, 17</td>
</tr>
<tr>
<td>Yang and colleagues (16) 2004</td>
<td>C-C</td>
<td>UK; population-based</td>
<td>1987-2004</td>
<td>Pharmacy prescription database</td>
<td>Read diagnostic codes, with independent validation</td>
<td>1,320</td>
<td>125</td>
<td>16.8</td>
<td>—</td>
<td>41.4</td>
<td>9.8</td>
<td>1-3, 6, 10-11, 15</td>
</tr>
<tr>
<td><strong>Randomized controlled trials</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>ADOPT (36) 2006</td>
<td>RCT</td>
<td>USA, Europe; hospital-based</td>
<td>2000-2006; 4.0</td>
<td>RCT</td>
<td>Adverse event review</td>
<td>4,351</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; 6.2</td>
<td>RCT</td>
<td>Adverse event review</td>
<td>12,537</td>
<td>146</td>
<td>27.4</td>
<td>—</td>
<td>50.0</td>
<td>—</td>
<td>1-3, 6, 10-12, 15, 16</td>
</tr>
</tbody>
</table>

Abbreviations: C-C, case-control; CRC, colorectal cancer; DM, diabetes mellitus; NR, not reported; SU, sulfonylureas.

*Where required, the number in brackets represents the number of patients with colorectal cancer with preceding diagnosis of diabetes mellitus; variables adjusted for: 1, age; 2, sex; 3, BMI; 4, ethnicity; 5, family H/O colorectal cancer; 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 ADMS; 16, other comorbidities (coronary artery disease, chronic kidney disease, etc.); 17, socioeconomic status; 18, GI procedures (lower gastrointestinal endoscopy, colonoscopy).
United States, 5 based in Europe, and 1 multicenter RCT; refs. 13, 14, 16–19, 35, 36, 38–42), one study was performed in an Asian population (Taiwan; ref. 34), and one study was a multicenter RCT across the United States, 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 ADMs for management of diabetes mellitus, and the comparator group for estimation of OR was based on exposure to medication of interest and nonexposure to the same medication. Three studies included only patients on monotherapy for diabetes mellitus, 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 ADMs (14, 17, 19, 34, 35, 37).

Quality of included studies
The overall methodologic quality of this body of evidence was moderate to high. Supplementary Tables 1 and 2 show 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 nonresponse rate in case–control studies were inconsistently reported. Most studies adjusted for the following confounders: age (15 of 15), sex (15/15), BMI (seven of 15), diabetes mellitus duration and/or severity (10 of 15), smoking (seven of 15), family history of colorectal cancer (two of 15), use of aspirin and/or nonsteroidal anti-inflammatory drugs (seven of 15), or use of statins and/or hormone replacement therapy (three of 15). Colonoscopy rates were reported and adjusted for in only one study (Table 1) (18). The quality of the randomized trials was moderate.

Table 2. Subgroup analysis of studies comparing the association between metformin and colorectal cancer risk

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>Metformin</th>
<th>P value for the difference between subgroups</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 ADMs</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>

NOTE: For each ADM, subgroup analyses were performed by grouping studies on the basis of study design, geographic location of study sample, and whether the studies adjusted for concomitant use of other ADMs. PInteraction refers to P value for a test of interaction to assess for (statistically significant) differences in summary estimates based on subgroups; a value of <0.10 was considered statistically significant.
diabetes mellitus (unadjusted OR, 0.97; 95% CI, 0.92–1.03; adjusted OR, 0.96; 95% CI, 0.87–1.05; Supplementary Fig. S2). The results were consistent across all studies with low heterogeneity (Cochran Q test $P = 0.75$; $I^2 = 0\%$). No significant difference was noted in subgroup analysis based on study design, location, or adjustment for concomitant use of other ADMs (Table 3).

**Table 3.** Subgroup analysis of studies comparing the association between TZD and colorectal cancer risk

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>$N$</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$ value for difference between subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case–control</td>
<td>2</td>
<td>0.98</td>
<td>0.84–1.14</td>
<td>0.74</td>
</tr>
<tr>
<td>Cohort</td>
<td>3</td>
<td>0.95</td>
<td>0.83–1.07</td>
<td></td>
</tr>
<tr>
<td>Study location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td>4</td>
<td>0.97</td>
<td>0.86–1.08</td>
<td>0.81</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>0.94</td>
<td>0.78–1.14</td>
<td></td>
</tr>
<tr>
<td>Adjusted for other ADMs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
<td>0.92</td>
<td>0.82–1.04</td>
<td>0.28</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>1.04</td>
<td>0.88–1.23</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** For each ADM, subgroup analyses were performed by grouping studies on the basis of the study design, geographic location of the study sample, and whether the studies adjusted for concomitant use of other ADMs. $P_{\text{interaction}}$ refers to a $P$ value for a test of interaction to assess for (statistically significant) differences in summary estimates based on subgroups; a value of $<0.10$ was considered statistically significant.

**Sulfonylureas and risk of colorectal cancer**

Of eight studies (seven observational and one RCT) that reported on the association between sulfonylurea use and colorectal cancer risk, three studies found an increased risk of colorectal cancer with sulfonylurea use (as compared with nonuse; refs. 13, 34, 41) and five showed no significant association (16, 17, 19, 36, 40). Meta-analysis of seven observational studies demonstrated that there was a statistically insignificant increased colorectal cancer 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 Fig. S3). 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 that adjusted for concomitant effects of other ADMs, there was 13% increased risk of colorectal cancer ($n = 7$ studies; adjusted OR, 1.13; 95% CI, 1.00–1.29). There was considerable heterogeneity across studies (Cochran Q test $P < 0.01$; $I^2 = 79\%$), which could be explained on the basis of study location (Western vs. Asian) and concomitant effect of other ADMs (Table 4). Unlike metformin, the association between sulfonylurea use and colorectal cancer risk was

**Table 4.** Subgroup analysis of studies comparing the association between sulfonylureas and colorectal cancer risk

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>$N$</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$ value for the difference between subgroups</th>
</tr>
</thead>
<tbody>
<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>
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<td>1.39</td>
<td>1.22–1.58</td>
<td></td>
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<tr>
<td>Adjusted for other ADMs</td>
<td></td>
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<td>1.00–1.29</td>
<td>0.09</td>
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<td>1</td>
<td>0.80</td>
<td>0.55–1.17</td>
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</table>

**NOTE:** For each ADM, subgroup analyses were performed by grouping studies on the basis of the study design, geographic location of the study sample, and whether the studies adjusted for concomitant use of other ADMs. $P_{\text{interaction}}$ refers to a $P$ value for a test of interaction to assess for (statistically significant) differences in summary estimates based on subgroups; a value of $<0.10$ was considered statistically significant.
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 colorectal cancer; 1,441 patients on glibenclamide) on oral antidiabetic monotherapy revealed no significant chemopreventive or oncogenic effect of sulfonylureas (n = 1 study; adjusted OR, 1.84; 95% CI, 0.78–4.35; ref. 36).

**Insulin and risk of colorectal cancer**

Ten studies (nine observational and one RCT) reported on the association between insulin use (long and/or short-acting) and colorectal cancer risk in patients with diabetes mellitus. Three studies demonstrated an increased risk of colorectal cancer (13, 16, 34), whereas seven studies reported null association (17–19, 37, 38, 40, 42). On meta-analysis of nine observational studies, there was a trend toward increased colorectal cancer risk associated with insulin use (as compared with nonuse), both on unadjusted (unadjusted OR, 1.28; 95% CI, 0.88–1.86) and adjusted analysis (adjusted OR, 1.33; 95% CI, 1.91–1.94), although this was not statistically significant (Supplementary Fig. S4). The results were considerably heterogeneous (Cochran Q test P < 0.01; I² = 96%), which was explained by location where the study was performed (Table 5). On exclusion of the one outlier Asian study (34), the heterogeneity decreased (Cochran Q test P = 0.02; I² = 57%). Post-hoc analysis of the ORIGIN trial (76 cases of colorectal cancer; 6,264 patients on insulin glargine) did not show a significant difference in colorectal cancer risk with insulin glargine use (as compared with "standard of care"; n = 1 study; adjusted OR, 1.09; 95% CI, 0.79–1.51; ref. 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 irrespective of whether analysis was adjusted for concomitant use of other ADMs.

**Stratified analysis**

On the basis of data from four studies, duration–response relation between insulin use and colorectal cancer risk was not observed [short duration insulin use (0–2 years): adjusted OR, 1.27; 95% CI, 0.98–1.63; long duration insulin use (2–5 years): adjusted OR, 1.37; 95% CI, 0.93–2.01; refs. 16–18, 42]. On subgroup analysis, there was no appreciable difference in the effects of insulin on colorectal cancer risk, based on sex [n = 2 studies; males vs. females; adjusted OR (95% CI): 0.93 (0.62–1.41) vs. 0.97 (0.70–1.34); refs. 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; refs. 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 ADMs (metformin, TZD, or sulfonylureas) and risk of colorectal cancer.

**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 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 and colleagues for metformin and sulfonylureas, Chang and colleagues for TZD and insulin; refs. 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

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**Table 5. Subgroup analysis of studies comparing the association between insulin and colorectal cancer risk**

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>N</th>
<th>OR</th>
<th>95% CI</th>
<th>P value for the difference between subgroups</th>
</tr>
</thead>
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<td></td>
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<td>0.87–2.53</td>
<td>0.39</td>
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<td>Cohort</td>
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<td>1.15</td>
<td>0.94–1.40</td>
<td></td>
</tr>
<tr>
<td>Study location</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Western</td>
<td>8</td>
<td>1.18</td>
<td>0.99–1.40</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
<td>2.56</td>
<td>2.40–2.72</td>
<td></td>
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<tr>
<td>Adjusted for other ADMs</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>1.34</td>
<td>0.80–2.25</td>
<td>0.88</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>1.28</td>
<td>0.92–1.78</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: For each ADM, subgroup analyses were performed by grouping studies on the basis of the study design, geographic location of the study sample, and whether the studies adjusted for concomitant use of other ADMs. Pinteraction refers to a P value for a test of interaction to assess for (statistically significant) differences in summary estimates based on subgroups; a value of <0.10 was considered statistically significant.

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significant change in overall association of colorectal cancer 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). Because of significant heterogeneity between studies, a single summary estimate for number needed to treat with metformin to prevent one case of colorectal cancer (or number needed to treat with sulfonylureas or insulin to cause one case of colorectal cancer) could not be 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 ADMs and colorectal cancer risk in more than 840,000 patients with primarily type II diabetes mellitus, 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 with nonuse 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 ADMs, 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. On the basis of the data from our study, we speculate that the variable effects of different ADMs 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 antineoplastic 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 that 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 chemo-preventive effect of metformin has been demonstrated in nondiabetic animal models of colorectal cancer. In the adenomatous polyposis coli (APC<sup>Min/+</sup>) 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 colorectal cancer, 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 nondiabetic 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 populations in our analysis should be interpreted with caution as 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 antineoplastic activity in mice receiving a high-energy diet associated with hyperinsulinemia as compared with mice receiving a control diet (59). The oncogenic association between insulin use and colorectal cancer 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 ADMs on risk modification of colorectal cancer; 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 subgroup analysis to ensure stability of the association and identify factors responsible for heterogeneity. Although Zhang and colleagues recently performed a meta-analysis of metformin and colorectal cancer risk (21), they did not account for the potential cancer-modifying effects of other ADMs. In their analysis of four studies, they observed a 37% lower colorectal cancer risk with metformin use; furthermore, subgroup analyses were not reported. In our study, the inclusion of more studies and simultaneous assessment of cancer-modifying effect of other ADMs resulted in a lower risk estimate associated with metformin than has been reported in other meta-analyses (20–22). Soranna and colleagues 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 colorectal cancer risk separately (22).

Limitations

There were several limitations to our meta-analysis that merit consideration. First, the cancer-modifying association between ADM and colorectal cancer risk were based on data from observational studies, which accounted for nearly all of the included colorectal cancer cases (n = 13,704 cases; 98.9%); no statistically significant association...

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was apparent based on the RCT cases (167 cases; 1.1%). These RCTs were not adequately powered to detect a significant difference between classes of ADMs with respect to colorectal cancer risk reduction and subjects included in these studies were not systematically screened for colorectal cancer, which might conceivably have introduced some degree of detection bias. Observational studies of ADMs 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 overestimate 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 (62, 63). Moreover, the included studies could not account for “healthy user effect”, wherein the diagnosis of diabetes mellitus 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 ADMs, which may have inherent cancer-modifying effects. We tried to account for this by performing a subgroup analysis restricted to those studies that reported OR after adjusting for the effect of other ADMs and observed stable results. Finally, the individual studies were limited in reporting an association between classes of ADMs and site-specific colorectal cancer risk modification. Hence, we could not establish whether different ADMs are differentially associated with risk of proximal or distal colorectal cancer.

Conclusion
On the basis of the results of this meta-analysis, it seems that metformin use may be associated with a lower risk of colorectal cancer in diabetic patients, whereas sulfonylureas and insulin do not significantly increase colorectal cancer risk. These data support the hypothesis that in diabetic patients at high risk for colorectal cancer (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 suggest that the treatment of diabetes mellitus with metformin, in combination with other ADMs, is not associated with an increased risk for colorectal cancer, however, this observation needs further investigation. Because the observed magnitude of colorectal cancer risk reduction associated with metformin was relatively modest, the number needed to treat to prevent one case of colorectal cancer would be large. A definitive and randomized chemoprevention trial is needed to rigorously assess the effects of metformin on incident colorectal cancer in diabetic patients, but would be lengthy, logistically challenging, and resource intensive. To facilitate further clarification of metformin’s colorectal cancer chemopreventive potential, clinical evaluation in an enriched patient population (i.e., history of sporadic colorectal neoplasia) is ongoing (64).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: S. Singh, M.H. Murad, P.J. Limburg
Development of methodology: S. Singh, H. Singh, M.H. Murad
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Singh, H. Singh, P.P. Singh, M.H. Murad
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Singh, P.P. Singh
Writing, review, and/or revision of the manuscript: S. Singh, H. Singh, P.P. Singh, M.H. Murad
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H. Singh
Study supervision: M.H. Murad, P.J. Limburg

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References
Risk of Colorectal Cancer with Antidiabetic Medications


Antidiabetic Medications and the Risk of Colorectal Cancer in Patients with Diabetes Mellitus: A Systematic Review and Meta-analysis


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