Reduced Risk of Colorectal Cancer With Metformin Therapy in Patients With Type 2 Diabetes

A meta-analysis

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OBJECTIVE—Both in vitro and in vivo studies indicate that metformin inhibits cancer cell growth and reduces cancer risk. Recent epidemiological studies suggest that metformin therapy may reduce the risks of cancer and overall cancer mortality among patients with type 2 diabetes. However, data on its effect on colorectal cancer are limited and inconsistent. We therefore pooled data currently available to examine the association between metformin therapy and colorectal cancer among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS—The PubMed and SciVerse Scopus databases were searched to identify studies that examined the effect of metformin therapy on colorectal cancer among patients with type 2 diabetes. Summary effect estimates were derived using a random-effects meta-analysis model.

RESULTS—The analysis included five studies comprising 108,161 patients with type 2 diabetes. Metformin treatment was associated with a significantly lower risk of colorectal neoplasm (relative risk [RR] 0.63 [95% CI 0.50–0.79]; $P < 0.001$). After exclusion of one study that investigated colorectal adenoma, the remaining four studies comprised 107,961 diabetic patients and 589 incident colorectal cancer cases during follow-up. Metformin treatment was associated with a significantly lower risk of colorectal cancer (0.63 [0.47–0.84]; $P = 0.002$). There was no evidence for the presence of significant heterogeneity between the five studies ($Q = 4.86, P = 0.30$; $I^2 = 18\%$).

CONCLUSIONS—From observational studies, metformin therapy appears to be associated with a significantly lower risk of colorectal cancer in patients with type 2 diabetes. Further investigation is warranted.

Colorectal cancer is one of the most frequent malignant tumors and a leading cause of cancer-related death worldwide (1). The incidence of colorectal cancer continues to increase in economically transitioning countries such as Asia, Eastern Europe, and selected countries in South America (2,3), whereas a declining trend has been noted in several developed countries in recent years (1).

Type 2 diabetes is also a common disease, and it is well established that type 2 diabetes is associated with a higher risk of colorectal cancer (4–8). Metformin is a relative of isoamylene guanidine and has been recommended as the initial glucose-lowering therapy for diabetes. Emerging evidence from both in vitro and in vivo studies indicates that metformin may inhibit cancer cell growth and reduce cancer risks. Previous research suggests that metformin may be involved in the tumor suppressor pathway by indirectly activating AMP-activated protein kinase (9)—a key sensor of cellular ATP and AMP balance—and plays a role on activating tumor suppressor genes, e.g., *LKB1*. Subsequent in vitro studies have shown that metformin inhibits cancer cell proliferation (10,11) and selectively kills cancer stem cells (12). Animal experiments concur with these findings. Rodent models have shown that metformin suppresses colonic epithelial proliferation and colorectal aberrant crypt foci formation (13,14). Similarly, animal models of colon cancer have shown that metformin inhibits colon carcinoma growth (11,15). Given these encouraging findings, interest has arisen that metformin could potentially serve as a new antineoplasm drug to prevent colorectal cancer.

Results from preliminary studies conducted in humans are encouraging. In a short-term randomized clinical trial among nondiabetic patients with rectal aberrant crypt foci, a significant decrease in the mean number of aberrant crypt foci was observed after metformin treatment for 1 month as compared with no significant changes in the control group (16). Findings from several epidemiological studies also support an antineoplastic role of metformin on cancer risks (17,18). If metformin therapy ultimately proves effective on reducing the risk of colorectal cancer, it would likely be recommended for the overwhelming majority of diabetes patients for both blood glucose control and cancer prevention. Nonetheless, despite accumulating evidence from population studies that indicate a lower risk of cancer at large with metformin therapy (17,19,20), data on its effect on colorectal cancer are limited and inconsistent.

Accordingly, we performed a meta-analysis to pool studies currently available to examine the effect of metformin treatment on colorectal cancer risk among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study selection

A comprehensive literature search was performed using the PubMed (January 1966–March 2011) and SciVerse Scopus databases. Keywords for searching included metformin, biguanides, cancer, neoplasms, colorectal cancer, colon cancer, rectal cancer, and bowel cancer. We selected studies that investigated the effect of metformin on colorectal cancer or bowel cancer (ICD-9 153–154, ICD-10 C18–C20) in patients with type 2 diabetes. The search was restricted to studies conducted in humans. Because colorectal cancer develops from precursor lesions (21), we also included studies that investigated the association between metformin therapy and colorectal adenoma. We required either information on sample size, effect estimate, and corresponding 95% CI or published results in which these parameters could be derived. References from recent review articles were also checked for relevant articles. The most complete or more recent publications were given precedence if there were multiple publications from the same study.

Data extraction and statistical analyses

Two members independently reviewed titles and abstracts of all identified citations. The full text of any article that was deemed potentially eligible was evaluated for the decision on inclusion or exclusion. Figure 1 depicts the process of study selection. The results of the data extraction were summarized in a structured table to explore the variation in study design, region of study, source population, number of participants, length of follow-up (if applicable), and control for confounding. The relative risk (RR) was used as the common measure of association across studies. Odds ratios were assumed to be a reasonable estimate for relative risks for the present study. Forest plots were used to compare results across studies. For those studies consisting of multiple pairwise comparisons, we pooled the effect estimates with an inverse variance weight and used the combined estimate for that study. The resulting variance of
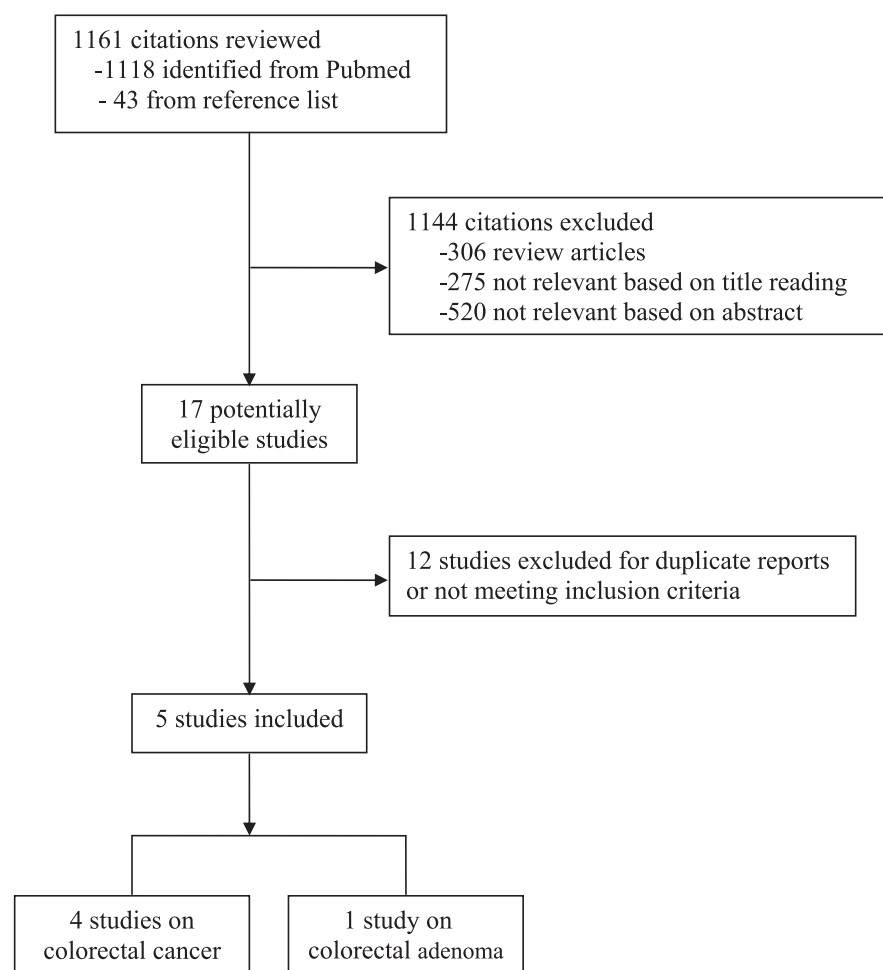

Figure 1—*Flowchart of study selection process.*

the pooled estimate does not allow for the correlation between the multiple effect estimates in the same study and can be either too large or too small, depending on the correlation. Thus, to examine the influence of the correlation, we performed sensitivity analyses by including one pairwise comparison at a time when recalculating the summary RRs. The pooled RR was derived by averaging per-study natural logarithmic RRs weighted by the inverses of their variances. We used the DerSimonian and Laird random-effects models to incorporate between-study variability and to report pooled effect estimates (22).

As part of sensitivity analyses, we excluded one small study (23) that investigated the association between metformin therapy and colorectal adenoma to examine its influence on the summary effect estimate. To assess for heterogeneity between studies, we calculated the Cochran Q statistic with significance level of $P < 0.10$ (24). P values were obtained

by comparing the statistic with a χ^2 distribution with $k-1$ degrees of freedom (where k is the number of studies). Because the power of the Q test is low to detect heterogeneity in circumstances of small number of studies, we also calculated the I^2 statistic, which quantifies the percentage of total variation across studies that is due to heterogeneity rather than chance (25). An I^2 value of <50% was considered low heterogeneity. Publication bias was assessed by visually examining a funnel plot and performing the Begg test (26). A two-tailed P value <0.05 was considered significant for statistical tests for metformin effects. All analyses were performed using Stata version 10.0 (StataCorp, College Station, Texas).

RESULTS—Five relevant studies were retrieved, including two case-control studies (6,23) and three retrospective cohort studies (17,18,27), comprising a total of 108,161 patients with type 2 diabetes.

Information on region, source population, and confounding adjustment is presented in Table 1. One study was based in China (27), one study in Korea (23), and three studies in the U.K. (6,17,18). Four studies investigated the association between metformin therapy and colorectal cancer (6,17,18,27), and the other one investigated the association for colorectal adenoma (23).

Compared with nonmetformin treatment, metformin was associated with a significantly lower risk of colorectal neoplasm among patients with type 2 diabetes (pooled RR 0.63 [95% CI 0.50–0.79]; $P < 0.001$). Figure 2 shows the estimated RR and 95% CI for each individual study comparing metformin with nonmetformin treatment. There was no evidence for the presence of significant heterogeneity between the five studies ($Q = 4.86$, $P = 0.30$; $I^2 = 18\%$). There was also no evidence of publication bias from the funnel plot examination or the Begg test (data not shown).

After exclusion of one small case-control study that investigated colorectal adenoma (23), the database consisted of three retrospective cohort studies (17,18,27) and one nested case-control study (6). Among a total of 107,961 patients with type 2 diabetes, 589 colorectal cancer events were documented over follow-up. Metformin therapy was associated with a lower risk of colorectal cancer (RR 0.63 [95% CI 0.47–0.84]; $P = 0.002$). Thus, exclusion of the small case-control study had no appreciable effects on the overall results. Figure 3 shows the estimated RR and 95% CI for each individual study comparing metformin with nonmetformin treatment. Again, there was no evidence for the presence of significant heterogeneity between the four studies ($Q = 4.75$, $P = 0.19$; $I^2 = 37\%$). Although the results showed a reduction of similar magnitude in the risk of colorectal cancer with metformin treatment when compared with two other treatment groups (18), we performed sensitivity analysis by including one of the two effect estimates at a time. The results did not change materially after excluding either comparison (data not shown).

CONCLUSIONS—In this study, we pooled all studies currently available and evaluated the association between metformin and colorectal cancer risk among patients with type 2 diabetes. The results indicate that metformin therapy was associated with an estimated reduction of

Table 1—Designs of studies included in the present meta-analysis

1st author, year	Study type	Region	Source population	Total participants (events)	Follow-up (years)	Confounding adjustment
Yang, 2004 (6)	Nested case-control study	U.K.	A cohort of patients with type 2 diabetes in the General Practice Research Database from 1987 to 2002	24,918 (125)	5.6*	Sex, history of cholecystectomy, smoking, duration of type 2 diabetes, BMI, 3 or more years of sulfonylurea use prior to index date, 1 or more years of recent NSAID/aspirin use
Chung, 2008 (23)	Case-control study	Korea	A cohort of patients with colorectal adenoma from 2003 to 2006	200 (100)	—	Matching on age (± 1 year) and sex, adjusting with age, sex, BMI, diabetes duration, HbA$_{1c}$, lipids, insulin, aspirin
Libby, 2009 (17)	Retrospective cohort study	Scotland, U.K.	A cohort of patients with type 2 diabetes in Tayside, Scotland, U.K. from 1994 to 2003	8,000 (116)	Open cohort, Jan 1994–Dec 2003	Sex, age, BMI, HbA$_{1c}$, deprivation, smoking, other drug use
Currie, 2009 (18)	Retrospective cohort study	U.K.	A cohort of diabetes patients (diagnosed >40 years of age) in The Health Information Network, after 2002	59,609 (292)	2.4	Age, sex, smoking status, and a diagnosis of a prior cancer
Lee, 2011 (27)	Retrospective cohort study	Taiwan, China	A cohort of participants ≥20 years, diabetes-cancer-free in Jan 2000	15,434 (56)	3.5	Age, sex, other oral antihyperglycemic medication, CCI score

*Mean follow-up for the 125 cases. CCI, Charlson Comorbidity Index; NSAID, nonsteroidal anti-inflammatory drug.
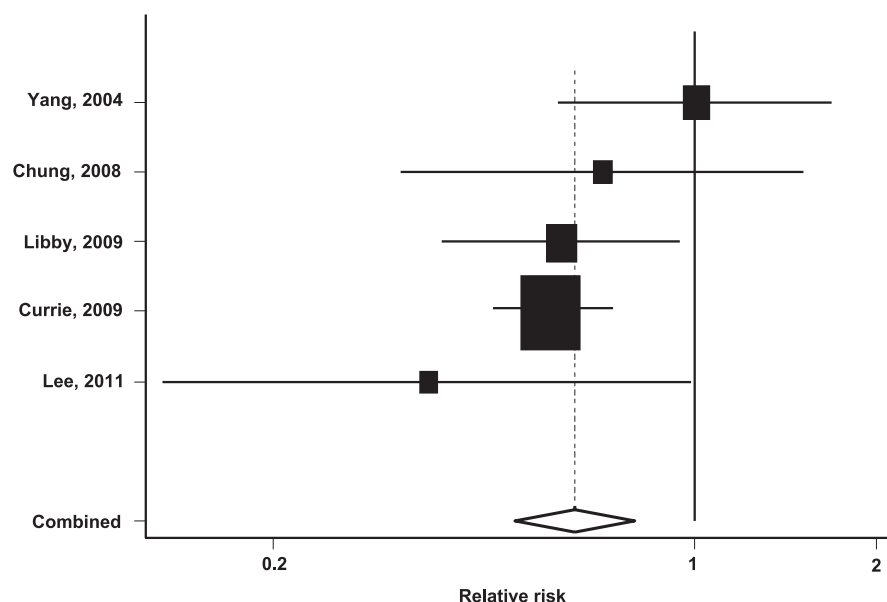
Figure 2—*Pooled estimate of relative risk and 95% CIs of colorectal neoplasm associated with metformin therapy based on five studies comprising 108,161 patients with type 2 diabetes. Squares indicate relative risk in each study. The square size is proportional to the weight of the corresponding study in the meta-analysis; the length of horizontal lines represents the 95% CI. The unshaded diamond indicates the pooled relative risk and 95% CI.*

37% in the risk of colorectal cancer among patients with type 2 diabetes. The effect estimates were homogeneous across studies of different designs, including retrospective cohort and nested case-control studies. The multiple sensitivity analyses showed that the results were robust.

Other lines of evidence support the antineoplastic role of metformin on colorectal cancer. In vitro studies have shown that metformin inhibits the proliferation of colorectal cancer cells (28). In vivo studies have demonstrated that metformin delays tumor onset in mouse models for *p53* mutant colon cancer (11). Another animal model of colon cancer has shown that metformin inhibits colon carcinoma growth stimulated by a high-energy diet (15). Two animal models of colorectal aberrant crypt foci showed that metformin significantly suppresses colonic epithelial proliferation by inhibiting the mammalian target of rapamycin pathway (13,14). A randomized clinical trial among nondiabetic patients with a follow-up of 1 month demonstrated that the number of aberrant crypt foci decreased significantly in the metformin group (8.78 before treatment vs. 5.11 at 1 month follow-up, $P = 0.01$) but not in the nonmetformin group (7.23 before treatment vs. 7.56 at 1 month follow-up, $P = 0.61$) (16). These findings are encouraging as metformin, in addition to its apparent anticancer properties, has the advantage of high tolerance, affordability, and good compatibility with other hypoglycemic agents.

The mechanisms underlying this antineoplastic potential of metformin for colorectal cancer are manifold and not yet completely understood. A previous study showed that metformin indirectly activates AMP-activated protein kinase (9), which induces glucose uptake in muscles (29). Because AMP-activated protein kinase is also activated by the product of the Peutz-Jegher tumor suppressor gene *LKB1* (30), it may play a role in suppressing colorectal cancer development (31,32). This relationship between metformin and *LKB1* represents one of the more plausible mechanisms for a potential protective role of metformin against colorectal cancer. Another possible mechanism is amelioration of endogenous hyperinsulinemia by use of metformin therapy (33,34). Insulin stimulates cellular proliferation, and multiple signaling pathways are activated after insulin receptors or insulin-like growth factor receptors interact with their ligands (35,36). Metformin therapy decreases levels of insulin-like growth factors and insulin in circulation which, in turn, may reduce the risk of colorectal cancer. Other possible mechanisms underlying this potential antitumor effect could be antagonizing obesity (37), anti-inflammatory effects (38), *p-53* activation (11), downregulation of cyclin D1 (39), and killing of cancer stem cells (12). Further studies investigating potential underlying mechanisms are needed.

Our meta-analysis pooled all published data currently available and provided strong evidence of antineoplastic effect on colorectal cancer with metformin treatment. However, caution is needed when interpreting these results.
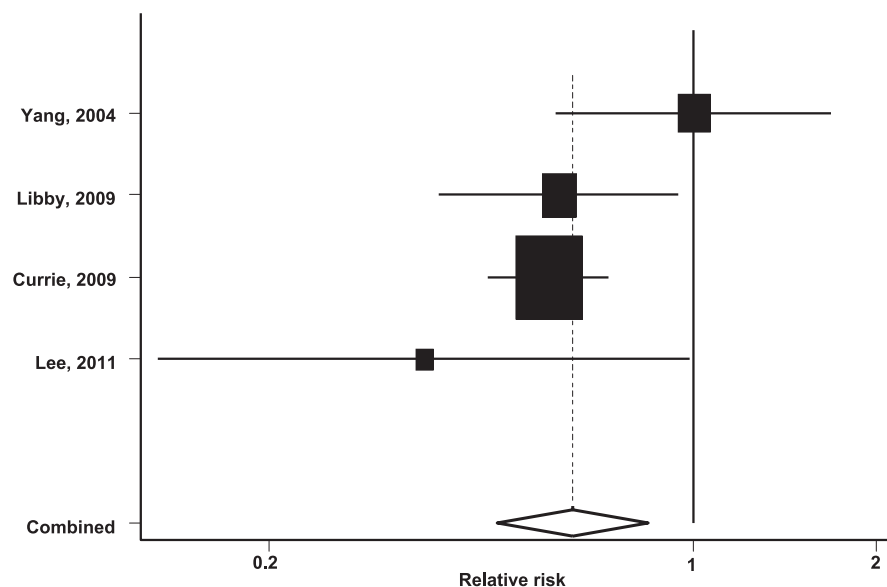

Figure 3—*Pooled estimate of relative risk and 95% CIs of colorectal cancer associated with metformin therapy based on four studies comprising 107,961 diabetic patients and 589 incident colorectal cancer cases. Squares indicate relative risk in each study. The square size is proportional to the weight of the corresponding study in the meta-analysis; the length of horizontal lines represents the 95% CI. The unshaded diamond indicates the pooled relative risk and 95% CI.*

Information on metformin use was collected retrospectively in all of the included observational (uncontrolled) studies. Most of the included studies were based on historical medical data or insurance data that were not specifically designed to assess the effect of metformin therapy on colorectal cancer. Details on dose, duration, variation over time for metformin treatment, and other adjunctive therapy were incomplete. The possibility of immortal bias was not completely ruled out in some included studies. Most of the included studies did not collect or analyze data on pathological type or site of colorectal cancer. In the present study, metformin therapy was compared with other hypoglycemic therapies, including insulin, sulfonylureas, thiazolidinediones, or other oral medicines. It should be noted that insulin and insulin analogs have been reported to be associated with a higher risk of colorectal cancer (6,7). The observed apparent beneficial effect of metformin could thus be an overestimate partly due to the potential hazardous effect associated with other hypoglycemic agents in the reference group. On the other hand, metformin receivers were reported to be more likely to receive lower endoscopy (40), which could lead to early detection of colorectal cancer in metformin receivers and bias the effect estimate toward the null (i.e., no anticancer effect). Finally, the possibility of publication bias cannot be ruled out although we found no evidence of this through the funnel plot examination and the Begg test.

In conclusion, our meta-analysis suggests that metformin treatment appears to be associated with a significantly lower risk of colorectal cancer in patients with type 2 diabetes. Further investigation is warranted.

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