

Original Article

Metformin may lower the risk of colorectal adenoma in diabetic patients: a meta-analysis

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Abstract: Previous studies have reported discordant results regarding the relationship between metformin use and the development of colorectal adenoma. Therefore, a meta-analysis of retrospective studies was performed to examine whether metformin use lowers the risk of colorectal adenoma in diabetic patients. Literature searches of the Pubmed, Embase, and Cochrane Library databases were made for all entries up to 16 June 2015. Observational studies and clinical trials were included if they met the following inclusion criteria: all of the enrolled patients had undergone a colonoscopy; exposure to metformin was evaluated; odds ratio (OR), relative risk (RR), and/or data for estimations were provided. A total of 1068 citations were screened and three retrospective cohort studies and two case-control studies met the eligibility criteria. Heterogeneity across the studies was not significant (inconsistency index (I^2) = 39%, P = 0.16), thereby allowing the results from these five studies to be analyzed using a fixed effects model. Consequently, 1172 cases of colorectal adenoma in 4538 patients were examined. Metformin use was associated with a lower risk of colorectal adenoma (pooled OR = 0.77, 95% confidence interval (CI): 0.63 to 0.95), especially compared with the non-metformin group that only included diabetic patients (pooled OR = 0.70, 95% CI: 0.56 to 0.87). These findings suggest that metformin may lower the risk of colorectal adenoma in patients with diabetes mellitus.

Keywords: Metformin, diabetes mellitus, colorectal adenoma, chemoprevention, endoscopy, meta-analysis

Introduction

Currently, colorectal cancer (CRC) is the third most common cause of cancer-related deaths worldwide [1]. Colorectal adenomas (CRAs) are premalignant lesions of CRC, and it is generally accepted that the development of adenomas leads to CRC within 10-15 years based on the theory that adenomas precede the formation of carcinomas [2, 3]. CRAs have a higher detection rate than CRC, and the detection and removal of adenomas has been shown to decrease the incidence of CRC, and to prevent death due to CRC [4]. Unfortunately, access, expense, and patient discomfort limit the utilization of screening colonoscopies.

In a recent meta-analysis that included 29 articles, the relative risk of diabetes mellitus (DM) patients developing CRA was 1.26 (95% confidence interval (CI): 1.11-1.44), thus identifying DM as a high-risk factor for CRA [5]. To date,

sulfonylureas, insulin, and metformin are first-line drugs for the treatment of type 2 DM and it is hypothesized that these antidiabetic drugs may also modify the risk of CRA. For example, in a meta-analysis that included 840,787 diabetic patients, the use of sulfonylureas and insulin were associated with an increased risk for CRA [6]. In contrast, metformin has been reported to reduce the risk of developing CRA in mice [7], and in humans, metformin use has been found to inhibit colorectal carcinogenesis by suppressing the proliferation of colonic epithelial cells and the formation of rectal aberrant crypt foci [8].

Metformin is an oral antidiabetic drug that is widely used for the treatment of type 2 DM and it activates liver kinase B1-dependent AMP-activated protein kinase (AMPK) in the liver. Activated AMPK can subsequently inhibit the mammalian target of the rapamycin (mTOR) pathway to affect cell proliferation and tumor

growth [9]. The relationship between metformin and CRA has been investigated in multiples studies. However, while some studies have reported that patients exposed to metformin exhibited a lower risk of CRA [10, 11], other studies showed no significant association [12-14]. In a previous meta-analysis that included five observational studies, metformin appeared to significantly reduce the risk of colorectal neoplasms in diabetic patients [15]. However, four of the studies investigated CRC, and only one study investigated CRA. Furthermore, only 200 subjects were examined. Hence, in the present study, a meta-analysis was performed with retrospective studies in order to identify a possible association between metformin and the risk of CRA.

Materials and methods

Literature search

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement was used as a guideline for this meta-analysis [16]. All of the entries available in the Pubmed, Embase, and Cochrane Library databases up until 16 June 2015 were searched using the following terms: “colorectal”, “colonic”, “colon”, “adenoma”, “neoplasia”, “neoplasm”, “cancer”, “polyp”, “metformin”, “biguanide”, “hypoglycemic agents”, “dimethylbiguanidine”, and “dimethylguanylguanidine”. The reference lists of the full text and relevant review articles that were examined were also manually searched.

Selection and exclusion criteria

ZHJ and CY independently assessed all of the titles and abstracts of the eligible papers, and then reviewed the full text of the remaining articles. When at least one of the reviewers considered a full text to be acceptable, it was selected for further consideration. Any disagreements were resolved by discussion with HXX.

Both observational studies and clinical trials were included if they met the following inclusion criteria: (1) all of the included patients had undergone a complete colonoscopy; (2) exposure to metformin was evaluated; (3) reported relative risk (RR), odds ratio (OR), and/or estimation data were provided. Inclusion was not restricted by language, study size, or design. Conversely, editorials, case reports, reviews,

letters, and animal experimental studies, as well as studies which did not meet the inclusion criteria, were excluded. When the same population was reported more than once, only data from the most comprehensive study were included. Reported adenomas were classified as tubular, villous, or mixed tubular-villous [17]. Advanced adenomas were defined as an adenoma larger than 10 mm, an adenoma of any size with a villous or tubulovillous component, or a high-grade dysplasia.

Data extraction and quality assessment

Several variables were recorded from each included study: first author, year of publication, country, study design, sample size, mean age, gender, body mass index (BMI), duration of DM, family history of CRC, smoking status, alcohol use, insulin use, reporting of relevant outcomes, outcome measures, controlled confounders, and unadjusted and/or adjusted effects estimates. If data were not presented, the authors were contacted by email.

The methodological quality of each of the selected retrospective studies was assessed with a modified Newcastle-Ottawa scale (NOS) [18]. The NOS consists of three factors: patient selection, assessment of outcomes, and comparability of study groups. The patient selection section addresses: “representativeness of the exposed group”, “representativeness of the non-exposed group”, and the “definition of the non-exposed group”. The second section includes an “assessment of outcome” and “sufficient follow-up to evaluate outcome”. Finally, comparability of the study groups was assessed based on patient age, patient gender, BMI, DM status, family history of CRC, smoking status, alcohol use, and insulin use. One point was recorded for each category that matched between the two study groups evaluated. The patient characteristics that did not significantly differ between the two groups, or that were able to be adjusted by multivariate regression analysis, were also considered to represent a match. Each study received a score that ranged from 0-9. Retrospective studies that received scores of 6 or greater were considered high-quality studies.

Statistical analysis

Analyses were performed with STATA version 12 (StataCorp LP, TX, USA) and Review Manager

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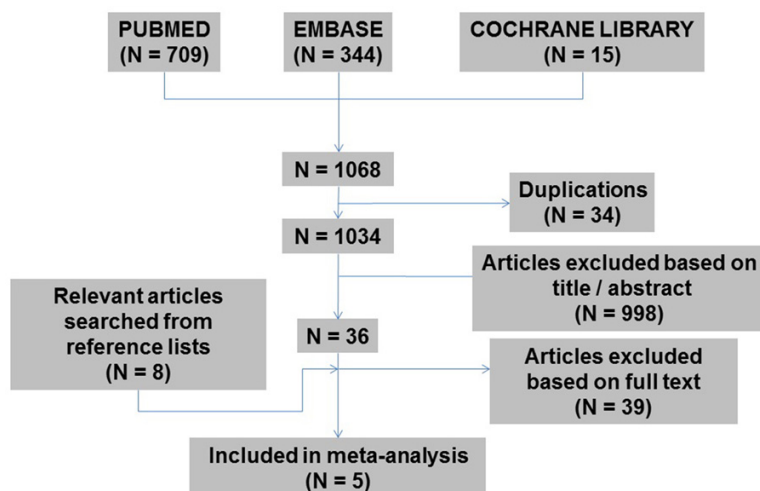


Figure 1. Selection process for the studies examined.

Version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Outcomes were assessed as ORs with 95% confidence intervals (CIs). Subgroup analyses and comparisons stratified according to study design, study location, patient characteristics, and presence of advanced adenoma were also performed. Sensitivity analyses were conducted for the high-quality studies. The Chi-square test and inconsistency index (I^2) statistics were used to measure statistical heterogeneity. A P -value < 0.1 or $I^2 > 50\%$ indicated obvious heterogeneity. If heterogeneity was observed, then a random effects model was selected; otherwise, a fixed effects model was used. A funnel plot, Begg's test, and Egger's test were used to assess potential publication bias.

Results

Search results and study characteristics

A literature search was performed (see Methods) and 1068 relevant citations were identified. After a review of the titles and abstracts for these citations, 36 articles were selected. After reviewing the full text for each article, 30 articles were excluded. The full text of eight additional articles that were identified from the reference lists of the 36 articles were also assessed, although none of them met the inclusion criteria. Of the remaining six articles, one article required clarification regarding the definition of a cancerous polyp as an adenoma. When the author was contacted to request the raw data by email, no response was received.

Therefore, the present meta-analysis included five studies composed of three retrospective cohort studies and two case-control studies [10-14]. **Figure 1** shows the selection process for the literature search that was performed.

Of the five selected studies, four were conducted in Asia [10-12, 14] and one was conducted in the United States [13]. In one study [10], diabetic patients who underwent colonoscopic surveillance after curative resection of CRC were included, while the other four studies did not include

patients who had previously been diagnosed with CRC. **Table 1** summarizes the study characteristics that were recorded.

Study quality

Table 2 outlines the quality assessment that was performed for the studies included in our meta-analysis. In four of the studies selected, only diabetic patients were included in the metformin group and in the non-metformin group, while in the fifth study [13], patients without DM were accepted in the non-metformin group. We subsequently investigated whether the conditions of the latter led to selection bias (see below). In another study [12], the definition of the non-metformin group was not clarified to indicate whether the patients had not received metformin or had used metformin for less than one year. Outcomes were measured based on colonoscopy and histologic findings. Patients in the metformin group were administered metformin for more than one month prior to their colonoscopy, and this was considered a sufficient time period to evaluate follow-up outcome [8]. However, in two studies [10, 13] the duration of metformin use prior to the colonoscopies performed was not indicated. Finally, four of the five selected studies received a score of 6 or higher on a modified NOS, and thus, were considered to be of high quality.

Outcome results

A total of 1172 cases of colorectal adenoma were examined, and this included 4538 patients. An analysis with a fixed effects model

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Table 1. Characteristics of the studies examined

First author, (year)	Country	Study design	Sample size	Metformin group	Non-Metformin group	Controlled confounders	Unadjusted and/or adjusted effects estimate
Chung, 2008	Korea	Case-control	200	Diabetic patients without CRC	Diabetic patients without CRC	Age, gender, BMI, duration of diabetes, serum levels of hemoglobin A1c and lipids, insulin therapy, metformin	0.63 (0.36-1.11); adjusted 0.7 (0.3-1.4)
Lee, 2012	Korea	Retro-spective cohort	238	Diabetic patients with previous CRC	Diabetic patients with previous CRC	Age at diagnosis, gender, stage of cancer, BMI, family history of CRC, follow-up duration, number of total colonoscopies, interval to first follow-up colonoscopy, number of baseline colorectal adenomas, treatment modality, use of aspirin, use of insulin, use of thiazolidinediones	0.49 (0.29-0.85)
Eddi, 2012	USA	Case-control	783	Diabetic patients without CRC	Diabetic and non-diabetic patients without CRC	Age, gender, levels of TGs, LDLs, and HDLs, smoking status, family history of CRC, use of aspirin, NSAIDs, and statins	1.21 (0.76-1.93)
Cho, 2014	Korea	Retro-spective cohort	3077	Diabetic patients without CRC	Diabetic patients without CRC	Age, gender, BMI, TGs, glycated hemoglobin, aspirin use, statin use, smoking status, DM duration	0.70 (0.57-0.86); adjusted 0.738 (0.554-0.983)
Kim, 2015	Korea	Retro-spective cohort	240	Diabetic patients without CRC	Diabetic patients without CRC	Age, gender, BMI, aspirin use, smoking status, alcohol use	0.77 (0.450-1.301); adjusted 0.866 (0.453-1.623)

Abbreviations: CRC, colorectal cancer; BMI, body mass index; TG, triglyceride; LDL, low density lipoprotein; HDL, high density lipoprotein; NSAID, nonsteroidal anti-inflammatory drug.

Table 2. Evaluation of the selected studies using an adjusted Newcastle-Ottawa Scale

First author, Year	Represent-ativeness of exposed group	Represent-ativeness of non-exposed group	Non-exposed group defined	Assessment of outcome	Sufficient follow-up to evaluate outcome	Matching [#]	Score
Chung, 2008	★	★		★	★	1, 2, 3, 4, 7	6
Lee, 2012	★		★	★		1, 2, 3, 4, 5, 6, 7, 8	7
Eddi, 2012	★	★	★	★		1, 2, 5	5
Cho, 2014	★	★	★	★	★	1, 2, 3, 4, 5, 6, 7, 8	9
Kim, 2015	★	★	★	★	★	1, 2, 3, 4, 5, 6, 7, 8	9

★: The column criteria was fulfilled. #1 = age; 2 = gender; 3 = body mass index; 4 = duration of diabetes; 5 = family history of colorectal cancer; 6 = smoking status; 7 = alcohol use; 8 = insulin use.

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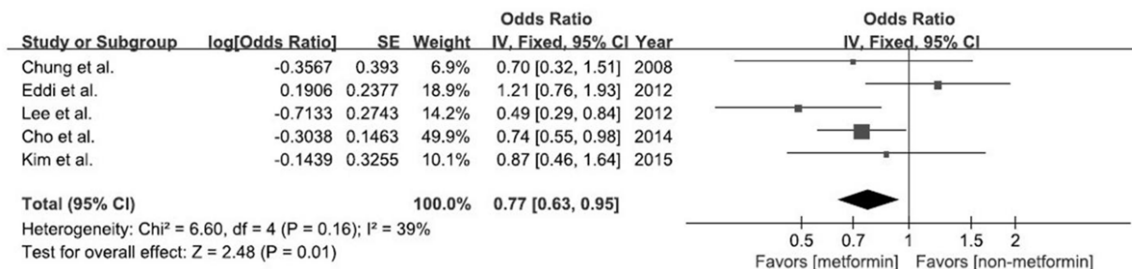


Figure 2. Forest plot of the relationship between metformin use and risk of CRA (SE: standard error; CI: confidence interval).

Table 3. Subgroup analyses and comparisons

Subgroup/Comparisons	No. of studies	Pooled OR (95% CI)	Heterogeneity (P; I ²)
All studies	5	0.77 (0.63-0.95)	0.16; 39%
Study design			
Retrospective cohort	3	0.70 (0.55-0.88)	0.33; 11%
Case-control	2	1.04 (0.70-1.56)	0.23; 30%
Study location			
Asia	4	0.70 (0.56-0.87)	0.52; 0%
North America	1	1.21 (0.76-1.93)	-
Patients in non-metformin group			
Diabetic	4	0.70 (0.56-0.87)	0.52; 0%
Diabetic and non-diabetic	1	1.21 (0.76-1.93)	-
Diabetic patients CRC status			
With previous CRC	1	0.49 (0.29-0.84)	-
Without previous CRC	3	0.75 (0.59-0.96)	0.89; 0%
Advanced adenoma	2	0.33 (0.04-2.63)	0.07; 70%

Abbreviations: OR, odds ratio; CI, confidence interval; I², inconsistency index.

was used since obvious heterogeneity was not observed among the selected studies ($P_{\text{heterogeneity}} = 0.16$, $I^2 = 39\%$). Overall, metformin use was associated with a decreased risk of CRA (pooled OR = 0.77, 95% CI: 0.63-0.95) according to the fixed effects model (**Figure 2**), yet not according to the random effects model (pooled OR = 0.78, 95% CI: 0.58-1.03).

Table 3 lists the results from the subgroups analyses and comparisons that were performed. When a subgroups analysis of study design was performed, the retrospective cohort studies [10, 11, 14] showed a positive influence of metformin use against CRA (pooled OR = 0.70, 95% CI: 0.55-0.88, n = 3) in contrast with the case-control studies [12, 13] (pooled OR = 1.04, 95% CI: 0.70-1.56, n = 2). When a subgroup analysis of study location was performed, the results showed that the relationship between metformin therapy and CRA was

significant in the Asian populations examined (pooled OR = 0.70, 95% CI: 0.56-0.87, n = 4), and was not significant in the United States study (OR = 1.21, 95% CI: 0.76-1.93). When a subgroups analysis was performed of the patients with or without DM that were in the non-metformin group, metformin use was found to have a stronger relationship with a lower risk of CRA in the studies that only included diabetic patients in the non-metformin group (pooled OR = 0.70, 95% CI: 0.56-0.87, n = 4), compared with the non-metformin group of the study by Eddi et al. [13] where both diabetic and non-diabetic patients were included (OR = 1.21, 95% CI: 0.76-1.93).

In four studies [10-12, 14], the relationship between metformin use and diabetic patients with or without previous CRC was examined. Metformin was associated with a lower risk of CRA not only in the patients who had been diagnosed without CRC (pooled OR = 0.70, 95% CI: 0.59-0.96, n = 3), but also in those who had undergone curative resection of CRC (OR = 0.49, 95% CI: 0.29-0.84). Finally, there were only two studies [10, 14] that were pooled to analyze whether metformin use was linked to a low risk of CRA, and no significant association between metformin use and the risk of advanced adenoma was observed (pooled OR = 0.33, 95% CI: 0.04-2.63).

Sources of heterogeneity

To examine possible sources of heterogeneity, the five selected studies were divided into a

“non-metformin group including only diabetic patients” and a “non-metformin group including both diabetic and non-diabetic patients”. The heterogeneity values significantly decreased among the four studies that had a non-metformin group that only included diabetic patients ($P_{\text{heterogeneity}} = 0.52$, $I^2 = 0\%$). Thus, the sources of heterogeneity observed may derive from the study [13] which had obvious selection bias involving the non-metformin group.

Sensitivity analysis

Four retrospective studies [10-12, 14] achieved scores of 6 or higher on a modified NOS and were included in a sensitivity analysis. However, no change in the significance of the results was observed (pooled OR = 0.70, 95% CI: 0.56-0.87, $P_{\text{heterogeneity}} = 0.52$, $I^2 = 0\%$), thereby confirming a positive association between metformin use and CRA risk.

Publication bias

No significant asymmetry was observed in the funnel plot generated. In addition, both Begg's test ($P = 1.0$, continuity corrected) and Egger's test ($P = 0.983$) showed no evidence of obvious publication bias.

Discussion

In a recent meta-analysis, a few antidiabetic medications were evaluated for their effects on CRC risk [6]. In particular, thiazolidinedione and metformin showed preventive effects [19]. In the present meta-analysis, five retrospective studies provided direct support for the hypothesis that metformin mediates a protective effect against CRA in diabetic patients, with a 30% reduction in risk observed. To the best of our knowledge, this is the first meta-analysis to investigate this relationship, and it provides preliminary support for further investigations of the potential for metformin to serve as a chemopreventive drug against CRA.

Previously, metformin use has been significantly associated with a lower risk of CRA when the non-metformin groups examined have only included diabetic patients, compared with studies where the non-metformin group included both diabetic and non-diabetic patients. Moreover, it is well-known that patients with DM have a higher CRA risk than those without DM [5], and this can potentially lead to incom-

parability between metformin and non-metformin groups. When the present subgroups were stratified according to study location, it was revealed that metformin use was associated with an inconsistent effect against CRA in diabetic patients from different continents. This may be due to differences in the susceptibility profile and molecular epidemiology of CRA in different populations. Moreover, since the ethnic proportion for each of the five selected studies was not indicated, a subgroup analysis according to ethnicity could not be performed. However, of particular interest was the subgroup analysis to evaluate CRA risk for diabetic patients independent of their CRC history. Based on the significantly lower risk of CRA that was observed for diabetic patients with and without a history of CRC, it appears that metformin use had a preventive effect for both sets of patients. Furthermore, although there was no statistically significant difference, the metformin group exhibited a lower risk of advanced adenoma. These results remain to be confirmed since the sample size analyzed was relatively small.

Possible mechanisms

Many theories have been proposed to explain the relationship between DM and an increased risk of CRA or CRC. One theory proposes that hyperinsulinemia, or increased levels of insulin-like growth factors (IGFs), contribute to the proliferation of colon epithelial cells and this leads to a survival benefit for transformed cells [20]. Insulin resistance may also contribute in part to the association between obesity and the incidence of CRA [21]. Metformin has been found to lower insulin levels and to reduce levels of the insulin sensitizer, IGF [22]. Furthermore, mechanisms regarding the antitumor effects of metformin have been reported. For example, metformin inhibits the mTOR pathway which has a downstream effect on the control of cell proliferation and tumor growth [9]. Metformin has also been shown to inhibit the growth of p53-deficient tumor cell growth [23], to induce apoptosis in tumor cells [24], to inhibit angiogenesis [25], and to suppress HER2 (erbB-2) oncoprotein overexpression [26]. Moreover, these studies and hypotheses are consistent with the effects of metformin that were observed in the present meta-analysis.

Comparisons with other studies

In a previous meta-analysis that included 37 studies and 1,535,636 participants, use of metformin was associated with a lower incidence of pancreatic, breast, and liver cancers [27]. Based on the results of the present meta-analysis, metformin exhibited the potential to mediate an anti-tumor effect *in vivo*, specifically regarding colorectal cancer. Similarly, in a recent study of 11,148 diabetic patients with long-term exposure to metformin, it was observed that metformin use was associated with a decreased risk of CRC [28]. However, Bodmer et al. reported the opposite effect [29]. Despite these discordant results, previous meta-analyses have shown that metformin has the potential to lower the risk of CRC and colorectal neoplasms [15, 30, 31]; although, in these meta-analyses, there was no strong evidence to confirm the relationship between metformin and CRA risk due to the lack of studies that investigated CRA. In a study by Mei et al., diabetic patients with CRC that were treated with metformin exhibited an improved survival outcome and a reduced risk of all causes of death [32]. Taken together, these results support the hypothesis that metformin use leads to a decreased risk of CRC, and diabetic patients may obtain the same benefit towards CRA, which is currently regarded as a precursor lesion of CRC.

There have been other studies that have shown an association between metformin use by diabetic patients and a significantly lower risk of CRA [33, 34]. These studies were not included in our meta-analysis because cancerous polyps and invasive CRC were defined as adenomas in these studies, and this definition was inconsistent with the definition of adenoma used in the present meta-analysis. Wong et al. [35] reported that metformin use was relative to an increased risk of CRA, although a statistically significant difference was not observed. It is possible this result was affected by the small sample size and the definition of carcinomas as adenomas. In other studies of CRC risk, antidiabetic drugs such as thiazolidinediones, sulfonylureas, and insulin did not significantly reduce CRC risk, and a trend towards a higher CRC risk was observed [6]. Hence, it appears that metformin is potentially the most effective antidiabetic drug against colorectal tumors that is currently available.

Strengths and limitations

The present study represents the limitations of existing research, while it maintained several strengths. First, comparability between a metformin group and a non-metformin group was emphasized by adjusting the NOS. Accordingly, this may have greatly influenced our assessment of the effects of metformin since age, gender, BMI, DM, family history of CRC, smoking status, alcohol use, and insulin use were found to be associated with the risk of CRA [5, 34, 36-42]. Fortunately, most of these items were considered to be comparable between the two groups, or were adjusted by multivariate regression analysis if needed. In addition, a comparison was performed by dividing the five selected studies into a “non-metformin group including only diabetic patients” and a “non-metformin group including both diabetic and non-diabetic patients”, and this may partly explain the heterogeneity associated with the present study.

There were also limitations associated with the present study. First, only two studies were included that involved diabetic patients who had undergone excision of all of the adenomas that were detected by screening colonoscopies in order to allow an assessment of CRA occurrence to be evaluated according to metformin use. Secondly, the least and mean duration of metformin use widely varied among the selected studies, and this may have influenced the risk of CRA. Thirdly, other confounders, such as metformin dose, skill-level of the endoscopists involved, colonoscopy withdrawal time, use of other diabetic drugs, as well as other factors were not considered in the present analysis. Lastly, there were only five studies included in our meta-analysis. Hence, the assessment of potential publication bias that was performed may not be sufficiently accurate. Given these limitations, it is important that the present results are interpreted with caution due to the potential for overestimations or underestimations of the data.

In conclusion, the present meta-analysis demonstrates that metformin use may lower the risk of CRA in patients with DM. Thus, metformin may represent a chemopreventive drug to reduce the burden of CRA and CRC in diabetic patients. However, due to the limitations of this meta-analysis, randomized, prospective stud-

ies with a larger sample are needed to validate the observed association.

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Disclosure of conflict of interest

None.

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References

- [1] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; 62: 10-29.
- [2] Morson B. President's address. The polyp-cancer sequence in the large bowel. *Proc R Soc Med* 1974; 67: 451-457.
- [3] Fearon ER and Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; 61: 759-767.
- [4] Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET and Waye JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; 366: 687-696.
- [5] Luo S, Li JY, Zhao LN, Yu T, Zhong W, Xia ZS, Shan TD, Ouyang H, Yang HS and Chen QK. Diabetes mellitus increases the risk of colorectal neoplasia: An updated meta-analysis. *Clin Res Hepatol Gastroenterol* 2016; 40: 110-23.
- [6] Singh S, Singh H, Singh PP, Murad MH and Limburg PJ. Antidiabetic medications and the risk of colorectal cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2013; 22: 2258-2268.
- [7] Tomimoto A, Endo H, Sugiyama M, Fujisawa T, Hosono K, Takahashi H, Nakajima N, Nagashima Y, Wada K, Nakagama H and Nakajima A. Metformin suppresses intestinal polyp growth in ApcMin/+ mice. *Cancer Sci* 2008; 99: 2136-2141.
- [8] Hosono K, Endo H, Takahashi H, Sugiyama M, Sakai E, Uchiyama T, Suzuki K, Iida H, Sakamoto Y, Yoneda K, Koide T, Tokoro C, Abe Y, Inamori M, Nakagama H and Nakajima A. Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. *Cancer Prev Res (Phila)* 2010; 3: 1077-1083.
- [9] Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M and Andreelli F. Cellular and molecular mechanisms of metformin: an overview. *Clin Sci (Lond)* 2012; 122: 253-270.
- [10] Lee JH, Jeon SM, Hong SP, Cheon JH, Kim TI and Kim WH. Metformin use is associated with a decreased incidence of colorectal adenomas in diabetic patients with previous colorectal cancer. *Dig Liver Dis* 2012; 44: 1042-1047.
- [11] Cho YH, Ko BM, Kim SH, Myung YS, Choi JH, Han JP, Hong SJ, Jeon SR, Kim HG, Kim JO and Lee MS. Does metformin affect the incidence of colonic polyps and adenomas in patients with type 2 diabetes mellitus? *Intest Res* 2014; 12: 139-145.
- [12] Chung YW, Han DS, Park KH, Eun CS, Yoo KS and Park CK. Insulin therapy and colorectal adenoma risk among patients with Type 2 diabetes mellitus: a case-control study in Korea. *Dis Colon Rectum* 2008; 51: 593-597.
- [13] Eddi R, Karki A, Shah A, DeBari VA and DePasquale JR. Association of type 2 diabetes and colon adenomas. *J Gastrointest Cancer* 2012; 43: 87-92.
- [14] Kim YH, Noh R, Cho SY, Park SJ, Jeon SM, Shin HD, Kim SB and Shin JE. Inhibitory effect of metformin therapy on the incidence of colorectal advanced adenomas in patients with diabetes. *Intest Res* 2015; 13: 145-152.
- [15] Zhang ZJ, Zheng ZJ, Kan H, Song Y, Cui W, Zhao G and Kip KE. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis. *Diabetes Care* 2011; 34: 2323-2328.
- [16] Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
- [17] Ben Q, An W, Jiang Y, Zhan X, Du Y, Cai QC, Gao J and Li Z. Body mass index increases risk for colorectal adenomas based on meta-analysis. *Gastroenterology* 2012; 142: 762-772.
- [18] Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa Hospital Research Institute Web site. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed March 15, 2012.
- [19] Colmers IN, Bowker SL and Johnson JA. Thiazolidinedione use and cancer incidence in type 2 diabetes: a systematic review and meta-analysis. *Diabetes Metab* 2012; 38: 475-484.
- [20] Berster JM and Goke B. Type 2 diabetes mellitus as risk factor for colorectal cancer. *Arch Physiol Biochem* 2008; 114: 84-98.
- [21] Yoon YS, Keum N, Zhang X, Cho E and Giovannucci EL. Hyperinsulinemia, insulin resis-

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- tance and colorectal adenomas: A meta-analysis. *Metabolism* 2015; 64: 1324-33.
- [22] Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 2008; 8: 915-928.
- [23] Buzzai M, Jones RG, Amaravadi RK, Lum JJ, DeBerardinis RJ, Zhao F, Violette B and Thompson CB. Systemic treatment with the anti-diabetic drug metformin selectively impairs p53-deficient tumor cell growth. *Cancer Res* 2007; 67: 6745-6752.
- [24] Ben Sahra I, Laurent K, Giuliano S, Larbret F, Ponzio G, Gounon P, Le Marchand-Brustel Y, Giorgetti-Peraldi S, Cormont M, Bertolotto C, Deckert M, Auberger P, Tanti JF and Bost F. Targeting cancer cell metabolism: the combination of metformin and 2-deoxyglucose induces p53-dependent apoptosis in prostate cancer cells. *Cancer Res* 2010; 70: 2465-2475.
- [25] Ersoy C, Kiyici S, Budak F, Oral B, Guclu M, Duran C, Selimoglu H, Erturk E, Tuncel E and Imamoglu S. The effect of metformin treatment on VEGF and PAI-1 levels in obese type 2 diabetic patients. *Diabetes Res Clin Pract* 2008; 81: 56-60.
- [26] Vazquez-Martin A, Oliveras-Ferraro C and Menendez JA. The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression via inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells. *Cell Cycle* 2009; 8: 88-96.
- [27] Zhang P, Li H, Tan X, Chen L and Wang S. Association of metformin use with cancer incidence and mortality: a meta-analysis. *Cancer Epidemiol* 2013; 37: 207-218.
- [28] Cardel M, Jensen SM, Pottegard A, Jorgensen TL and Hallas J. Long-term use of metformin and colorectal cancer risk in type II diabetics: a population-based case-control study. *Cancer Med* 2014; 3: 1458-1466.
- [29] Bodmer M, Becker C, Meier C, Jick SS and Meier CR. Use of metformin is not associated with a decreased risk of colorectal cancer: a case-control analysis. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 280-286.
- [30] Soranna D, Scotti L, Zamboni A, Bosetti C, Grassi G, Catapano A, La Vecchia C, Mancina G and Corrao G. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist* 2012; 17: 813-822.
- [31] Noto H, Goto A, Tsujimoto T and Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. *PLoS One* 2012; 7: e33411.
- [32] Mei ZB, Zhang ZJ, Liu CY, Liu Y, Cui A, Liang ZL, Wang GH and Cui L. Survival benefits of metformin for colorectal cancer patients with diabetes: a systematic review and meta-analysis. *PLoS One* 2014; 9: e91818.
- [33] Lewis JD, Capra AM, Achacoso NS, Ferrara A, Levin TR, Quesenberry CP Jr and Habel LA. Thiazolidinedione therapy is not associated with increased colonic neoplasia risk in patients with diabetes mellitus. *Gastroenterology* 2008; 135: 1914-1923, 1923 e1911.
- [34] Kanadiya MK, Gohel TD, Sanaka MR, Thota PN and Shubrook JH Jr. Relationship between type-2 diabetes and use of metformin with risk of colorectal adenoma in an American population receiving colonoscopy. *J Diabetes Complications* 2013; 27: 463-466.
- [35] Wong P, Weiner MG, Hwang WT and Yang YX. Insulin therapy and colorectal adenomas in patients with diabetes mellitus. *Cancer Epidemiol Biomarkers Prev* 2012; 21: 1833-1840.
- [36] Ferlitsch M, Heinze G, Salzl P, Britto-Arias M, Waldmann E, Reinhart K, Bannert C, Fasching E, Knoflach P, Weiss W, Trauner M and Ferlitsch A. Sex is a stronger predictor of colorectal adenoma and advanced adenoma than fecal occult blood test. *Med Oncol* 2014; 31: 151.
- [37] Ashktorab H, Paydar M, Yazdi S, Namin HH, Sanderson A, Begum R, Semati M, Etaati F, Lee E, Brim H, Zenebe A, Nunlee-Bland G, Laiyemo AO and Nouraei M. BMI and the risk of colorectal adenoma in African-Americans. *Obesity (Silver Spring)* 2014; 22: 1387-1391.
- [38] Sasaki Y, Takeda H, Sato T, Orii T, Nishise S, Nagino K, Iwano D, Yaoita T, Yoshizawa K, Saito H, Tanaka Y and Kawata S. Serum Interleukin-6, insulin, and HOMA-IR in male individuals with colorectal adenoma. *Clin Cancer Res* 2012; 18: 392-399.
- [39] Voutsinas J, Wilkens LR, Franke A, Vogt TM, Yokochi LA, Decker R and Le Marchand L. Heterocyclic amine intake, smoking, cytochrome P450 1A2 and N-acetylation phenotypes, and risk of colorectal adenoma in a multiethnic population. *Gut* 2013; 62: 416-422.
- [40] Shin A, Hong CW, Sohn DK, Chang Kim B, Han KS, Chang HJ, Kim J and Oh JH. Associations of cigarette smoking and alcohol consumption with advanced or multiple colorectal adenoma risks: a colonoscopy-based case-control study in Korea. *Am J Epidemiol* 2011; 174: 552-562.
- [41] Kim KS, Moon HJ, Choi CH, Baek EK, Lee SY, Cha BK, Lee HW, Kim HJ, Do JH and Chang SK. The Frequency and Risk Factors of Colorectal Adenoma in Health-Check-up Subjects in South Korea: Relationship to Abdominal Obesity and Age. *Gut Liver* 2010; 4: 36-42.
- [42] Choi MY, Kim BG, Kim JW, Lee KL, Jeong JB, Lee JK, Jung YJ, Kim W, Ahn DW, Kim YH, Joo SK, Chang MS and Kwon HJ. [The effects of family history of colorectal cancer on the development of colorectal adenoma]. *Korean J Gastroenterol* 2012; 60: 36-41.