Review Article

Metformin as a Chemopreventive Agent for Colorectal Adenoma Recurrence: Evidence from Randomized Controlled Trials

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Background: Colorectal adenomas are well-established precursors of colorectal cancer (CRC), with recurrence rates of up to 50% following polypectomy. Safe and effective chemopreventive strategies are needed. Metformin, a widely used antidiabetic agent, has demonstrated potential anticancer effects, but its role in adenoma prevention among non-diabetic individuals remains uncertain.
Objective: To evaluate the efficacy and safety of metformin in preventing metachronous colorectal adenoma recurrence in non-diabetic adults following complete endoscopic polypectomy.
Methods: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted in accordance with PRISMA guidelines. Databases including PubMed, Embase, Cochrane CENTRAL, Web of Science, and Scopus were searched from inception to December 2025. Eligible studies included RCTs comparing metformin with placebo or no intervention in non-diabetic adults with prior adenoma resection, reporting recurrence at ≥12 months. Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using a random-effects model.
Results: Two RCTs comprising 405 participants were included. Metformin significantly reduced the risk of adenoma recurrence at 1 year compared with the control (RR 0.61, 95% CI 0.48–0.78; I^2 = 0%). This corresponds to an approximate 39% relative risk reduction. The effect was consistent across different dosing regimens (250–1000 mg/day). Both trials demonstrated a low risk of bias and reported good tolerability, with only mild gastrointestinal adverse events and no serious toxicity.
Conclusion: Metformin significantly reduces metachronous colorectal adenoma recurrence in non-diabetic patients after polypectomy, with a favorable safety profile. These findings support its potential role as a cost-effective chemopreventive agent. Larger, long-term trials are warranted to confirm its impact on colorectal cancer incidence and clinical outcomes.

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Introduction

Colorectal cancer (CRC) is a major global public health concern and remains one of the leading causes of cancer morbidity and mortality worldwide. According to GLOBOCAN 2020 estimates, approximately 1.9 million new CRC cases and 930,000 deaths occurred globally, making it the third most commonly diagnosed cancer and the second leading cause of cancer death [1]. Incidence rates demonstrate considerable geographic heterogeneity: the highest age-standardized incidence is reported in Australia, New Zealand, and parts of Europe, exceeding 40 per 100,000 males, whereas the lowest rates occur in regions of Africa and Southern Asia, often below 5 per 100,000 females [2]. Mortality patterns closely mirror incidence, with Eastern Europe experiencing the highest death rates, while Southern Asia reports comparatively lower fatality burdens [1]. With ongoing population aging, lifestyle transitions, and rising prevalence of modifiable risk factors, annual CRC incidence is projected to surpass 2.2 million cases and 1.1 million deaths by 2030 [3].

CRC develops through a well-characterized adenoma–carcinoma sequence, in which conventional adenomatous polyps represent the dominant precursors of malignancy [4]. Colonoscopic detection and removal of adenomas substantially lowers long-term CRC incidence and mortality, as demonstrated in long-term follow-up of randomized and cohort studies [5][6]. Despite complete endoscopic resection, metachronous adenomas recur in 30–50% of individuals within 3–5 years, particularly among those with high-risk features, including multiple adenomas, villous histology, or high-grade dysplasia [7]. Consequently, strategies to reduce adenoma recurrence are central to contemporary CRC prevention frameworks.

Chemoprevention has emerged as a complementary approach to endoscopic surveillance. Aspirin has shown consistent reductions in adenoma recurrence and CRC risk, but its widespread use is limited by gastrointestinal and bleeding complications, especially in older populations [8]. Other agents, such as calcium, vitamin D, and selective COX-2 inhibitors, have demonstrated variable efficacy and, in some cases, unacceptable cardiovascular toxicity [9]. These limitations underscore the need for safe, well-tolerated, and widely accessible chemopreventive options.

Metformin, a biguanide and first-line therapy for type 2 diabetes, has garnered considerable interest as a potential CRC chemopreventive agent [10]. Epidemiologic studies have repeatedly associated metformin

use with reduced CRC incidence among diabetic individuals, though these findings are often confounded by methodological biases, including immortal time bias and diabetes-related factors [10]. Mechanistic evidence supports a plausible anticancer role: metformin activates AMP-activated protein kinase (AMPK), inhibits the mTOR signaling pathway, reduces insulin/IGF-1-mediated mitogenic activity, and modifies colonic microbiota and inflammatory responses, mechanisms implicated in colorectal tumorigenesis [11].

Given its favorable safety profile, low cost, and mechanistic rationale, metformin has been evaluated in prospective trials for adenoma prevention in non-diabetic individuals. Early randomized evidence suggests a potential reduction in metachronous adenoma recurrence; however, data remain limited and heterogeneous. Additional synthesis of randomized trials is therefore necessary to clarify the efficacy of metformin in post-polypectomy chemoprevention and to inform future clinical recommendations. Therefore, the present study aims to systematically evaluate randomized controlled trial evidence on the efficacy of metformin in preventing metachronous colorectal adenomas in non-diabetic individuals. By synthesizing available data, we seek to clarify the magnitude, consistency, and clinical relevance of metformin's chemopreventive effect and inform future CRC prevention strategies.

Methods

Study Design and Registration

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the effect of metformin on the recurrence of colorectal adenomas in non-diabetic adults following complete endoscopic polypectomy. All methodological steps adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and followed standard Cochrane methodological recommendations.

Eligibility Criteria

Studies were eligible for inclusion if they were randomized or randomized, double-blind, placebo-controlled clinical trials evaluating non-diabetic adults aged 18 years or older who had undergone complete endoscopic removal of colorectal adenomas at baseline. Trials were required to compare metformin, at any dose and duration, with placebo or no pharmacological intervention and to report colorectal adenoma recurrence at follow-up colonoscopy after a minimum follow-up of 12 months. Studies from any geographic region or clinical setting were considered. Exclusion criteria included trials

involving participants with type 1 or type 2 diabetes mellitus; observational, quasi-experimental, or preclinical studies; studies evaluating patients with hereditary colorectal cancer syndromes such as familial adenomatous polyposis or Lynch syndrome; inflammatory bowel disease; prior colorectal cancer; or studies lacking extractable data related to adenoma recurrence.

Search Strategy

A comprehensive search of PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus was performed from database inception to December 2025. The strategy incorporated both controlled vocabulary (MeSH/Emtree) and free-text keywords related to metformin, biguanides, colorectal adenomas, adenoma recurrence, chemoprevention, and randomized controlled trials. Reference lists of relevant publications were manually reviewed to identify additional eligible studies. No language or geographic restrictions were applied.

Study Selection

Two reviewers independently screened all titles and abstracts, followed by full-text assessment of potentially relevant articles using predefined eligibility criteria. Any disagreements were resolved through discussion or consultation with a third reviewer. Only two trials, Higurashi et al. (2016) and Wang et al. (2025), fulfilled all inclusion criteria and were retained for analysis.

Data Extraction

Data were extracted independently by two investigators using a standardized, pilot-tested form. Extracted variables included study characteristics, participant demographics, baseline adenoma risk, metformin dose and duration, comparator details, adherence and follow-up duration, and the number of participants with one or more recurrent adenomas at follow-up colonoscopy. Adverse events and safety outcomes were also recorded. In trials that included multiple metformin dose groups, such as Wang et al., dose arms were retained separately for descriptive reporting but were combined for pooled effect estimation according to Cochrane guidance.

Risk of Bias Assessment

Risk of bias for each included trial was evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, assessing the randomization process, deviations from intended interventions, missing outcome data, measurement

of outcomes, and selection of reported results. Each domain was rated as low risk, some concerns, or high risk. Both included RCTs were ultimately judged to have an overall low risk of bias.

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4. The primary effect measure was the risk ratio (RR) for adenoma recurrence at one year. A DerSimonian–Laird random-effects model was prespecified due to expected variability across studies, although heterogeneity was minimal (I^2 = 0%). For Wang et al., the two metformin dose arms (500 mg and 1000 mg daily) were combined by summing the number of events and total participants to generate a single pooled comparison with the control group, following Cochrane recommendations. Heterogeneity was evaluated using Cochran's Q and the I^2 statistic. A sensitivity analysis using a fixed-effect model was performed to assess robustness. Publication bias was not assessed using funnel plots or Egger's test due to the small number of included studies.

Outcome Measures

The primary outcome was metachronous colorectal adenoma recurrence, defined as the detection of at least one new adenoma during surveillance colonoscopy one year after baseline clearance. Secondary outcomes included adverse events and other safety data reported by the included studies.

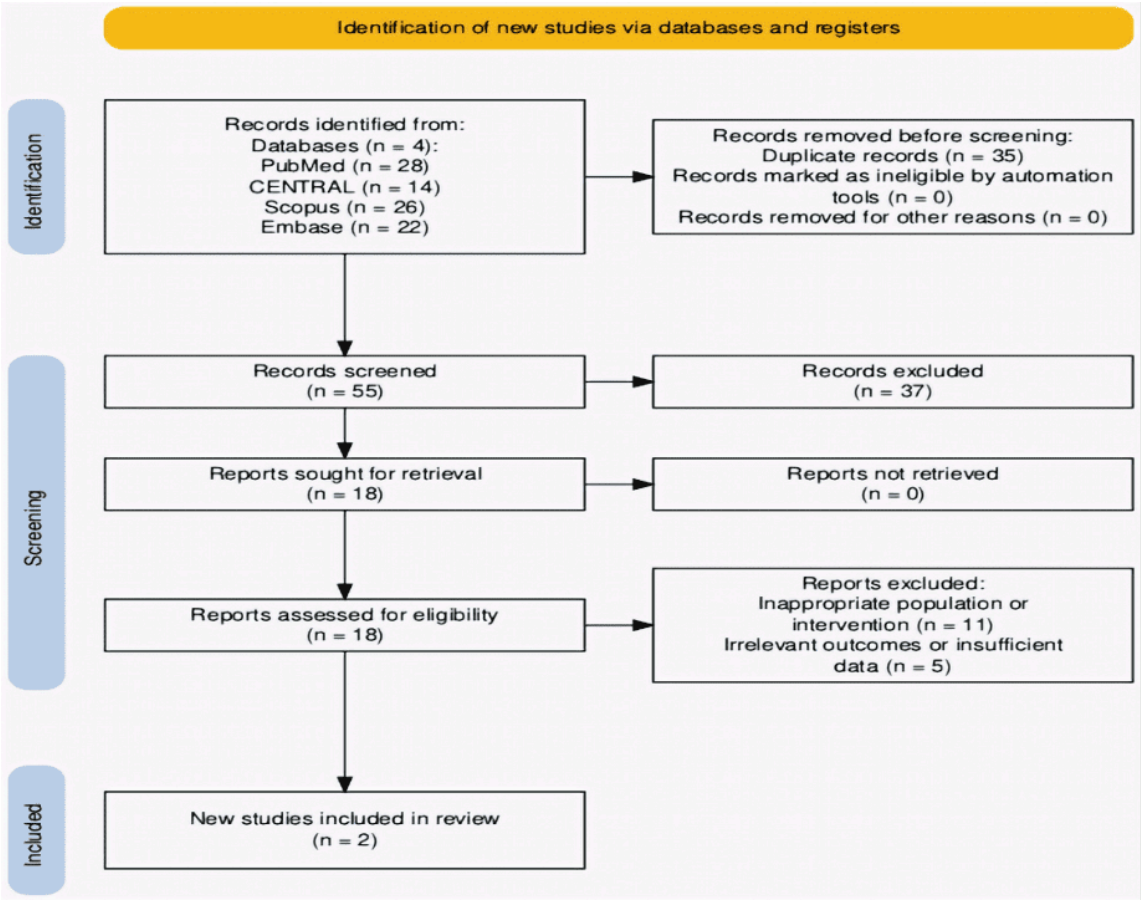

Figure 1. Flow Diagram of selected studies

Results

Baseline Characteristics

Two randomized controlled trials (RCTs) were included, enrolling a total of **n=405** non-diabetic adults after complete endoscopic removal of colorectal adenomas. **Higurashi et al. (2016, Japan)** randomized **n=151** patients and analyzed **n=133** at 1 year (**metformin n=71; placebo n=62**). Participants were aged 40–80 years (mean ≈60 years), with an average body mass index (BMI) of 23–24 kg/m^2. Randomization was stratified by age, sex, BMI, and study center. Patients with diabetes mellitus, prior colorectal cancer, inflammatory bowel disease, hereditary syndromes (e.g., familial adenomatous polyposis, Lynch syndrome), or regular NSAID/aspirin use were excluded.

Wang et al. (2025, China) randomized **n=300** and analyzed **n=272** at 1 year (**metformin 500 mg/day n=91; metformin 1000 mg/day n=87; control n=94**). Eligible patients were 40–70 years old (mean ≈57 years) and required to have ≥3 adenomas at index colonoscopy. Approximately 70% of participants were male, and the mean BMI was 24 kg/m² across arms. Exclusion criteria included diabetes, hereditary polyposis syndromes, inflammatory bowel disease, colorectal cancer history or surgery, and recent use of chemopreventive agents. Adequate bowel preparation and complete baseline clearance were mandated in both trials.

Characteristic	Higurashi et al., 2016 (Japan)	Wang et al., 2025 (China)
Sample size analyzed	71 metformin, 62 placebo (n=133)	91 (Met 500 mg), 87 (Met 1000 mg), 94 control (n=272)
Age (years)	Mean 60; range 40–80	Mean 57; range 40–70
Gender distribution		70% male, 30% female
BMI (kg/m²)		Control: 23.9 ± 2.8; Met 500: 24.4 ± 2.6; Met 1000: 24.2 ± 1.9
Risk profile at entry	≥1 adenoma or polyp resected	≥3 adenomas resected at baseline
Key exclusions	Diabetes, prior CRC, IBD, hereditary syndromes, NSAID/aspirin use	Diabetes, hereditary syndromes, IBD, CRC history/surgery, recent NSAID use
Setting	5 centers in Japan	3 centers in China
Follow-up period	1 year	1 year

Table 1. Baseline characteristics of included randomized controlled trials

Outcomes (Adenoma Recurrence at 1 Year)

Both RCTs demonstrated a reduction in metachronous adenoma recurrence with metformin compared to control. In Higurashi et al., recurrence was observed in 22/71 (30.6%) patients receiving metformin versus 32/62 (51.6%) in the placebo group (RR 0.60, 95% CI 0.39–0.92). In Wang et al., recurrence occurred in

28/91 (30.8%) in the 500 mg arm and 26/87 (29.9%) in the 1000 mg arm, compared with 46/94 (48.9%) in controls (RR 0.63, 95% CI 0.43–0.91 and RR 0.61, 95% CI 0.42–0.90, respectively). Adverse events were limited to mild gastrointestinal symptoms in both trials, with no serious toxicity reported.

Study	Group	N	Events (recurrence)	Recurrence %	Effect vs control (RR, 95% CI)
Higurashi et al., 2016 (Japan)	Metformin 250 mg/day	71	22	30.6	**0.60 (0.39–0.92)**
	Placebo	62	32	51.6	Reference
Wang et al., 2025 (China)	Metformin 500 mg/day	91	28	30.8	**0.63 (0.43–0.91)**
	Metformin 1000 mg/day	87	26	29.9	**0.61 (0.42–0.90)**
	Control (no intervention)	94	46	48.9	Reference

Table 2. One-year adenoma recurrence and effect estimates (per trial arm)

Risk of Bias

Both RCTs were judged to have a **low overall risk of bias**. Randomization and allocation concealment were appropriate, blinding was maintained, attrition was minimal, and outcomes were assessed objectively at 1-year colonoscopy. Protocol registration and prespecified outcomes reduced reporting bias.

Domain	Higurashi et al., 2016	Wang et al., 2025
Randomization process	Low risk (stratified randomization)	Low risk (computer-generated)
Deviations from intended interventions	Low risk (double-blind, placebo-controlled)	Low risk (identical tablets, follow-up)
Missing outcome data	Low risk (<15% attrition)	Low risk (<10% attrition)
Measurement of the outcome	Low risk (blinded endoscopy + video review)	Low risk (blinded colonoscopy)
Selection of reported results	Low risk (protocol published)	Low risk (registered)
Overall judgment	Low risk	Low risk

Table 3. Risk of Bias assessment (RoB 2)

Meta-analysis of Adenoma Recurrence

For quantitative synthesis, the two metformin arms in **Wang et al.** were combined (events **54/178**) and compared against the single control group (**46/94**). This, together with **Higurashi** (metformin **22/71** vs. placebo **32/62**), yielded a total of **n=405** patients (**metformin n=249; control n=156**).

The pooled random-effects model demonstrated that metformin significantly reduced adenoma recurrence at 1 year (**RR 0.61, 95% CI 0.48-0.78; I^2 = 0%**). Fixed-effect analysis produced identical estimates. **Figure 1** presents the forest plot of the included trials, with both point estimates favoring metformin and the pooled effect indicating a clinically meaningful reduction in recurrence risk.

Figure 1 presents the forest plot of the included trials. In both studies, point estimates favored metformin, and the pooled effect indicated a clinically meaningful reduction in recurrence risk.

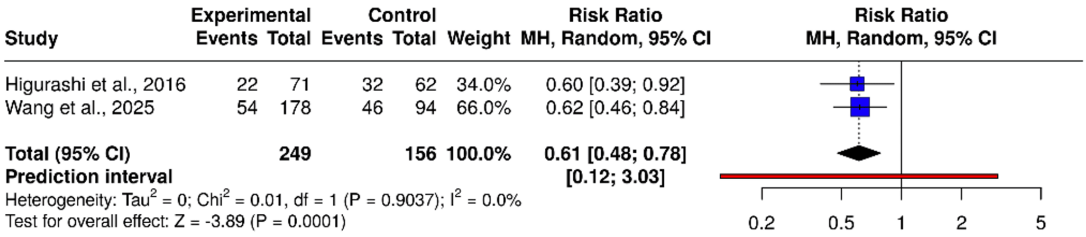

Figure 2. Forest plot of metformin vs. control for adenoma recurrence at 1 year.

Discussion

CRC predominantly affects older adults, but certain hereditary syndromes, such as familial adenomatous polyposis (FAP), confer a near 100% lifetime risk of CRC through the adenoma-carcinoma sequence. Current clinical guidelines recommend prophylactic colectomy in FAP patients to prevent malignant transformation [12]. Beyond hereditary syndromes, sporadic adenomatous polyps represent the principal precursors of CRC, and their removal during colonoscopy is a cornerstone of prevention. However, recurrence of adenomas after endoscopic polypectomy remains a significant challenge, occurring in approximately 30-50% of patients within three years, particularly among those with multiple or advanced lesions [13][14].

Several pharmacologic and nutritional agents have been investigated for the prevention of adenoma recurrence. Aspirin has demonstrated a significant reduction in adenoma recurrence in randomized trials, though its use is limited by gastrointestinal bleeding risk [15]. Calcium supplementation has shown modest benefit, and combined calcium and vitamin D interventions have been explored with mixed results [16][17]. Non-steroidal anti-inflammatory drugs (NSAIDs), such as celecoxib, have also proven effective but are constrained by cardiovascular toxicity [18]. Against this backdrop, metformin emerges as a promising alternative due to its favorable safety profile and metabolic benefits.

Through our review, we evaluated the effect of metformin on the recurrence of colorectal adenomas in non-diabetic individuals following complete endoscopic clearance. Across both RCTs analyzed (n=405), metformin demonstrated a greater prophylactic impact compared with placebo and control groups. The pooled risk ratio of 0.61 (95% CI 0.48-0.78) indicates a nearly 40% relative risk reduction, which is clinically meaningful given that adenoma recurrence is a well-established surrogate marker for CRC risk.

Importantly, this effect was observed across different dosing regimens, ranging from 250 mg/day in Higurashi et al. to 500-1000 mg/day in Wang et al., suggesting that even low doses may exert chemopreventive benefits. Both trials reported excellent tolerability, with adverse events limited to mild gastrointestinal symptoms and no serious toxicity, reinforcing metformin's favorable safety profile in this preventive setting.

The significance of these findings lies in the context of CRC prevention strategies. Current chemopreventive agents, such as aspirin and NSAIDs, have demonstrated efficacy but are limited by adverse effects [15][18], restricting their widespread use. In contrast, metformin is inexpensive, widely available, and has an established safety record from decades of use in type 2 diabetes. The magnitude of benefit observed in these trials is comparable to that reported for aspirin in adenoma prevention (RR ≈ 0.81, 95% CI 0.69-0.96) [15], but without the associated bleeding risk, positioning metformin as a potentially attractive alternative.

While observational studies have long suggested an association between metformin use and reduced CRC incidence, these findings have been confounded by diabetes-related factors and methodological biases such as immortal time bias [19][20][21]. The RCTs included in this review provide more robust evidence by eliminating these confounders and focusing on non-diabetic populations. Notably, the consistency of effect across two independent trials, conducted in different East Asian cohorts, strengthens the validity of the findings. However, it is important to acknowledge that both studies were limited to Asian populations, which may differ in genetic susceptibility, dietary patterns, and microbiome composition compared to Western populations. Therefore, generalizability remains uncertain and warrants confirmation in diverse cohorts.

The biological plausibility of metformin's protective effect is supported by extensive mechanistic evidence. Metformin activates AMP-activated protein kinase (AMPK), a key energy sensor that inhibits the mammalian target of rapamycin (mTOR) pathway, thereby reducing cellular proliferation and promoting apoptosis in colonic epithelial cells [22]. Additionally, metformin lowers circulating insulin and IGF-1 levels, attenuating insulin-mediated mitogenic signaling implicated in colorectal carcinogenesis [23]. Beyond systemic metabolic effects, metformin may exert local actions within the gut, including modulation of microbiota composition, reduction of bile acid-induced mucosal injury, and suppression of cancer stem cell populations [24]. Preclinical studies have demonstrated that metformin

can inhibit polyp formation in animal models and reduce proliferation markers such as Ki-67 in human colorectal mucosa, providing further mechanistic support for its role in adenoma prevention [25].

Despite these promising results, several limitations must be considered. First, the follow-up duration in both trials was restricted to one year, which is insufficient to assess long-term outcomes such as advanced adenoma recurrence or CRC incidence. Second, neither study incorporated biomarker analyses nor stratified results by molecular subtypes, which could help identify subgroups most likely to benefit. Third, while Wang et al. evaluated two doses of metformin, the absence of a clear dose-response relationship suggests that higher doses may not confer additional benefit, but this requires confirmation in longer-term studies. Finally, the trials were conducted in specialized centers with rigorous colonoscopic surveillance, which may not reflect real-world practice.

From a clinical perspective, these findings have important implications. Metformin could potentially be integrated into post-polypectomy surveillance strategies for individuals at high risk of recurrence, such as those with multiple adenomas or advanced histology. Its low cost, favorable safety profile, and widespread availability make it an attractive candidate for chemoprevention, particularly in resource-limited settings. However, before such recommendations can be implemented, larger multicenter trials with extended follow-up and diverse populations are essential to confirm the durability of benefit and assess the impact on CRC incidence and mortality. Future research should also explore predictive biomarkers, interactions with lifestyle factors, and potential synergy with other preventive interventions such as aspirin or dietary modification.

In conclusion, randomized evidence indicates that metformin significantly reduces the risk of metachronous adenoma recurrence in non-diabetic patients following complete polypectomy, with minimal toxicity. These findings provide a strong rationale for further investigation into metformin as a component of CRC prevention strategies. If confirmed in larger, long-term trials, metformin could represent a safe, cost-effective, and widely accessible approach to reducing the global burden of colorectal cancer.

References

1. [a], [b] *Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, Vignat J, Ferlay J, Murphy N, Bray F (2023). "Global Burden of Colorectal Cancer in 2020 and 2040: Incidence and Mortality Estimates from GLOBOCAN." Gut.* **72**(2):338–344. doi:10.1136/gutjnl-2022-327736. PMID 36604116.

2. ^Osama M, Moosa H, Rangwala HS, Rangwala BS, Farrukh A, Fayaz S, Nalwala M, Shafique MA, Iqbal M (2025). "Analysis of Demographic Associations and Survival Outcomes in Patients With Colorectal Cancer at a Tertiary Care Hospital in Pakistan. A Retrospective Cross-Sectional Study." Cancer Control. **32**:10732748251351423. doi:10.1177/10732748251351423.

3. ^Siegel RL, Wagle NS, Cercek A, Smith RA, Jemal A (2023). "Colorectal Cancer Statistics, 2023." CA Cancer J Clin. **73**(3):233–254. doi:10.3322/caac.21772.

4. ^De Palma FDE, D'Argenio V, Pol J, Kroemer G, Maiuri MC, Salvatore F (2019). "The Molecular Hallmarks of the Serrated Pathway in Colorectal Cancer." Cancers (Basel). **11**(7):1017. doi:10.3390/cancers11071017.

5. ^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, Waye JD (2012). "Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths." N Engl J Med. **366**(8):687–96. doi:10.1056/NEJMoa1100370.

6. ^Martínez ME, Sampliner R, Marshall JR, Bhattacharyya AK, Reid ME, Alberts DS (2001). "Adenoma Characteristics as Risk Factors for Recurrence of Advanced Adenomas." Gastroenterology. **120**(5):1077–83. doi:10.1053/gast.2001.23247.

7. ^Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU (2003). "A Randomized Trial of Aspirin to Prevent Colorectal Adenomas." N Engl J Med. **348**(10):891–9. doi:10.1056/NEJMoa021735.

8. ^Hoang KD, Chen JH, Huang TW, Kang YN, Chen C (2024). "Oral Aspirin for Preventing Colorectal Adenoma Recurrence: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials." PLoS One. **19**(3):e0279784. doi:10.1371/journal.pone.0279784.

9. ^Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, Petrelli N, Pipas JM, Karp DD, Loprinzi CL, Steinbach G, Schilsky R (2003). "A Randomized Trial of Aspirin to Prevent Colorectal Adenomas in Patients With Previous Colorectal Cancer." N Engl J Med. **348**(10):883–90. doi:10.1056/NEJMoa021633.

10. a, bMyung S, Park YY, Kim MS (2025). "Metformin in Colorectal Cancer: Epidemiological Evidence, Predictive Biomarkers, and Implications for Prevention and Treatment." Int J Mol Sci. **26**(13):6040. doi:10.3390/ijms26136040.

11. ^Kamarudin MNA, Sarker MMR, Zhou JR, Parhar I (2019). "Metformin in Colorectal Cancer: Molecular Mechanism, Preclinical and Clinical Aspects." J Exp Clin Cancer Res. **38**(1):491. doi:10.1186/s13046-019-1495-2.

12. ^Vasen HF, et al. (2008). "Guidelines for the Clinical Management of Familial Adenomatous Polyposis (FAP)." Gut. **57**(5):704–713.

13. ^Winawer SJ, et al. (2003). "Colorectal Cancer Screening and Surveillance: Clinical Guidelines and Rationale—Update Based on New Evidence." Gastroenterology. **124**(2):544–560.

14. ^Zauber AG, et al. (2012). "Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths." N Engl J Med. **366**(8):687–696.

15. a, b, cBaron JA, et al. (2003). "A Randomized Trial of Aspirin to Prevent Colorectal Adenomas." N Engl J Med. **348**(10):891–899.

16. ^Bonithon-Kopp C, et al. (1996). "Calcium Supplementation and Colorectal Adenoma Recurrence: A Randomized Intervention Trial." Lancet. **348**(9024):911–915.

17. ^Wu K, et al. (2007). "Vitamin D and Calcium Supplementation and Risk of Colorectal Adenomas." Am J Clin Nutr. **85**(6):1580–1586.

18. a, bSandler RS, et al. (2003). "A Randomized Trial of Celecoxib for the Prevention of Colorectal Adenomas." N Engl J Med. **348**(10):891–899.

19. ^Yu OH, Suissa S (2023). "Immortal Time Bias in Pharmacoepidemiology: Examples from Studies of Metformin and Cancer." Diabetes Care. **46**(3):e67–e69.

20. ^Smiechowski B, et al. (2013). "The Use of Metformin and the Incidence of Colorectal Cancer in Patients With Type 2 Diabetes." Diabetes Care. **36**(11):3316–3322.

21. ^Sehdev A, et al. (2015). "Metformin for Colorectal Cancer Prevention: A Case-Control Study." Cancer Med. **4**(11):1705–1713.

22. ^Kalender A, et al. (2010). "Metformin, Independent of AMPK, Inhibits mTORC1 in a Rag GTPase-Dependent Manner." Cell Metab. **11**(5):390–401.

23. ^Pollak M (2010). "Metformin and Other Biguanides in Oncology: Advancing the Research Agenda." Cancer Prev Res. **3**(9):1060–1065.

24. ^Lee H, et al. (2021). "Metformin and Colorectal Cancer: Mechanisms and Clinical Applications." Cancer Lett. **503**:36–47.

25. ^Higurashi T, et al. (2016). "Metformin for Chemoprevention of Metachronous Colorectal Adenoma or Polyps in Non-Diabetic Patients: A Randomized Controlled Trial." Lancet Oncol. **17**(4):475–483.

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