

Chemopreventive Effects of Statins and Aspirin on Colorectal Cancer Among Patients with Inflammatory Bowel Disease: Evidence of a Synergistic Association from a Large Cohort

Joelle Sleiman¹, Christopher Khouri², Un Jung Lee³, Reem Dimachkie⁴, Omar Abureesh¹, Ryan Njeim¹, Liliane Deeb⁴

¹Department of Internal Medicine, Staten Island University Hospital, Northwell Health, Staten Island, NY, USA; ²Department of Internal Medicine, SUNY Downstate Health Sciences University, Brooklyn, NY, USA; ³Biostatistics Unit, Office of Academic Affairs, Northwell Health, New Hyde Park, NY, USA; ⁴Division of Gastroenterology, Department of Internal Medicine, Staten Island University Hospital, Northwell Health, Staten Island, NY, USA

Correspondence: Joelle Sleiman, Department of Internal Medicine, Staten Island University Hospital, Northwell Health, Staten Island, NY, USA, Tel +1 216 539 6998, Email jsleiman@northwell.edu

Background: Patients with Inflammatory Bowel Disease (IBD) are at an increased risk of developing colorectal cancer (CRC). While numerous studies have explored chemoprevention strategies in the general population, the specific roles of statins and aspirin in reducing CRC risk among IBD patients remain inconclusive.

Aim: This study aims to evaluate the effect of statins on CRC risk and investigates whether combining statins and aspirin further reduces CRC risk in this high-risk population.

Methods: We included 11,325 IBD patients from the Northwell Health Information Exchange (HIE) database (2008–2023). Demographic and clinical variables were collected. The primary endpoint was CRC development, while the secondary endpoint was the occurrence of any cancer. Multivariable logistic regression assessed the association between cancer development and statin use, adjusted for confounders. Subgroup analyses evaluated the combined effect of statins and aspirin compared to non-users and aspirin-only users. Statistical significance was defined as a p-value <0.05.

Results: Among 11,325 patients (mean age 65.1± 20.4 years, 54.5% females, 68% white), 2,809 (24.8%) used statins. Logistic regression analysis revealed that statin use was associated with lower odds of CRC, although it did not reach statistical significance (OR: 0.647, p = 0.0564). It was, however, significantly associated with a reduced risk of any cancer (OR: 0.630, p<0.0001). Furthermore, combining statins and aspirin significantly reduced the risk of CRC (OR: 0.163, p=0.0028) and any cancer (OR: 0.367, p<0.0001) compared to non-users. When compared to aspirin-only users, the statin-aspirin combination was associated with significantly lower odds of CRC (OR: 0.235, p=0.0289) and any cancer (OR: 0.522, p=0.0087).

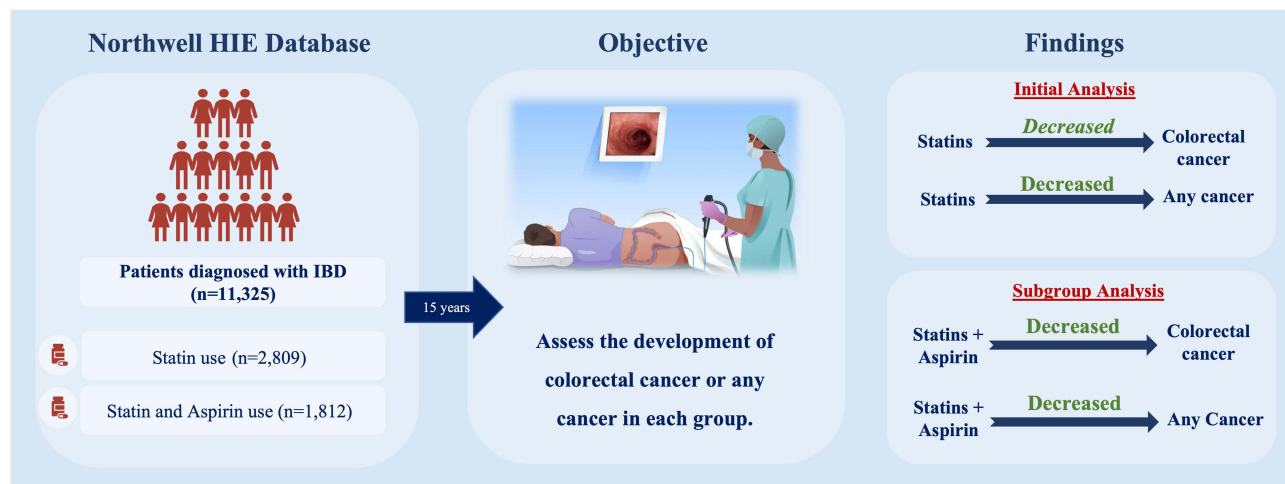
Conclusion: Statins are associated with a reduced risk of any cancer and a potential reduction in CRC in patients with IBD. The combination of statin-aspirin demonstrates a significant and synergistic protective effect, supporting its potential role in chemoprevention strategies for this high-risk population.

Keywords: statins, aspirin, chemoprevention, colorectal cancer, IBD

Introduction

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease and ulcerative colitis (UC), is a chronic disease marked by inflammation of the gastrointestinal (GI) tract. Patients with IBD face a significantly increased risk of colorectal cancer (CRC) compared to the general population, with a two to three-fold increased risk over time, especially in individuals with long-term disease or extensive colon involvement.^{1,2} Chronic inflammation, genetic factors, and dysregulation of immune responses play crucial roles in the development of CRC.³ In IBD, the chronically inflamed colonic microenvironment is characterized by

Graphical Abstract



increased oxidative stress, immune dysregulation, and cycles of epithelial injury and regeneration. These processes accelerate mutagenesis and dysplasia, ultimately progressing along the “inflammation–dysplasia–carcinoma” sequence rather than the classical adenoma–carcinoma pathway.⁴ This highlights the importance of targeting inflammation-driven mechanisms in chemopreventive strategies. Along with colorectal cancer, individuals with IBD are reported to face increased risks of other types of cancers, including small bowel adenocarcinoma, cholangiocarcinoma, and extraintestinal malignancies. This heightened cancer risk is attributed to chronic inflammation as well as prolonged immunosuppression therapies.⁵ Given this increased cancer risk, effective chemopreventive strategies are crucial for IBD patients.

Various chemopreventive agents have been studied for their potential to reduce the risk of several malignancies, particularly colorectal cancer (CRC), in the general population.⁶ Among the most encouraging agents are statins and aspirin. Statins, primarily known for their lipid-lowering effects, have demonstrated anti-inflammatory and anti-cancer effects through various mechanisms, including inhibiting mevalonate pathway enzymes, reduced cell proliferation, and increased apoptosis in cancerous cells.⁷ Several observational studies have reported an inverse association between statin use and cancer risk. For instance, a large cohort study demonstrated that statin use in the general population was associated with a 47% relative reduction in CRC risk after adjusting for known risk factors.^{8,9}

Conversely, aspirin, a commonly used nonsteroidal anti-inflammatory drug (NSAID), achieves its effects by inhibiting cyclooxygenase-1 and cyclooxygenase-2 (COX-2), enzymes that promote inflammation and carcinogenesis and are associated with increased tumor growth in several cancers, including CRC.¹⁰ Numerous studies have examined the effect of aspirin on preventing various types of cancer. However, the results are inconsistent; some research indicates a potential reduction in risk, where the association is most pronounced for esophageal, gastric, breast, and prostate cancer, while others show no significant association.¹¹ The data regarding colorectal cancer is more consistent, as several observational studies have reported an inverse association between aspirin use and CRC.¹²

When focusing on patients with IBD, the evidence regarding the efficacy of statin and aspirin exposure in cancer prevention remains controversial. Most studies have focused specifically on the risk of developing CRC rather than other types of cancer in this population, and as of today, there is no strong evidence supporting their routine use in this high-risk group. A limited number of studies indicate that statins could lower the risk of CRC in patients with IBD; however, the results have been inconsistent, and there is a lack of randomized controlled trials (RCTs) supporting their use.^{13,14} Similarly, although aspirin is known to reduce the risk of CRC in the general population, its effect on CRC development in patients with IBD remains unclear. Some studies suggest a benefit, while others show no significant impact.^{15,16}

The effect of the combined use of statins and aspirin for cancer prevention has not been thoroughly investigated in the general population. Most research has primarily focused on CRC prevention, with data that has been inconsistent.^{17,18} In patients with IBD, a high-risk population susceptible to cancer, this area remains as well understudied, with recent data suggesting promising results.¹⁹ Our study aims to investigate the impact of statins on cancer prevention, particularly CRC, in patients with IBD and assess whether the combination of statins and aspirin further reduces this risk.

Materials and Methods

Study Design and Participants

This is a multi-center retrospective observational study involving 11,325 patients aged ≥ 18 years diagnosed with IBD, identified from the Northwell Health Information Exchange (HIE) database between January 2008 and December 2023. The diagnosis of IBD was identified using the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) codes. Patients were excluded from the study if they had a documented diagnosis of colorectal cancer (CRC) or any other type of malignancy at the time of IBD diagnosis. Additional exclusion criteria included incomplete clinical data, such as missing follow-up encounters, absent medication or prescription records, or insufficient details on medication dispensing, which would preclude accurate determination of statin or aspirin use during the observation period. Demographic and clinical variables were collected at the time of IBD diagnosis, including age, gender, race, body mass index (BMI), tobacco use, alcohol use, type of IBD (Crohn's disease or ulcerative colitis), comorbidities such as hypertension, dyslipidemia, and diabetes, and IBD treatments including immunosuppressive therapy and biologics.

Exposure Definitions and Outcomes Assessment

Statins exposure was evaluated using prescription records from the database. Patients were identified as statin users if they had received at least a prescription for statins for 6 months. Similarly, aspirin use was recorded based on prescription data, with patients classified as aspirin users if they had at least a documented prescription for 6 months. The combined impact of statins and aspirin was analyzed by dividing patients into three groups: users of both statins and aspirin, aspirin-only users, and non-users.

Patient records were reviewed over a 15-year observation period, with follow-up extending from the date of IBD diagnosis until the earliest occurrence of one of the following events: a first diagnosis of cancer, death, or the last available follow-up date (December 31, 2023). The primary outcome was the incidence of colorectal cancer (CRC) during the follow-up period. The secondary outcome was the occurrence of any malignancy. Cancer diagnoses were ascertained using ICD-9 and ICD-10 codes documented in the electronic medical records database.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the cohort. Continuous variables are reported as mean $\pm$ standard deviation (SD), and categorical variables as frequencies and percentages. Comparisons between the statin-user and non-user groups were performed using the Student's *t*-test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate. The primary analysis involved multivariable logistic regression to assess the association between statin use and colorectal cancer (CRC) development, adjusting for potential confounders. The same model was applied to the secondary outcome, the development of any type of cancer, to evaluate the association between statin use and overall cancer risk in the cohort. A subgroup analysis based on the type of IBD assessed the association between statin exposure and the primary and secondary outcomes in patients with Crohn's disease and ulcerative colitis. Additionally, another subgroup analysis examined the combined effect of statins and aspirin on cancer prevention compared to non-users and aspirin-only users. Sensitivity analyses were conducted using multiple imputation methods to address missing data (eg, tobacco, alcohol use), where appropriate. All statistical tests were two-sided, with a significance level of $p < 0.05$. Analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).

Ethical Considerations

This study received approval from the Institutional Review Board of Northwell Health (24–0319-SIUHN) and was conducted in accordance with the principles of the Declaration of Helsinki. Individual informed consent was waived because the study was register-based and utilized de-identified patient data.

Results

Among the 11,325 patients included in the analysis, the mean age was 65.1 ± 20.4 years, 54.5% were females, and 68% were white. Of these, 44.2% had Crohn's disease, and 55.8% had ulcerative colitis. Statins were used by 2,809 patients (24.8%), while 8,516 (75.2%) were non-users. Additionally, 23.6% were on aspirin. Dyslipidemia was present in 21.7% of the total cohort and was substantially more common among statin users compared to non-users (66.2% vs 7.1%). Additional baseline characteristics of the study population, along with corresponding p-values, are reported in Table 1.

Table 1 Demographic and Clinical Characteristics

Variable	Total Population (N = 11325)		No Statin Use (N = 8516)		Statin Use (N = 2809)		p-value
Age	65.11	20.37	59.2	17.99	86.68	12.29	< 0.001
Sex							< 0.0001
Female	6171	54.49%	4722	55.45%	1449	51.58%	
Male	5154	45.51%	3794	44.55%	1360	48.42%	
Race							< 0.0001
Black	1228	10.84%	957	11.24%	271	9.65%	
White	7702	68.01%	5668	66.56%	2034	72.41%	
Asian	515	4.55%	372	4.37%	143	5.09%	
Others	1880	16.60%	1519	17.83%	361	12.85%	
Obesity	795	7.02%	446	5.24%	349	12.42%	< 0.0001
Alcohol Use							0.17
Alcohol use	120	1.06%	76	0.89%	44	1.57%	
Former	11	0.10%	7	0.08%	4	0.14%	
Occasional	208	1.84%	153	1.80%	55	1.96%	
No alcohol use	1757	15.51%	1168	13.72%	589	20.97%	
Tobacco Use							< 0.0001
Current	737	6.51%	568	6.67%	169	6.02%	
Former	1657	14.63%	1016	11.93%	641	22.82%	
Never	6556	57.89%	5013	58.87%	1543	54.93%	
Dyslipidemia	2462	21.74%	603	7.08%	1859	66.18%	< 0.001
Crohn's Disease	5005	44.19%	4032	47.35%	973	34.64%	< 0.0001
Ulcerative Colitis	6320	55.81%	4484	52.65%	1836	65.36%	< 0.0001
Aspirin	2678	23.65%	866	10.17%	1812	64.51%	< 0.0001

(Continued)

Table 1 (Continued).

Variable	Total Population (N = 11325)		No Statin Use (N = 8516)		Statin Use (N = 2809)		p-value
Colorectal Cancer	202	1.78%	125	1.47%	77	2.74%	< 0.0001
Any Cancer Type	979	8.64%	562	6.60%	417	14.85%	< 0.0001

Notes: Values are expressed as mean (SD) or n (%).

Table 2 Association Between Statin Use and Risk of Cancer in Patients with IBD

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Colorectal Cancer	0.647	0.414–1.012	0.0564
Any cancer	0.630	0.500–0.794	<0.0001

Notes: Odds ratios represent the association of statin use (vs non-use) with cancer outcomes in IBD patients. Multivariable logistic regression models were adjusted for gender, age, obesity, race, tobacco, and alcohol usage. P-values <0.05 were considered statistically significant.

Multivariable logistic regression was performed to evaluate the association between statin use and the risk of cancer development while adjusting for potential confounders, including age, gender, obesity, race, tobacco, and alcohol use. Although the crude prevalence of CRC was higher among statin users (2.74% vs 1.47%), statin users were older and had more comorbidities compared to nonusers. After multivariable adjustment for these confounders, statin use was associated with 35% lower odds of developing CRC compared to non-users (OR: 0.647, 95% CI: 0.41–1.01, $p = 0.0564$); however, this was not statistically significant. Statin use was significantly associated with a 37% reduction in the risk of developing any cancer (OR: 0.63, 95% CI: 0.50–0.79, $p < 0.0001$) (Table 2).

Subgroup Analysis

Subgroup analyses were conducted based on aspirin use and IBD subtype, Crohn's disease vs ulcerative colitis, to further examine the association between statin use and cancer development. These analyses aimed to evaluate whether the protective effect of statins differed across various patient groups. Adjusted odds ratios, 95% confidence intervals, and p -values for all subgroup analyses are presented in Tables 3–6 and summarized in Figure 1.

Statin Use in Crohn's Disease

This analysis evaluated whether the impact of statins on cancer risk varied among patients with Crohn's disease. After adjusting for gender, age, obesity, race, tobacco, and alcohol usage in patients with Crohn's, statin users had 48% lower odds of developing colorectal cancer compared to non-users (OR: 0.524; 95% CI: 0.27–1.02, $p = 0.0568$), which was not

Table 3 Association Between Statin Use and Risk of Cancer in Patients with Crohn's Disease

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Colorectal Cancer	0.524	0.270–1.019	0.0568
Any cancer	0.509	0.352–0.736	0.0003

Notes: Odds ratios represent the association of statin use (vs non-use) with cancer outcomes in patients with Crohn's Disease. Multivariable logistic regression models were adjusted for gender, age, obesity, race, tobacco and alcohol usage. P-values <0.05 were considered statistically significant.

Table 4 Association Between Statin Use and Risk of Cancer in Patients with Ulcerative Colitis

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Colorectal Cancer	0.745	0.407–1.362	0.3389
Any cancer	0.726	0.543–0.970	0.0304

Notes: Odds ratios represent the association of statin use (vs non-use) with cancer outcomes in patients with Ulcerative Colitis. Multivariable logistic regression models were adjusted for gender, age, obesity, race, tobacco, and alcohol usage. *P*-values <0.05 were considered statistically significant.

Table 5 Association Between Statin Plus Aspirin Use and Risk of Cancer in Patients with IBD

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Colorectal Cancer	0.163	0.050–0.537	0.0028
Any cancer	0.367	0.239–0.563	<0.0001

Notes: Odds ratios represent the association of statin plus aspirin use (vs non-use) with cancer outcomes in IBD patients. Multivariable logistic regression models were adjusted for gender, age, obesity, race, tobacco, and alcohol usage. *P*-values <0.05 were considered statistically significant.

Table 6 Association Between Statin Plus Aspirin Use Compared to Aspirin-Only Use and Risk of Cancer in Patients with IBD

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Colorectal Cancer	0.235	0.064–0.861	0.0289
Any cancer	0.522	0.321–0.848	0.0087

Notes: Odds ratios represent the association of statin plus aspirin use (vs aspirin-only use) with cancer outcomes in IBD patients. Multivariable logistic regression models were adjusted for gender, age, obesity, race, tobacco, and alcohol usage. *P*-values <0.05 were considered statistically significant.

statistically significant. Statin users had a significant 49% lower odds of developing any type of cancer than non-users (OR: 0.509; 95% CI: 0.35–0.74, *p*=0.0003) (Table 3).

Statin Use in Ulcerative Colitis

The association between statin use and cancer risk was evaluated separately in patients with ulcerative colitis. After adjusting for gender, age, obesity, race, tobacco, and alcohol usage in patients with ulcerative colitis, statin users were 25% less likely to develop colorectal cancer compared to those not exposed (OR: 0.745, 95% CI: 0.41–1.36, *p*=0.3389), though this was not statistically significant. Statin use was, however, significantly associated with a 27% reduction in the risk of developing any cancer compared to non-users (OR: 0.726, 95% CI: 0.54–0.97, *p*=0.0304) (Table 4).

Combined Use of Statin and Aspirin Versus Non-Use

This comparison evaluated whether the combined use of statins and aspirin provided greater protection against CRC than non-use. After adjusting for gender, age, obesity, race, tobacco and alcohol usage, patients who were exposed to statin plus aspirin were significantly (84%) less likely to develop colorectal cancer compared to non-users (OR: 0.163, 95% CI: 0.05–0.54, *p*=0.0028). Similarly, patients who were exposed to statin plus aspirin were significantly (63%) less likely to develop any cancer compared to those who were not exposed (OR: 0.367, 95% CI: 0.24–0.56, *p*<0.0001) (Table 5).

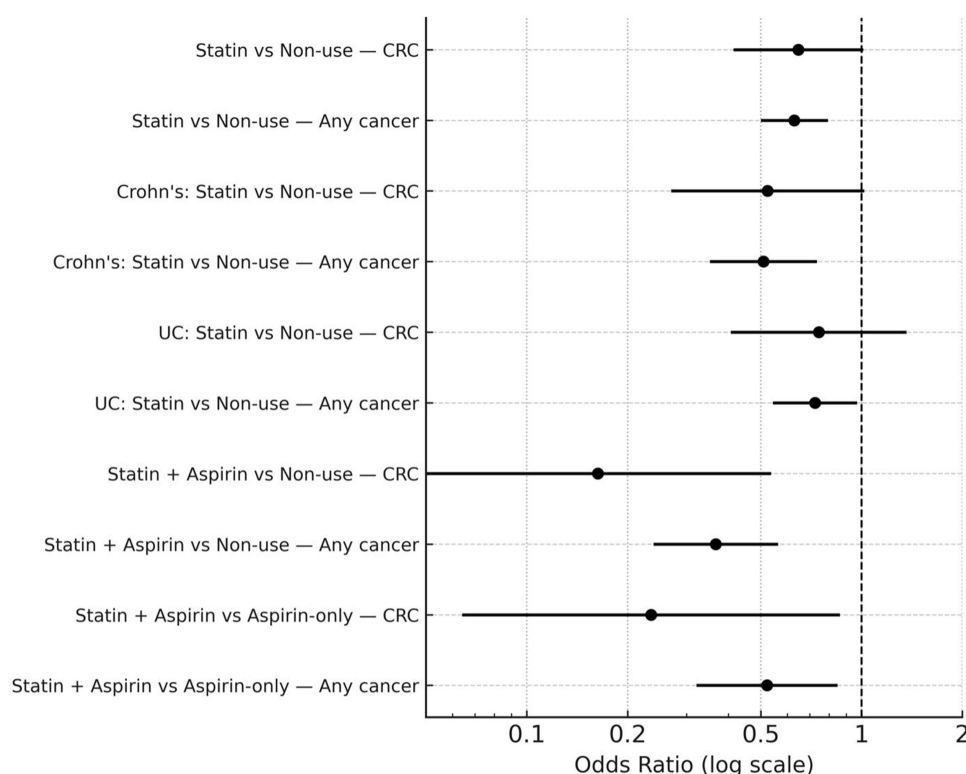


Figure 1 Forest Plot: Cancer Risk in IBD (Statin and Aspirin Use). Adjusted odds ratios (points) and 95% confidence intervals (horizontal lines) for colorectal cancer (CRC) and any cancer across prespecified contrasts on a logarithmic scale. All models were adjusted for age, sex, obesity, race, tobacco use, and alcohol use. The vertical dashed line denotes an odds ratio of 1.0 (no association).

Figure 1 presents a graphical representation of the cancer risk reduction observed in our cohort, along with the corresponding confidence intervals.

Combined Use of Statin and Aspirin Versus Use of Aspirin Alone

This comparison assessed whether adding statins to aspirin therapy provided additional protection against the development of colorectal cancer (CRC) compared to aspirin use alone. After adjusting for gender, age, obesity, race, tobacco and alcohol usage, patients exposed to both statins and aspirin were significantly (76%) less likely to develop CRC than patients exposed only to aspirin (OR: 0.235, 95% CI: 0.06–0.86, $p=0.0289$). Furthermore, patients who took statins and aspirin were significantly (48%) less likely to develop any cancer than those exposed only to aspirin (OR: 0.522, 95% CI: 0.32–0.85, $p=0.0087$) (Table 6).

Discussion

In this large, multicenter observational study involving a cohort of 11,325 patients diagnosed with IBD, we investigated the impact of statins on cancer prevention, specifically CRC, and whether the combined administration of statins and aspirin leads to an additional reduction in this risk. Inflammation-driven mutagenesis, increased reactive oxygen species, and cycles of epithelial regeneration are central to the pathogenesis of IBD-associated CRC. These factors underscore the rationale for targeting inflammation-mediated pathways with agents such as statins and aspirin. In our study, statin use was associated with a lower risk of CRC, but this finding did not reach statistical significance. Notably, it was significantly linked to a reduced overall cancer incidence, suggesting a promising chemopreventive potential. These results align with previous reports. Subgroup analyses showed that this protective trend was consistent across IBD subtypes, with a particularly notable reduction observed among patients with Crohn's disease compared to Ulcerative Colitis. Our findings also showed a significant protective effect of statins in combination with aspirin for all types of cancer, including CRC. This enhanced reduction in cancer risk observed with the combined use of statins and aspirin

suggests a potential synergistic effect, highlighting their role in prevention strategies for this high-risk population, given the common concurrent use of both medications.

Mechanism of Action of Statins and Aspirin in Cancer Prevention

The observed associations between statin and aspirin use and reduced cancer risk in IBD patients in our study are supported by biological mechanisms that can potentially explain their chemopreventive effects. Statins inhibit HMG-CoA reductase, a rate-limiting enzyme in the mevalonate pathway that generates essential compounds for cellular functions, including membrane integrity, cell signaling, protein synthesis, and cell cycle regulation. Disruption of these functions in cancer cells could affect tumor initiation, growth, and metastasis.²⁰ Statins may also hinder cell adhesion and angiogenesis, exert antioxidant effects, and diminish inflammation. Furthermore, they downregulate and inhibit matrix metalloproteinases, thereby reducing the risk of cancer cell invasion and metastasis.^{21,22}

On the other hand, aspirin exerts anti-cancer effects through multiple mechanisms beyond its well-known inhibition of cyclooxygenase (COX). It influences cancer progression by modulating energy metabolism, inflammation, and platelet-driven pro-carcinogenic activity. Additionally, aspirin plays a role in DNA repair, particularly in colorectal cancer, by reducing microsatellite instability, a key feature of Lynch syndrome and other cancers.²³ The cellular effects of both agents suggest their potential as chemopreventive agents in cancer prevention. To visually summarize these mechanisms, we have included a schematic diagram illustrating the anti-inflammatory and anti-carcinogenic pathways of statins and aspirin (Figures 2 and 3).

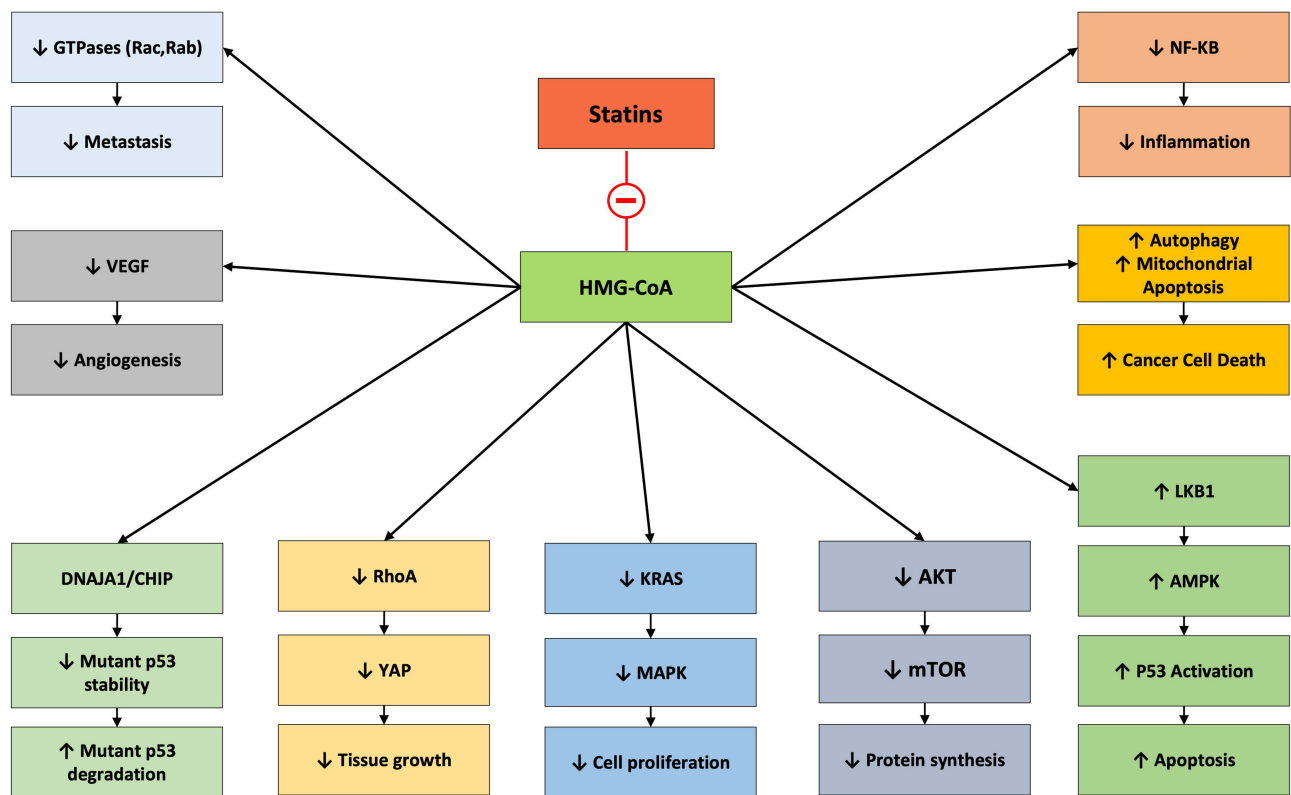


Figure 2 Mechanistic Pathways of Statins in Cancer Prevention. Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, thereby reducing downstream intermediates of the mevalonate pathway. This inhibition exerts pleiotropic anticancer effects through multiple mechanisms: suppression of GTPases (Rac, Rab) decreases metastasis; downregulation of vascular endothelial growth factor (VEGF) reduces angiogenesis; inhibition of RhoA, KRAS, MAPK, AKT, and mTOR signaling leads to reduced tissue growth, cell proliferation, and protein synthesis; and activation of DNAJA1/CHIP promotes degradation of mutant p53. Additional effects include decreased NF-κB activity with consequent reduction in inflammation, induction of autophagy and mitochondrial apoptosis leading to increased cancer cell death, and activation of LKB1-AMPK signaling resulting in p53 activation and apoptosis. Collectively, these pathways highlight the multifaceted role of statins in modulating tumor biology and promoting cancer cell death.

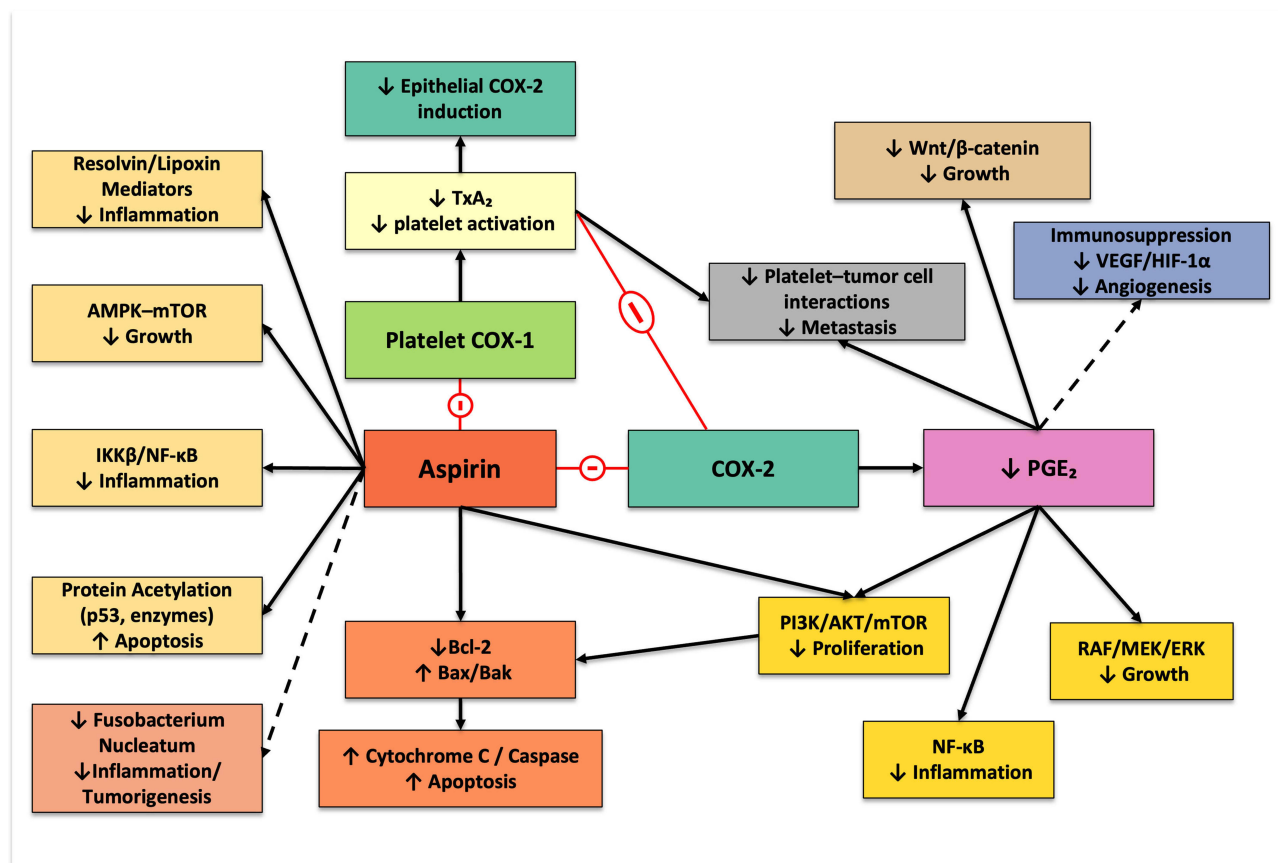


Figure 3 Molecular Mechanisms of Aspirin in Cancer Prevention. Aspirin inhibits platelet cyclooxygenase-I (COX-I), resulting in decreased thromboxane A₂ (TxA₂), decreased cyclooxygenase-2 (COX-2), reduced platelet activation, and impaired platelet–tumor cell interactions, thereby limiting metastasis. Suppression of COX-2–derived prostaglandin E₂ (PGE₂) reduces Wnt/β-catenin, PI3K/AKT/mTOR, RAF/MEK/ERK, and NF-κB signaling, attenuating proliferation, growth, angiogenesis, and inflammation. Aspirin also promotes apoptosis through downregulation of Bcl-2, upregulation of Bax/Bak, cytochrome c/caspase activation, and protein acetylation of p53 and other enzymes. Additional effects include modulation of AMPK–mTOR signaling, increased resolvin/lipoxin production, and suppression of Fusobacterium nucleatum–driven tumorigenesis. Together, these mechanisms highlight aspirin’s broad role in restraining tumor progression and enhancing cancer cell death.

Statins and Cancer Prevention

Existing literature on statins and overall cancer prevention remains inconclusive, with most studies conducted on the general population focusing on the esophagus, liver, prostate, breast, and pancreatic cancers.^{24–26} A meta-analysis by Singh et al showed a significant reduction in esophageal cancer risk among statin users, particularly in patients with Barrett’s esophagus.²⁷ Similarly, another meta-analysis by Singh et al reported a reduced risk of hepatocellular carcinoma among statin users, with a more pronounced effect observed in Asian populations.²⁸ Another meta-analysis by Zhang et al suggested that statins have a protective effect on pancreatic cancer.²⁹ Furthermore, Bansal D. et al, in their meta-analysis on statin use and prostate cancer, concluded that there was a reduced relative risk of prostate cancer in statin users compared to non-users.³⁰ Conversely, a meta-analysis evaluating statin and breast cancer reported that there is no association between statin use and breast cancer risk.³¹

In the IBD population, the literature is scarce, with most studies focusing on CRC rather than other types of cancer. Only one Chinese cohort investigated the effect of statins on cancer prevention in patients with IBD who have received one or more prescriptions of 5-aminosalicylic acid (5-ASA), showing that statin use was not significantly associated with a reduced risk of cancer development, with an adjusted hazard ratio of 0.48 and a 95% confidence interval (CI) of 0.14–1.59, indicating no statistically significant protective effect.³²

Existing literature on statins and cancer prevention, especially in IBD patients, has been limited and often inconclusive. By showing a significant reduction in overall cancer risk with statin use in our large IBD cohort, our study provides much-needed clarity and adds meaningful evidence to a sparsely studied area.

Statins and Colorectal Cancer Prevention

Multiple observational studies suggest that statin use may lower CRC risk, particularly for individuals with a history of colorectal adenomas or those at higher risk for cancer.^{9,33} Multiple meta-analyses have also supported these findings, including a meta-analysis of 40 studies by Lytras et al showing a reduction of CRC risk; however, this was more pronounced in observational studies than randomized controlled trials (RCTs).³⁴ Another meta-analysis by Liu et al also found similar results, indicating that statin use is associated with a lower risk of colorectal cancer, especially for lipophilic statins.³⁵ RCTs have yielded inconsistent results, with some RCTs indicating a slight protective effect while others showed no significant association between statin use and CRC risk reduction in the general population.⁸

Patients with IBD are at an increased risk of developing colorectal cancer (CRC); however, research specifically addressing the chemopreventive role of statins in this at-risk population remains scarce. Some studies suggest that statins may reduce CRC risk in IBD patients by affecting the inflammatory responses associated with the condition.^{36,37} While recent studies have emerged with promising results, the evidence lacks consistency. There is still paucity of large, prospective studies that clearly demonstrate the benefits of statins for preventing CRC in patients with IBD.^{9,14,38,39} Notably, in a case-control study by Poynter et al, statin use was associated with a reduction in CRC development, and this association was even more pronounced in patients with IBD.⁹ A recent meta-analysis by Li et al demonstrated a significantly lower risk of CRC among statin users compared to non-users in IBD patients.⁴⁰ Given the focus on CRC within the IBD population, our current study findings build on prior mixed evidence by showing a meaningful reduction in CRC risk with statin use, especially in Crohn's disease.

Aspirin and Cancer Prevention

Aspirin, recognized as a potential cancer preventive agent, has garnered increasing interest, with new research exploring its beneficial effects. Song Y. et al reported that aspirin showed potential preventive effects on certain cancers, with the strongest evidence for aspirin's impact on esophageal squamous cell carcinoma and highly suggestive evidence supporting aspirin's role in reducing overall cancer risk, breast cancer, non-cardia gastric cancer, and prostate cancer.⁴¹ Recently, Skriver et al suggest that particularly the long-term use of aspirin is associated with a decreased risk for several cancers, including colon, rectum, esophagus, stomach, liver, pancreas, small intestine, head and neck, brain tumors, meningioma, melanoma, thyroid, non-Hodgkin lymphoma, and leukemia.⁴²

This chemopreventive effect has not been studied extensively in IBD patients, with the majority of the studies focused on CRC specifically. The previously mentioned Chinese cohort study by Mak et al also investigated aspirin use in cancer prevention in IBD patients on 5-ASA, showing no significant association. This smaller retrospective study, including only 1,891 patients treated with 5-aminosalicylic acid (5-ASA), aspirin, or statins, reported no significant benefit of adding statins or aspirin in reducing overall cancer risk.³² However, this study's limited sample size, narrow demographic focus, and retrospective design limit the generalizability of its findings.

Aspirin and Colorectal Cancer Prevention

Aspirin has been linked to a lower risk of CRC in the general population, particularly among individuals with increased cardiovascular risk or chronic inflammatory conditions.⁴³ It has consistently been shown that regular aspirin use is associated with a reduced incidence of CRC, with a dose-dependent relationship and long-term use proving more effective.⁴⁴⁻⁴⁷ Frampton M. et al suggested that a prevention model combining aspirin use and lifestyle changes can significantly prevent CRC development in the general population.⁴⁸ Aspirin use after CRC diagnosis is linked to improved survival, with a meta-analysis of 27 studies comprising 237,245 patients showing a 26% reduction in cancer-related deaths. Patients with high cox-2 expression and the pik3ca mutation experienced even greater benefits, suggesting that genetic factors influence aspirin effectiveness.⁴⁹ These findings suggest that aspirin's therapeutic effects may extend beyond cancer prevention to improve survival outcomes in CRC patients.

In contrast, literature specifically addressing aspirin's effectiveness in reducing CRC risk among IBD patients has produced conflicting evidence. Chronic inflammation in IBD is linked to elevated cox-2 expression, potentially contributing to carcinogenesis. Therefore, aspirin's capacity to inhibit cox-2 might theoretically lower CRC rates in these patients.⁵⁰ However, the evidence is still very limited. An observational study showed that aspirin use was

associated with a 70% decrease in the risk of developing CRC in patients with ulcerative colitis.⁵¹ Conversely, another study by Eaden et al showed no significant reduction in the risk of CRC in aspirin users compared to non-users in ulcerative colitis patients.⁵² Notably, a more recent meta-analysis by Burr et al concluded that due to high studies heterogeneity, being small retrospective studies, and the lack of high-quality evidence in the IBD population, their findings did not demonstrate any significant benefit from aspirin or other NSAIDs in preventing IBD-associated CRC.¹⁵ Based on the discussed literature, our current study findings strengthen the argument for aspirin's chemopreventive benefit in IBD by demonstrating a notable reduction in CRC risk among aspirin users when combined with statins. This suggests that aspirin may play a meaningful role in CRC prevention in this high-risk group and opens the door to exploring potential synergistic effects when combined with statins.

Combination Therapy: Statins and Aspirin

In clinical practice, aspirin and statins are often prescribed together. Their concomitant use, they may target multiple carcinogenic pathways through different mechanisms, enhancing chemopreventive efficacy.⁵³ A biomarker-based pharmacodynamic study by Gottschall H. et al showed that participants using combined aspirin and statins had a more pronounced suppression of COX-derived eicosanoids than those on aspirin alone. This finding points to a potential synergistic effect between the two drugs in reducing eicosanoid formation, possibly contributing to CRC prevention.⁵⁴ Several observational studies in the general population have examined the impact of combined statin and aspirin use on cancer risk across different malignancies. A case-control study reported a stronger reduction in gallbladder cancer risk with dual therapy.⁵⁵ While Cho et al observed a modest attenuation of gastric cancer risk when adjusting for concurrent use of statin, aspirin, and metformin,⁵⁶ a large case-control study by Wang et al reported that the combination of statin and aspirin indicated a significantly decreased overall risk of all cancers. However, the exact percentage varies depending on the cancer type and duration of use.⁵⁷ Similarly, a retrospective cohort among individuals with systemic inflammatory diseases found that consistent use of aspirin and statins was linked to a significantly reduced incidence of various cancers, including colorectal, breast, and lung cancer.¹⁹ These findings suggest a potential chemopreventive role for aspirin and statins in high-risk populations characterized by chronic inflammation, potentially including patients with IBD.

Yet, despite statin and aspirin being potential chemopreventive agents for colorectal cancer, this combination was scarcely studied, especially in patients with IBD. In a German case-control study, Hoffmeister M. et al found that using low-dose aspirin in combination with statins reduced the risk by 62% after five or more years (OR 0.38, 95% CI 0.15–0.97). This combinational use of low-dose aspirin and statins may offer greater risk reduction than using either drug alone for at least 5 years.¹⁵

Our current study builds on this limited yet promising evidence to specifically evaluate the combined impact of statins and aspirin in a large cohort of patients with IBD. We show that concurrent use of statins and aspirin is associated with a significant 84% reduction in CRC risk and a 63% reduction in overall cancer risk among IBD patients, which is markedly greater than the effects of either agent alone. These findings highlight a potential synergistic effect and have important clinical implications. Given the routine use of statins and aspirin in patients with cardiovascular comorbidities, their potential dual benefit in cancer prevention, particularly in a high-risk, chronically inflamed population such as IBD, warrants serious consideration in preventive care strategies and future guideline development.

Limitations

Our study has some limitations that merit consideration. First, its retrospective observational design is subject to inherent biases and confounding that cannot be fully excluded despite adjustment for key demographic and clinical variables. Second, medication exposure was defined based on prescription records, which lacked precise adherence, dosage data, or duration, potentially affecting the accuracy of the exposure definition. Third, detailed information on IBD duration and severity was not consistently available, which could influence outcomes and limit our ability to fully adjust for all potential confounders. Additionally, LDL values were not available in our dataset, which might have limited our ability to fully account for potential prescription bias in statin users. Some variables, including tobacco and alcohol use, were incompletely captured. Although we applied multiple imputation to reduce bias, residual misclassification cannot be

excluded. Despite these limitations, the large sample size, multi-center nature, and consistency of associations across subgroups strengthen the validity of our findings.

Conclusion

Statin use is associated with a reduced risk of any cancer and a potential reduction in the risk of colorectal cancer in patients with inflammatory bowel disease. The combination of statin and aspirin demonstrates a significant and synergistic protective effect. These findings suggest significant implications for cancer prevention strategies. Future prospective studies and randomized controlled trials are needed to confirm the chemopreventive role of statins and aspirin in patients with IBD, clarify optimal dosing strategies, and better define patient populations that may benefit most from such interventions.

Data Sharing Statement

Data of the current study is available from the corresponding author upon reasonable request.

Ethics Approval

This study received approval from the Institutional Review Board of Northwell Health (24-0319-SIUHN).

Consent

Individual informed consent was waived because the study was register-based and utilized de-identified patient data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare that are relevant to the content of this article.

References

1. Eaden JA. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001;48(4):526–535. doi:10.1136/gut.48.4.526
2. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of colorectal cancer in patients with ulcerative colitis: a meta-analysis of population-based cohort studies. *Clin Gastroenterol Hepatol*. 2012;10(6):639–645. doi:10.1016/j.cgh.2012.01.010
3. Itzkowitz SH, Yio XI, Cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol-Gastrointest Liver Physiol*. 2004;287(1):G7–17. doi:10.1152/ajpgi.00079.2004
4. Porter RJ, Arends MJ, Churchhouse AMD, Din S. Inflammatory bowel disease-associated colorectal cancer: translational risks from mechanisms to medicines. *J Crohns Colitis*. 2021;15(12):2131–2141. doi:10.1093/ecco-jcc/jjab102
5. Laredo V, García-Mateo S, Martínez-Domínguez SJ, López de la Cruz J, Gargallo-Puyuelo CJ, Gomollón F. Risk of cancer in patients with inflammatory bowel diseases and keys for patient management. *Cancers*. 2023;15(3):871. doi:10.3390/cancers15030871
6. Dunn BK, Umar A, Richmond E. Introduction: cancer chemoprevention and its context. *Semin Oncol*. 2016;43(1):19–21. doi:10.1053/j.seminoncol.2015.11.002
7. Zaky MY, Fan C, Zhang H, Sun XF. Unraveling the anticancer potential of statins: mechanisms and clinical significance. *Cancers*. 2023;15(19):4787. doi:10.3390/cancers15194787
8. Lochhead P, Chan AT. Statins and colorectal cancer. *Clin Gastroenterol Hepatol*. 2013;11(2):109–118. doi:10.1016/j.cgh.2012.08.037
9. Poynter JN, Gruber SB, Higgins PDR, et al. Statins and the risk of colorectal cancer. *N Engl J Med*. 2005;352(21):2184–2192. doi:10.1056/NEJMoa043792
10. Sankaranarayanan R, Kumar DR, Altinoz MA, Bhat GJ. Mechanisms of colorectal cancer prevention by aspirin—a literature review and perspective on the role of COX-dependent and -independent pathways. *Int J Mol Sci*. 2020;21(23):9018. doi:10.3390/ijms21239018
11. Elwood PC, Pickering JE, Morgan G, et al. Systematic review update of observational studies further supports aspirin role in cancer treatment: time to share evidence and decision-making with patients? *PLoS One*. 2018;13(9):e0203957. doi:10.1371/journal.pone.0203957

12. Ma S, Han T, Sun C, et al. Does aspirin reduce the incidence, recurrence, and mortality of colorectal cancer? A meta-analysis of randomized clinical trials. *Int J Colorectal Dis.* 2021;36(8):1653–1666. doi:10.1007/s00384-021-03889-8
13. Ananthakrishnan AN, Cagan A, Cai T, et al. Statin use is associated with reduced risk of colorectal cancer in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2016;14(7):973–979. doi:10.1016/j.cgh.2016.02.017
14. Sun J, Halfvarson J, Bergman D, et al. Statin use and risk of colorectal cancer in patients with inflammatory bowel disease. *eClinicalMedicine.* 2023;63:102182. doi:10.1016/j.eclinm.2023.102182
15. Burr NE, Hull MA, Subramanian V. Does aspirin or non-aspirin non-steroidal anti-inflammatory drug use prevent colorectal cancer in inflammatory bowel disease? *World J Gastroenterol.* 2016;22(13):3679–3686. doi:10.3748/wjg.v22.i13.3679
16. Chan EP, Lichtenstein GR. Chemoprevention: risk reduction with medical therapy of inflammatory bowel disease. *Gastroenterol Clin North Am.* 2006;35(3):675–712. doi:10.1016/j.gtc.2006.07.003
17. Shadman M, Newcomb PA, Hampton JM, Wernli KJ, Trentham-Dietz A. Non-steroidal anti-inflammatory drugs and statins in relation to colorectal cancer risk. *World J Gastroenterol.* 2009;15(19):2336. doi:10.3748/wjg.15.2336
18. Hoffmeister M, Chang-Claude J, Brenner H. Individual and joint use of statins and low-dose aspirin and risk of colorectal cancer: a population-based case-control study. *Int J Cancer.* 2007;121(6):1325–1330. doi:10.1002/ijc.22796
19. Lin JR, Han DD, Wei W, et al. Regular use of aspirin and statins reduces the risk of cancer in individuals with systemic inflammatory diseases. *Cancer Res.* 2024;84(11):1889–1897. doi:10.1158/0008-5472.CAN-23-2941
20. Wong WWL, Dimitroulakos J, Minden M, Penn L. HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumor-specific apoptosis. *Leukemia.* 2002;16(4):508–519. doi:10.1038/sj.leu.2402476
21. Zhu Z, Cao Y, Liu L, Zhao Z, Yin H, Wang H. Atorvastatin regulates the migration and invasion of prostate cancer through the epithelial-mesenchymal transformation and matrix metalloproteinase pathways. *Investig Clin Urol.* 2022;63(3):350. doi:10.4111/icu.20210411
22. Mannello F, Tonti GA. Statins and breast cancer: may matrix metalloproteinase be the missing link. *Cancer Invest.* 2009;27(4):466–470. doi:10.1080/07357900802491444
23. Elwood P, Morgan G, Watkins J, et al. Aspirin and cancer treatment: systematic reviews and meta-analyses of evidence: for and against. *Br J Cancer.* 2024;130(1):3–8. doi:10.1038/s41416-023-02506-5
24. Chen Z, Wu P, Wang J, Chen P, Fang Z, Luo F. The association of statin therapy and cancer: a meta-analysis. *Lipids Health Dis.* 2023;22(1):192. doi:10.1186/s12944-023-01955-4
25. Boudreau DM, Yu O, Johnson J. Statin use and cancer risk: a comprehensive review. *Expert Opin Drug Saf.* 2010;9(4):603–621. doi:10.1517/14740331003662620
26. Browning DRL, Martin RM. Statins and risk of cancer: a systematic review and metaanalysis. *Int J Cancer.* 2007;120(4):833–843. doi:10.1002/ijc.22366
27. Singh S, Singh AG, Singh PP, Murad MH, Iyer PG. Statins are associated with reduced risk of esophageal cancer, particularly in patients with Barrett's esophagus: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol.* 2013;11(6):620–629. doi:10.1016/j.cgh.2012.12.036
28. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Statins are associated with a reduced risk of hepatocellular cancer: a systematic review and meta-analysis. *Gastroenterology.* 2013;144(2):323–332. doi:10.1053/j.gastro.2012.10.005
29. Zhang Y, Liang M, Sun C, et al. Statin use and risk of pancreatic cancer: an updated meta-analysis of 26 studies. *Pancreas.* 2019;48(2):142–150. doi:10.1097/MPA.0000000000001226
30. Bansal D, Undela K, D'Cruz S, Schifano F. Statin use and risk of prostate cancer: a meta-analysis of observational studies. *PLoS One.* 2012;7(10):e46691. doi:10.1371/journal.pone.0046691
31. MdM I, Yang HC, Nguyen PA, et al. Exploring association between statin use and breast cancer risk: an updated meta-analysis. *Arch Gynecol Obstet.* 2017;296(6):1043–1053. doi:10.1007/s00404-017-4533-3
32. Mak JWY, So J, Tang W, et al. Cancer risk and chemoprevention in Chinese inflammatory bowel disease patients: a population-based cohort study. *Scand J Gastroenterol.* 2020;55(3):279–286. doi:10.1080/00365521.2020.1731760
33. Bonovas S, Filioussi K, Flordellis CS, Sitaras NM. Statins and the risk of colorectal cancer: a meta-analysis of 18 studies involving more than 1.5 million patients. *J Clin Oncol.* 2007;25(23):3462–3468. doi:10.1200/JCO.2007.10.8936
34. Lytras T. Statins and the risk of colorectal cancer: an updated systematic review and meta-analysis of 40 studies. *World J Gastroenterol.* 2014;20(7):1858. doi:10.3748/wjg.v20.i7.1858
35. Liu Y, Tang W, Wang J, et al. Association between statin use and colorectal cancer risk: a meta-analysis of 42 studies. *Cancer Causes Control.* 2014;25(2):237–249. doi:10.1007/s10552-013-0326-6
36. Cho S, Kim JS, Kim JM, Lee JY, Jung HC, Song IS. Simvastatin induces apoptosis in human colon cancer cells and in tumor xenografts, and attenuates colitis-associated colon cancer in mice. *Int J Cancer.* 2008;123(4):951–957. doi:10.1002/ijc.23593
37. Lee JY, Kim JS, Kim JM, Kim N, Jung HC, Song IS. Simvastatin inhibits NF- κ B signaling in intestinal epithelial cells and ameliorates acute murine colitis. *Int Immunopharmacol.* 2007;7(2):241–248. doi:10.1016/j.intimp.2006.10.013
38. Samadder NJ, Mukherjee B, Huang S, et al. Risk of colorectal cancer in self-reported inflammatory bowel disease and modification of risk by statin and NSAID use. *Cancer.* 2011;117(8):1640–1648. doi:10.1002/cncr.25731
39. Shah SC, Glass J, Giustino G, et al. Statin exposure is not associated with reduced prevalence of colorectal neoplasia in patients with inflammatory bowel disease. *Gut Liver.* 2019;13(1):54–61. doi:10.5009/gnl18178
40. Li AJ, Jiang HY, Jia YH. Statin exposure and risk of colorectal cancer in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Front Med.* 2024;11:1507739. doi:10.3389/fmed.2024.1507739/full
41. Song Y, Zhong X, Gao P, et al. Aspirin and its potential preventive role in cancer: an umbrella review. *Front Endocrinol.* 2020;11:3. doi:10.3389/fendo.2020.00003/full
42. Skriver C, Maltesen T, Dehlendorff C, et al. Long-term aspirin use and cancer risk: a 20-year cohort study. *JNCI J Natl Cancer Inst.* 2024;116(4):530–538. doi:10.1093/jnci/djad231
43. Garcia-Albeniz X, Chan AT. Aspirin for the prevention of colorectal cancer. *Best Pract Res Clin Gastroenterol.* 2011;25(4–5):461–472. doi:10.1016/j.bpg.2011.10.015
44. Guo CG, Ma W, Drew DA, et al. Aspirin use and risk of colorectal cancer among older adults. *JAMA Oncol.* 2021;7(3):428. doi:10.1001/jamaoncol.2020.7338

45. Bosetti C, Santucci C, Gallus S, Martinetti M, La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol.* **2020**;31(5):558–568. doi:10.1016/j.annonc.2020.02.012
46. Shah D, Di Re A, Toh JWT. Aspirin chemoprevention in colorectal cancer: network meta-analysis of low, moderate, and high doses. *Br J Surg.* **2023**;110(12):1691–1702. doi:10.1093/bjs/znad231
47. Drew DA, Chan AT. Aspirin in the prevention of colorectal neoplasia. *Annu Rev Med.* **2021**;72(1):415–430. doi:10.1146/annurev-med-060319-120913
48. Frampton M, Houlston RS. Modeling the prevention of colorectal cancer from the combined impact of host and behavioral risk factors. *Genet Med.* **2017**;19(3):314–321. doi:10.1038/gim.2016.101
49. Mäde JC, Stallmach A, Kleebusch L, Schlattmann P. Meta-analysis of aspirin-guided therapy of colorectal cancer. *J Cancer Res Clin Oncol.* **2022**;148(6):1407–1417. doi:10.1007/s00432-022-03942-1
50. Fousekis FS, Mpakogiannis K, Filis P, et al. Exploring chemoprevention in colorectal cancer for patients with inflammatory bowel disease: mechanisms of action and clinical aspects. *Cancers.* **2025**;17(2):229. doi:10.3390/cancers17020229
51. Velayos FS, Loftus EV, Jess T, et al. Predictive and protective factors associated with colorectal cancer in ulcerative colitis: a case-control study. *Gastroenterology.* **2006**;130(7):1941–1949. doi:10.1053/j.gastro.2006.03.028
52. Eaden, Abrams, Ekbom, Jackson, Mayberry. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther.* **2000**;14(2):145–153. doi:10.1046/j.1365-2036.2000.00698.x
53. Xiao H, Yang CS. Combination regimen with statins and NSAIDs: a promising strategy for cancer chemoprevention. *Int J Cancer.* **2008**;123(5):983–990. doi:10.1002/ijc.23718
54. Gottschall H, Schmöcker C, Hartmann D, et al. Aspirin alone and combined with a statin suppresses eicosanoid formation in human colon tissue. *J Lipid Res.* **2018**;59(5):864–871. doi:10.1194/jlr.M078725
55. Prasai K, Tella SH, Yadav S, et al. Aspirin and statin use and the risk of gallbladder cancer. *Cancers.* **2021**;13(5):1186. doi:10.3390/cancers13051186
56. Cho MH, Yoo TG, Jeong SM, Shin DW. Association of aspirin, metformin, and statin use with gastric cancer incidence and mortality: a Nationwide Cohort Study. *Cancer Prev Res.* **2021**;14(1):95–104. doi:10.1158/1940-6207.CAPR-20-0123
57. Wang CH, Huang CW, Nguyen PA, et al. Chemopreventive effects of concomitant or individual use of statins, aspirin, metformin, and angiotensin drugs: a study using claims data of 23 million individuals. *Cancers.* **2022**;14(5):1211. doi:10.3390/cancers14051211

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