Chemoprevention of Colorectal Cancer with 5-Aminosalicylic Acids in adult patients with Inflammatory Bowel Disease

Joshua Beu
Pacific University

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Chemoprevention of Colorectal Cancer with 5-Aminosalicylic Acids in adult patients with Inflammatory Bowel Disease

Abstract
Background: 5-aminosalicylic acids (5-ASAs) have been integral medications in the maintenance and induction of remission in inflammatory bowel diseases (IBD) for the past several decades. These patients have a significantly increased risk for developing colorectal cancer (CRC) when compared to the general population due to the chronic relapsing and remitting inflammatory process that makes neoplasia more likely. It has been shown in recent studies that 5-ASAs have the potential to reduce the risk of CRC in patients with IBD, though the research is not in complete agreement. This review was designed to evaluate the most recent evidence concerning this topic.

Methods: An exhaustive search of available medical literature in MedLINE-Ovid, Web of Science, CINAHL, MD Consult, and Google Scholar databases produced a total of six articles that fit the criteria set before the search. Articles were included if they: 1) assessed CRC prevention using 5-ASA medications in IBD patients, 2) were published during or after 2005, and 3) included odds ratios with 95% confidence intervals or p-values to measure significance.

Results: A total of six retrospective case-control studies were analyzed with a cumulative total of 723 CRC cases and 2113 controls. Four studies resulted in a statistically significant (p<0.05 or CI<1) risk reduction in colorectal cancer for IBD patients while the other two studies demonstrated some risk reduction (23-70%) with trends toward significance (p=0.11 and p=0.10 respectively) though they did not reach a p-value less than 0.05.

Conclusion: This systematic review found that the majority of studies do show statistically significant risk reduction of colorectal cancer rates among patients with IBD. Although not all demonstrated statistical significance, all had an odds ratio of less than one, which signifies a certain level of risk reduction. The two studies that did not find statistically significant results both observed the effect of 5-ASA use in control patients for only one year prior to the date of a matched cancer patient’s diagnosis of CRC, leaving into question whether the length of exposure may have skewed the cancer preventing ability of the drug.

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Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

First Advisor
James Ferguson PA-C, MPH

Second Advisor
Annjanette Sommers MS, PAC

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Third Advisor
Rob Rosenow PharmD, OD

Keywords
5-ASA, colorectal neoplasms, inflammatory bowel disease, Ulcerative Colitis, Crohn's Disease

Subject Categories
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Chemoprevention of Colorectal Cancer with 5-Aminosalicylic Acids in adult patients with Inflammatory Bowel Disease

Joshua Beu

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR

For the Masters of Science Degree, August 14th, 2010

Faculty Advisor: James Ferguson PA-C
Clinical Graduate Project Coordinators: AJ Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

[Redacted for privacy]
Abstract

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**Keywords:** 5-ASA, colorectal neoplasms, inflammatory bowel disease, Ulcerative Colitis, Crohn’s Disease
Acknowledgements

To my wife: Thank you for your continual support as I pursue my goals. You of all people understand the stress involved with graduate work since you are also going through the same thing. I’ve been very fortunate and owe a lot of my success to you for standing by my side along the way.

To my family: I could not ask for a better family that has encouraged and motivated me to achieve my goals throughout life. I cannot begin to thank all of you enough for everything you have done for me. I am so lucky to have you all in my life.
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### List of Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>5-ASA</td>
<td>5-Aminosalicylic Acid</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal Cancer</td>
</tr>
<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s Disease</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory Bowel Disease</td>
</tr>
<tr>
<td>AOR</td>
<td>Adjusted Odds Ratio</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<td>RR</td>
<td>Risk Reduction</td>
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Chemoprevention of Colorectal Cancer with 5-Aminosalicylic Acids in adult patients with Inflammatory Bowel Disease

BACKGROUND

Colorectal cancer (CRC) rates among patients with inflammatory bowel disease (IBD) of the colon are significantly higher than in the general population. One study placed patients with ulcerative colitis (UC) at 18% increased risk for CRC after 30 years with the disease.\(^1\) Although the majority of studies have focused their research primarily on ulcerative colitis, the extent of risk involved in patients with Crohn’s disease (CD) of the colon appears to be the same according to the most recent studies.\(^2,3\)

Seeing as patients with IBD are at an increased risk of morbidity and mortality from CRC due to the chronic inflammatory nature of their disease, some with the disease are more prone to acquire CRC than others. Factors that have been shown to increase the likelihood of acquiring CRC include: first degree relatives with CRC, primary sclerosing cholangitis, age of IBD diagnosis, and extent of disease.\(^4-11\) On the other hand, certain treatment factors such as compliance with surveillance colonoscopy, use of 5-aminosalicylic acid medications (5-ASA), folic acid supplementation, regular physician follow up, and regular low-dose aspirin consumption have been shown to decrease risk for neoplasms of the colon in patients with IBD.\(^12-16\)

Since many of the factors that put patients at increased risk of colon cancer are non-modifiable, research has focused on remission maintenance and chemoprevention in an attempt to improve long-term outcomes for these patients. 5-ASAs are first-line anti-inflammatory medications used to induce and maintain remission in mild to moderate cases of active IBD. The chemical structure of 5-ASA contains the same bioactive compounds found in NSAIDs, including aspirin that are shown to inhibit the COX-2
pathway of prostaglandin and thromboxane synthesis, which in laboratory studies have been demonstrated to induce apoptosis and growth suppression of tumor cells.\textsuperscript{17,18}

Though 5-ASAs have been shown to have varying degrees of chemopreventative potential, not all studies agree with one another, and, in some cases, have been inconclusive in the past.\textsuperscript{11,19} This comes despite a systematic review and meta-analysis of this topic by Velayos et al in 2005, which concluded that 5-ASAs reduced CRC risk by 49\% with statistical significance.\textsuperscript{20} A number of studies included in that review lacked statistical significance or contained few patients in their research. The power of studies conducted after this systematic review have not been completely analyzed nor collectively looked at in a recent systematic review such as this.

The nature of this issue demands studies be performed in an observational manner that is retrospective. In an ideal study, participants would be watched prospectively for several years in a randomized control trial (RCT), however withholding treatment from the control group is unethical and therefore impossible. The purpose of this study is to examine the studies released in the last five years on CRC risk reduction with 5-ASAs in IBD patients, since systematic reviews and meta-analyses are the best way to assess the validity of clinical questions such as this.

**METHODS**

An exhaustive search of applicable studies was performed using the following search engines: MedLINE-Ovid, Web of Science, CINAHL, MD Consult, and Google Scholar. The majority of pertinent articles were produced by Web of Science, which was then used to broaden the search by means of viewing all other articles/studies that had cited a specific article that was deemed to be relevant. After the extensive search, each
article’s reference list was analyzed for titles that seemed to match the clinical question at hand, which may have not been found in the original online search. Some of these articles had to be requested through Pacific University’s interlibrary services system, or “ILLiad.”

**Inclusion Criteria**

Studies integrated in the review had to include adult IBD patients of either ulcerative colitis and/or Crohn’s Disease. Also, there had to be an intervention of any 5-ASA that was compared to either IBD patients not on 5-ASA treatment or who took varying doses or had taken the medicine for a different duration. All studies had to include an analysis on risk reduction (if any) of colorectal cancer with the 5-ASA treatment. In order to eliminate bias, all patients with IBD (ulcerative colitis and Crohn’s Disease of the colon) were included. This was done because Crohn’s Disease has been shown to have a similar magnitude of risk of CRC when compared to ulcerative colitis.²,³,⁷,²¹,²²

**Exclusion Criteria**

Articles published before 2005 were excluded in order to evaluate the most up to date research. Literature reviews, systematic reviews and meta-analyses were also excluded unless used as supplemental evidence to the studies reviewed, such as in the introduction and conclusion.

**RESULTS**

A total of six articles were found that matched the inclusion and exclusion criteria set (See Table 1). All studies were conducted as case-controls and all included patients older than 18 years of age with a diagnosis of IBD. Cases were defined as patients with
IBD (either UC or CD) with a diagnosis of CRC or colorectal dysplasia. Control patients were identified as patients with IBD, with at least some patients given a 5-ASA. The controls were matched to cases based on factors that varied from study to study, but these included age, sex, extent of IBD, years of IBD, duration of 5-ASA use, age at CRC diagnosis, family history of CRC, and time since last colonoscopy.23-28

In 2009, Tang et al25 published a case-control observational study that discussed the effect of a cumulative dose of mesalamine on 18 CRC case patients and 30 controls. Twenty-six control patients had a previous diagnosis of UC while the other four had CD. Twenty-five CRC patients had a diagnosis of UC and five had CD. Cases and controls were similar and were matched according to sex, race, IBD type, age at IBD diagnosis, and length of IBD diagnosis. This study also looked at past NSAID, steroid, and 6-mercaptopurine use, which were found to be similar in both groups.25

The total cumulative dose of mesalamine (a 5-ASA medication) was defined as greater or less than 4,500g compared to no mesalamine use whatsoever. Results of the multivariate analysis concluded that a total cumulative dose of \( \geq 4,500 \text{g} \) mesalamine reduced the risk of CRC by 97.6% and demonstrated statistical significance (OR=0.024; 95% CI=0.0-0.65; p=0.047) Tang et al was not able to prove that there was a significant reduction of CRC based on the average daily dose of mesalamine greater or less than 1.6g/day (p=0.328).25

In another study by Terdiman et al,23 the regularity of 5-ASA use in the year prior to CRC diagnosis in case patients (defined as the index date) was compared between cases and controls for chemoprevention of CRC. The study included a large population with a total of 364 case patients with CRC and a previous IBD diagnosis along with a
total of 1,172 matched controls. “Regularity” of 5-ASA use was determined by the investigators to be the number of filled prescriptions, including: zero, 1-2, 3-4, or ≥5. This study found no statistical significance with CRC risk reduction for 5-ASAs as a whole (p=0.11), nor for mesalamine (p=0.08) or sulfasalazine (p=0.27). Although the study did not reach statistical significance, the risk of CRC, according to the adjusted odds ratios, did appear to decrease as the number of prescriptions for “all 5-ASAs” and mesalamine increased.23

Investigators did not account for past 5-ASA use beyond the year prior to the index date due to the retrospective and observational nature of the study. There were several other crucial factors that were not accounted for in this study, including family history of CRC, IBD duration, extent, and severity, and exposure to non-prescription medications.23

The article written by Siegel et al in27 2006 was the only study in this systematic review that exclusively included patients with Crohn’s disease of the colon. This case-control investigation took 27 cases of CD with CRC and matched them 1:1 with 27 CD controls without CRC, then observed the effect of varying exposures (including 5-ASAs) before the CRC diagnosis in the case patient. More specifically, the study looked at regular 5-ASA use more than one year prior to the index date of CRC diagnosis, any use of 5-ASA in the past, and current use of 5-ASA at the time of the index date. The study revealed a non-significant trend toward protection for regular use of 5-ASA (OR=0.30; 95% CI=0.05-1.17; p=0.10), with less significant trends for any 5-ASA use (OR=0.50; 95% CI=0.11-1.87; p=0.39) and current 5-ASA use (OR=0.33; 95% CI=0.06-1.34; p=0.15).27
Another study that assessed the regular use of 5-ASAs in the year prior to CRC diagnosis similar to the article by Siegel et al was a study conducted by van Staa et al\textsuperscript{24} in 2005. Among 100 case patients and 600 controls of both CD and UC, patients were analyzed according to regular (≥ six prescriptions in twelve months before index date) and irregular (< six prescriptions in the same twelve months) use of 5-ASA medication. Overall, regular 5-ASA use from zero to twelve months was attributed to a 40% risk reduction in CRC (AOR=0.60; 95% CI=0.38-0.98). The risk reduction from 12-24 months was 49% (AOR=0.51; 95% CI=0.26-0.99). When the use of 5-ASAs was broken down into specific drugs (mesalamine vs. sulfasalazine vs. other 5-ASAs), mesalamine was found to have the greatest protection against cancer with a 69% risk reduction (AOR=0.31; 95% CI=0.11-0.84).\textsuperscript{24}

Since regular use of 5-ASAs in general and mesalamine in particular established 95% confidence intervals that were less than one, these findings can be conveyed as statistically significant. Dose effect demonstrated decreased risk in the mesalamine group. The trend of increased dose did not decrease the risk involved and lifetime 5-ASA use beyond two years before the index date was not measured. Additionally, the extent of IBD in cases and controls was not assessed nor was it available to the investigators.\textsuperscript{24}

Rubin et al\textsuperscript{28} completed a study in 2006 that found significant risk reduction of both CRC and dysplasia in patients with ulcerative colitis. In the study, 26 cases (8 CRC, 18 dysplasia) were matched to 96 controls and were followed on average for 9.5-11 years. This study measured a patient’s total mesalamine exposure in the same way the case-control study by Tang et al\textsuperscript{25} was performed.
Confounding factors were eliminated in this study after multiple conditional logistic regressions were used to control for potential bias. These factors were family history of CRC, age, and duration of UC. Once this model was applied to the univariate analysis, a daily dose of $\geq 1.2g$ of 5-ASA demonstrated a 72% risk reduction (AOR=0.28; 95% CI=0.09-0.85; p=0.024). This was be compared to the data on dose effect where there was a 16% risk reduction per 1000g increase up to 6025g on total cumulative dose (AOR=0.84; 95% CI=0.71-1.00; p=0.056) and a 56% risk reduction with every one gram increase per day (AOR=0.44; 95% CI=0.09-0.93; p=0.03).28

Rubin et al28 also accounted for as many variables as possible given the retrospective nature of the study and a cumulative 5-ASA dose exposure was monitored. Since this study reached statistical significance on a variety of different dosages of 5-ASA medications, it was deduced that if the patients were not adherent to their medication therapy the results should have been even less powerful than what they would have been if all patients were compliant with their treatment regime.28

In another article that looked solely at patients with ulcerative colitis, Velayos et al26 examined predictive and protective factors associated with colorectal cancer. This study had very strict matching standards between cases and controls. A total of 188 cases were matched 1:1 with 188 controls on five criteria: gender, maximal extent of ulcerative colitis, duration of UC, date of first visit for UC within three years, and year of UC diagnosis within five years. The extent of UC was broken down into area involved, including: proctitis; proctosigmoiditis, left-sided colitis, and extensive colitis of more than 55cm. Duration of 5-ASA therapy was surveyed for less than 1 year, 1-5 years, 6-10 years, and more than 10 years. Short term (less than 1 year) had no protective effect
(OR=1.0), while 1-5 years use was the only duration of therapy that had a statistically significant protective effect (OR=0.4; 95% CI=0.2-0.9; p<0.05). Long term use of 5-ASAs beyond five years was associated with a 40% risk reduction, though this was not statistically significant. It also showed a protective effect with past NSAID, aspirin, and corticosteroid use, which all showed significant results for CRC protection with p-values less than 0.05. A multiple variable model with conditional logistic regression was used to adjust for confounding factors that increased risk of CRC such as family history of CRC and pseudopolyps. In the end, a total of two articles looked specifically at 5-ASA dose and its effect on prevention, these were conducted by Rubin et al and Tang et al. Both of these studies analyzed the total cumulative medication dose, which allowed them to include patients who had changed their prescription dosage of 5-ASA at some point in their treatment. Rubin et al went further and examined the effect of a daily dose of 5-ASA in grams (+/- 1.2g).

Among the other four articles that assessed the duration of 5-ASA use, the article by Terdiman et al based its data on the use of 5-ASAs in the year prior to CRC diagnosis in the case patient. The other three articles observed the preventative outcomes of medication use during and beyond the year prior to when the CRC was discovered in the case patients.

**DISCUSSION**

The results from the six articles critically appraised in this review demonstrate that the majority of evidence supports the claim that 5-ASA medication use is associated with a reduced risk of CRC for IBD patients. The two studies that did not reach
statistically significant risk reduction for cancer (defined as a p-value less than 0.05), showed trends toward a protective effect in both their odds ratios and p-values.\textsuperscript{23,27}

**Limitations of Study**

Some studies produced more applicable results than others. Three studies only looked at treatment at or just beyond one year.\textsuperscript{23,24,27} One critical variable involved in this was the fact that none of these studies were able to account for a cumulative effect of 5-ASAs beyond that one year, meaning some patients may have had a large range of exposure to the medication. Additionally, dose effect was not incorporated into the data, leaving in question whether the two articles that did not reach statistical significance might have reached significance had they evaluated dose and further extended the duration.\textsuperscript{23,27}

Two studies based their data off of the number of prescriptions filled during a specified length of time.\textsuperscript{23,24} This also created bias in the sense that compliance with taking the medication was not accounted for, along with dosage, and number of pills in the prescriptions were not evaluated or accounted for. The fact that this information was not available to the investigators does not preclude the fact that it confounded the results. Dose effect was also not accounted for in the study by Velayos et al.\textsuperscript{26}

Despite the fact that the article published by Tang et al\textsuperscript{25} did show statistically significant results, it was limited by the fact that there were few patients involved in the study (48 total), not all case patients could be matched to controls so 12 were left out of the study, and like all studies included in this review, compliance of actual medication consumption was not entirely ensured since they were conducted retrospectively.\textsuperscript{25} However, the weaknesses found in this article are not strong enough to discount the data.
since the criteria for information collection and case/control matching was so stringent to begin with.

In order to provide more conclusive results, focusing on dose effect or duration of treatment solely, would have led to a more specific statement at the end of this review. Furthermore, the retrospective and observational nature of these studies was a limitation in itself that unfortunately cannot be surpassed with clinical hypotheses such as these.\textsuperscript{23-28} Patients cannot have treatment withheld when there is substantial evidence that the treatment reduces morbidity or mortality.

**Recommendations for Future Studies**

In order to provide more conclusive results, focusing on dose effect or duration of treatment solely, would have led to a more specific statement at the end of this review. Furthermore, the retrospective and observational nature of these studies was a limitation in itself that unfortunately cannot be surpassed with clinical hypotheses such as these.\textsuperscript{23-28}

Since mesalamine and other 5-ASAs are integral first-line medications for maintenance and active disease remission, denying these in a control group is unethical. Future studies should therefore concentrate on the effects of various doses, frequency, and durations of treatment with this drug class, preferably prospectively for several (>ten) years with large populations. Furthermore, more patient and laboratory studies should observe the relationship between 5-ASAs and dysplasia since this is the initial cellular abnormality that ultimately leads to cancer.

In an ideal study, a large population of CRC case patients would be matched and compared to control patients based on specific 5-ASA exposures like dose or duration of treatment. Furthermore, this type of study should be repeated by more studies that
conduct their research in the same way, then collectively analyzed in a systematic review, as opposed to making a blanket statement for the drug as a whole. It is clear that more studies and reviews need to be conducted in this manner to avoid generalizing for many studies that are not exactly similar.

**CONCLUSION**

In conclusion, the most current available research has determined that 5-ASAs may have the ability to prevent colorectal cancer in patients with IBD, though dose and duration have not yet been specified. Four out of the six studies reviewed ended with varying levels of chemoprevention with 5-ASAs with statistical power while the other two that focused on less than one year treatment did not, however, showed trends toward protection. The benefits from using 5-ASAs for long-term treatment of IBD far outweigh the risks, since they are commonly well tolerated medications with relatively few side effects, especially when compared to systemic oral corticosteroids.25

The promising findings of this review would seem to have little impact given that 5-ASAs are used first-line in mild to moderate cases of IBD. However, they do suggest that using them as maintenance therapy, and not in remission induction alone, may be a preferable option for long-term treatment. Other prevention strategies like regular physician visits, surveillance imaging, and alternative drug treatments such as folic acid are both encouraged and proven to be effective. A combination of all of these strategies along with 5-ASA use may ultimately result in a lower risk of CRC for patients with an inflammatory bowel disease.
REFERENCES


**Table 1: Statistical Results of Colorectal Cancer Prevention/Protection with 5-ASA use**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Cases/Controls</th>
<th>Disease</th>
<th>Medication</th>
<th>Intervention (Dose/Usage)</th>
<th>Length of Study (years)</th>
<th>Odds Ratio (Confidence Interval=95%)</th>
<th>Risk Reduction</th>
<th>Statistically Significant Prevention/Protection</th>
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</thead>
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<tr>
<td>Tang et al&lt;sup&gt;35&lt;/sup&gt; (2009)</td>
<td>18/30</td>
<td>Crohn’s &amp; Ulcerative Colitis</td>
<td>Mesalamine only</td>
<td>≥4,500g cumulative taken</td>
<td>1970-2005 (35)</td>
<td>0.024 (0.00-0.65)</td>
<td>98%</td>
<td>Yes (p=0.047)</td>
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<tr>
<td>Terdiman et al&lt;sup&gt;37&lt;/sup&gt; (2007)</td>
<td>364/1172</td>
<td>Crohn’s &amp; Ulcerative Colitis</td>
<td>5-ASA</td>
<td>&gt;5 prescriptions in 1 yr before CRC†</td>
<td>2000-2004 (4)</td>
<td>0.77 (0.54-1.08)</td>
<td>23%</td>
<td>No (p=0.11)</td>
</tr>
<tr>
<td>Rubin, et al&lt;sup&gt;38&lt;/sup&gt; (2006)</td>
<td>26/96</td>
<td>Ulcerative Colitis</td>
<td>5-ASA</td>
<td>&gt;1.2g/day</td>
<td>1985-2000 (15)</td>
<td>0.28 (0.09-0.85)</td>
<td>72%</td>
<td>Yes (p=0.011)</td>
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<td>Siegel et al&lt;sup&gt;39&lt;/sup&gt; (2006)</td>
<td>27/27</td>
<td>Crohn’s</td>
<td>5-ASA</td>
<td>&gt;1 year use before CRC</td>
<td>1990-2004 (14)</td>
<td>0.30 (0.05-1.17)</td>
<td>70%</td>
<td>No (p=0.10)</td>
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<td>Velayos et al&lt;sup&gt;40&lt;/sup&gt; (2006)</td>
<td>188/188</td>
<td>Ulcerative Colitis</td>
<td>5-ASA</td>
<td>1-5 years use</td>
<td>1976-2003 (27)</td>
<td>0.60 (0.30-1.21)</td>
<td>40%</td>
<td>Yes (p&lt;0.05)</td>
</tr>
<tr>
<td>van Staa, et al&lt;sup&gt;24&lt;/sup&gt; (2005)</td>
<td>100/600</td>
<td>Crohn’s &amp; Ulcerative Colitis</td>
<td>5-ASA</td>
<td>Use 1 year before CRC</td>
<td>1987-2001 (14)</td>
<td>0.60 (0.38-0.96)</td>
<td>40%</td>
<td>Yes (95% Confidence Interval is less than 1)</td>
</tr>
</tbody>
</table>

†Colorectal cancer
### Table 2: Summary Matrix of the Literature

<table>
<thead>
<tr>
<th>Author/ Title/ Journal</th>
<th>Yr. published</th>
<th>Patients/ Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome(s)</th>
<th>Study type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terdiman et al³</td>
<td>2007</td>
<td>1536 IBD† pts: 364 CRC‡ cases and 1172 controls</td>
<td>5-ASA</td>
<td>No 5-ASA use</td>
<td>23 % RR § in CRC</td>
<td>Observational/ Case Control</td>
<td>Did not account for severity or medication dose and only 1 year treatment: NO statistical proof of decreased risk but trend toward statistical significance with p-value</td>
</tr>
<tr>
<td>van Staa et al⁴</td>
<td>2005</td>
<td>700 IBD pts: 100 cases with CRC and 600 controls</td>
<td>5-ASA</td>
<td>No 5-ASA use</td>
<td>40% RR in CRC</td>
<td>Observational/ Case Control</td>
<td>Second largest study-accounted for disease duration; showed decreased risk of CRC</td>
</tr>
<tr>
<td>Tang et al⁵</td>
<td>2009</td>
<td>1594 IBD pts: 18 cases 30 controls</td>
<td>&lt;4.5g Mesalamine and &gt;4.5g mesalamine</td>
<td>No mesalamine, &lt;4.5g</td>
<td>98% RR in CRC</td>
<td>Observational/ Case Control</td>
<td>Very few limitations: accounted for age/sex/race/type of inflammatory bowel disease/body mass index/smoking history/family history of CRC/etc. Only study to associate dose of mesalamine with CRC risk reduction. 97.6% risk reduction with 4.5g/day of mesalamine p=0.047</td>
</tr>
<tr>
<td>Velayos et al⁶</td>
<td>2006</td>
<td>376 UC pts: 188 cases of ulcerative colitis with CRC and 188 controls with CUC</td>
<td>Varying years duration of 5-ASA therapy (&lt;1y&gt;-10y)</td>
<td>Other anti-inflammatories/ steroids/folate and no 5-ASA use</td>
<td>40% RR in CRC</td>
<td>Observational/ Case Control</td>
<td>Good study: cases were matched to controls 1:1 regarding sex/extent of ulcerative colitis/duration of ulcerative colitis/first visit at Mayo clinic/year of ulcerative colitis diagnosis; did not account for dose</td>
</tr>
<tr>
<td>Siegel et al⁷</td>
<td>2006</td>
<td>54 Crohn’s disease pts: 27 CRC cases and 27 controls</td>
<td>5-ASA</td>
<td>No 5-ASA use, any 5-ASA use, current 5ASA use and regular 5-ASA use</td>
<td>70% RR in CRC</td>
<td>Observational/ Case Control</td>
<td>Revealed non-significant trend toward protection, however duration of treatment in “regular” users of 5-ASAs was not investigated (only specified more than 1 year of use) nor was the dose patients were taking.</td>
</tr>
<tr>
<td>Rubin et al⁸</td>
<td>2006</td>
<td>122 ulcerative colitis pts: 26 cases with CRC and 96 controls</td>
<td>5-ASA</td>
<td>No 5-ASA use</td>
<td>72% RR in CRC</td>
<td>Observational/ Case Control</td>
<td>Measured total cumulative mesalamine exposure similar to Tang et al.²⁵ Demonstrated statistically significant risk reduction of 72% p=0.01.</td>
</tr>
</tbody>
</table>

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† Inflammatory Bowel Disease  
‡ Colorectal Cancer  
§ Risk Reduction