Does Cigarette Smoking Increase the Risk of Developing Ulcerative Colitis or Crohn's Disease?

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Abstract

Objective: Inflammatory Bowel Disease (IBD) consists of Ulcerative Colitis (UC) and Crohn's Disease (CD). The etiology of IBD has been studied and is still unknown, but several risk factors have been associated with the disease. Possible risk factors include genetic predisposition, oral contraceptive use and cigarette smoking. It is important to further research the link between cigarette smoking and IBD.
Methods: Reviews and studies were obtained in order to evaluate the relationship between IBD and smoking.
Discussion: Current cigarette smoking was found to increase the relative risk of developing Crohn's Disease and decrease the risk of developing Ulcerative Colitis.
Conclusion: Although cigarette smoking seems to be protective against developing UC, the other risks associated with cigarettes far outweigh the possible benefits. In order to better understand the connection between IBD and cigarette smoking, it would be necessary to further research the causative mechanism of UC and CD.

INTRODUCTION

Inflammatory bowel disease (IBD) is comprised of Crohn's Disease (CD) and Ulcerative Colitis (UC) and affects approximately 1 million Americans ([1]). The estimated total annual direct (including hospital visits and medications) and indirect (including productivity loss) cost of IBD in the United States ranges from $1.8 to $2.6 billion ([2]). Although the exact cause of IBD is not known, several genetic and environmental risk factors have been identified for developing this disease.

Cigarette smoking is the most examined risk factor for IBD and is said to have different effects on CD and UC ([1]). Healthcare practitioners are generally aware of the increased risk of COPD, various types of cancer and coronary artery disease that is associated with tobacco use; however, several studies have suggested that cigarette smoking can have a protective effect on UC and a causative relationship with UC ([1]). In fact, this controversy may lead patients with IBD to question providers about non-conventional treatments that involve nicotine ([1]). Therefore, it is important to know the impact that cigarette smoking has on IBD so practitioners can then counsel patients on all the risks of cigarette smoking versus the possible benefits.

BACKGROUND

IBD is defined as chronic inflammation of the digestive tract of unknown etiology and is divided into UC and CD. IBD most commonly affects Caucasians in Northern Europe and North America. Specifically, Ashkenazi Jews are four times more likely to have IBD than Caucasians ([3]). There seems to be a familial trend associated with IBD because family members of a patient with IBD have an increased risk of developing UC or CD; 50 times higher than the rest of the population ([3]). There also appears to be a bimodal distribution of diagnoses of IBD, as it peaks at age 15 to 25 and again at age 55 to 65 ([3]).

The etiology of UC is unknown. One theory is that patients are genetically predisposed to develop UC. These patients many incur an insult to the mucosa of the lining of the colon and have an altered immune system response to flora found naturally in the gut. There are several recognized risk factors for developing UC including being Jewish and chronically using non-steroidal anti-inflammatory agents ([2]). The nicotine in cigarettes is said to act as an immunosuppressant because cigarette smoking has been shown to decrease immunoglobulins including IgG, IgM and IgA ([4]). It has also been speculated that there is a relationship between UC and

oral contraception use, breast-feeding, second-hand smoke, the MDR1 gene, socioeconomic status, psychological conditions and childhood infections ([5]).

Ulcerative colitis causes chronic inflammation of the mucosa of the large intestine and affects the rectum. The severity of this disease varies greatly from patient to patient. The pattern of inflammation is continuous throughout parts of the colon. For example, proctosigmoiditis signifies that the inflammation affects the rectum and the sigmoid colon; left-sided colitis extends from the splenic flexure to the descending colon and if the entire colon is affected, the disease is classified as pancolitis.

The presentation of Ulcerative colitis most often includes frequent bouts of bloody diarrhea. Other symptoms consist of fever, tenesmus, weight loss, lower abdominal pain relieved with defecation and the passage of mucus. The onset of symptoms is usually insidious and patients will have intermittent bouts of inflammation, called “flares” followed by undetermined time periods of remission ([3]). It is important to decipher the extent and severity of the disease in order to make a complete and adequate treatment plan. The severity of inflammation is usually reflected by the severity of symptoms. Patients with extreme inflammation will often complain of passing blood, feces and purulent material with bowel movements. Symptoms may also help determine where the inflammation is located. For example, proctosigmoiditis presents with bright red blood per rectum and rectal pain. When the disease is more extensive, blood is mixed in with the feces.

Ulcerative colitis can also have skin, ophthalmic, rheumatologic and urologic manifestations. These include polyarthralgia of the large joints (including hips and elbows), erythema nodosum, uveitis, sacroileitis, pyoderma gangrenosum, sclerosing cholangitis and ureteral obstruction ([3]).

The gold standard of diagnosis for ulcerative colitis is colonoscopy with biopsy ([3]). Histologically, UC appears as “acute colitis with neutrophil infiltration of the colonic glands, crypt abscess formation and surface erosions” ([3]). Differentiating between UC and Crohn's disease can be difficult initially, and must be done histologically and endoscopically. Fistula formation, rectal sparing and small bowel inflammation are all associated with CD and not UC. In order to rule out acute infectious colitis, stool ova and parasite tests must be performed (including Amoeba, Clostridium dificile and Shigella). Also, ischemic bowel must be ruled out in patients with risks for thromboembolic events.

UC can be managed pharmacologically and surgically. The cornerstone of medical management of UC is sulfasalazine (5-ASA and sulfapyridine) ([4]). High doses of sulfasalazines are associated with side effects including headache and nausea. Therefore, patients are advised to take sulfasalazine with meals and to increase the dose slowly. Patients on sulfasalazine also must get regular blood work to look for agranulocytosis. Severe inflammation can be treated with corticosteroids and may require hospitalization for IV dosing as well as electrolyte management. Patients who cannot tolerate sulfasalazine, or who do not respond to this drug may respond to alternative immunosuppressants, such as Azathioprine or 6-MP. In the most extreme refractory cases, UC patients require surgical proctocolectomy. A controversial proposed treatment of UC is with nicotine ([4]). The mechanism by which nicotine decreases the inflammation of UC is not fully understood. It is suggested that nicotine suppresses the immune system that attacks the colon (i.e., immunoglobulins and T-cells) ([4]).

Crohn's disease is characterized by inflammation of any layer of the intestinal tract and is characterized by “skip lesions” that do not affect contiguous areas of the GI tract with a resulting cobblestone appearance of the mucosa ([3]). It can affect any part of the gastrointestinal tract and results in wall thickening and narrowing of the lumen. The most common places that CD affects are the small bowel and large bowel ([3]). On a microscopic level, CD appears as macrophages, plasma cells and neutrophils in any of the serosa, muscularis, submucosa or mucosa layers of the GI tract. Patients with CD often present with intermittent right upper quadrant abdominal pain and loose stools. Distal involvement is suggested by hematochezia and fecal urgency. Enterocolinic fistula formation, intestinal obstruction, low grade fever and weight loss are also seen in CD. Extra-intestinal manifestations of CD are similar to that of UC including uveitis and polyarthralgia. Certain symptoms are more common in CD, such as erythema nodosum which mimics that disease course.

The exact etiology of Crohn's disease is unknown. CD may be caused by micro-infarcts of the bowel. It seems to occur more often is people who smoke cigarettes ([4]). It is theorized that smoking increases the risk of thrombi, and therefore infarcts, by increasing coagulability ([4]).

The differential diagnosis for CD includes appendicitis

(which is ruled out via abdominal CT), parasitic infection (which is ruled out with stool ova and parasite cultures), ischemic colitis, diverticulitis, UC (which is ruled out with colonoscopy) and carcinoma. In order to diagnose CD, small bowel follow through, barium enema and colonoscopy with biopsy are used. Treatment of CD in the stomach and duodenum includes Lansoprazole (Prevacid), antihistamines, Mesalamine (Pentasa or Asacol) and Sucralfate (Carafate). Distal small bowel and colonic disease is treated with Mesalamine (Pentasa or Asacol), Sulfasalazine (Azulfidine) and Metronidazole (Flagyl). Patients who are unresponsive to conservative treatment are often placed on Prednisone. Remission is less likely in CD than in UC, but is possible. Many patients with CD are placed on a low-residue diet. Surgical treatment is not considered curative in CD since areas of inflammation are noncontiguous.

In this paper, several articles that examine the relationship between developing Crohn's Disease or Ulcerative Colitis and smoking cigarettes will be discussed.

METHODS

A search was conducted utilizing Academic Search Premiere (EBSCO), CINAHL with full text, MEDLINE with full text and PUBMED using “Inflammatory bowel disease AND smoking” as keywords. The search was further consolidated into those offering “free full text.” An advanced search was performed using the keywords “Inflammatory bowel disease AND smoking” with the additional search guideline of full text only, resulting in 101 articles. These articles were further narrowed down by searching for articles written in the English language and with a subject of “smoking.” Originally, articles were considered if they were published within the last 10 years, but due to the limited number of studies and reviews regarding the relationship between IBD and smoking, a review was included from 1992.

This is an etiology question and is best answered by level I/A evidence, such as a meta-analysis or a randomized control double-blind study. However, it would be considered unethical to allow some IBD patients to smoke cigarettes and give placebo cigarettes to others based on the risks associated with smoking cigarettes.

DISCUSSION

STUDY 1

The first study is a meta-analysis that studied the relationship between tobacco abuse and Ulcerative colitis entitled, “Smoking and Inflammatory Bowel Disease: a Meta-analysis” and was written by Suhal S. Mahid ([1]). In this study, articles were included if they contained specific clinical guidelines for IBD diagnoses, age and sex-matched controls, included only people of the Caucasian race (in order to exclude cultural biases), and had clear definitions for “former smoker,” “current smoker,” and “never smoker.” After being selected, each study was judged by the Newcastle-Ottawa Scale, which evaluated them on “outcome assessment, patient selection and comparability of study groups.” Twenty-nine of these studies were then excluded due to undesirable variables or ambiguous definitions and ultimately 15 studies were used in the meta-analysis.

In order to statistically rate the relative risk of developing ulcerative colitis with the three forms of smoking status, odds ratio (OR) was used. The OR indicates the likelihood of a person who smokes developing Ulcerative colitis versus the likelihood a person who does not smoke developing Ulcerative colitis. If the OR is less than 1.0, smoking is protective; if the OR is greater than 1.0, it indicates that smoking increases the risk of developing Ulcerative colitis. Among the 13 studies that studied the relationship between Ulcerative colitis and smoking, 12 of the studies were case-controlled and the remaining study was a cohort study. The OR of the 13 studies was 0.58, indicating that smoking had protective properties. However, when compared with the incidence of UC of former smokers, patients that never smoked had an OR of 1.79. Therefore, it was concluded that patients who formerly smoked had a higher risk of developing Ulcerative colitis than those who never smoked.

The relationship between smoking and CD was analyzed in 9 studies. Six studies showed that active smokers with CD compared to CD patients who had never smoked vs. the controls, had an increased risk of developing (OR of 1.59-2.92). Former smokers had an OR of 1.30 of developing CD when compared to people that had never smoked vs. controls. Researchers also concluded that there was an increased risk of developing Crohn's disease in patients who had ever smoked (current or past) with an OR of 1.61.

This study should be praised in that it attempted to reduce the number of variables by only involving Caucasian people. By only using Caucasians, the researchers decreased the probability that patients would be affected by cultural, dietary or genetic differences, in addition to the variables they set. However, I feel they should have done a concurrent study on another race to compare the data. It is just as important for other ethnicities to know if smoking will

increase their risk of developing UC as Caucasians. This study would have been more effective if it were not a meta-analysis of other articles found on databases (such as MEDLINE and CINAHL), but a case-control cohort study that examined data from patients in one study. It is impossible to assess the cumulative biases of authors from multiple studies. Also, it would have been more effective to have two different meta-analyses; one for UC and one for CD. The two Inflammatory Bowel Diseases are extremely different from one another in presentation, treatment and associated risk factors and should be examined separately. The researchers were sure to hold each study to the same standards by putting each one through the Cochrane Q and test them for "heterogeneity among the studies."

STUDY 2

"Risk of inflammatory bowel disease attributable to smoking, oral contraception and breastfeeding in Italy: a nationwide case-control study" is another article that examines the possible relationship between smoking and IBD ([6]). This article examined a case-control study that included 819 (225 with CD and 594 with UC) IBD patients that resided in 10 specific cities in Italy from 1989-1992 who were between the ages of 18 and 65. Patients were newly diagnosed with IBD (either UC or CD) and were interviewed by an unbiased technician one month after diagnosis. Controls were patients who also lived in the same geographic region in Italy as the cases and were matched by sex and age at diagnosis (within three years). Female patients were questioned about breastfeeding and oral contraceptives (OC). All patients were questioned about their smoking habits and were classified as smokers, non-smokers and former smokers. Former smokers were asked how long ago they quit and smokers were asked how long and how many cigarettes per day they smoked. Smoking load was determined based on average age of onset of smoking and average cigarettes per day.

The data collected by this study was analyzed using "several logistic regression models." Results were given as odds ratio (OR) and had a confidence interval of 95%. Each model was examined via the D-statistics ratio. The lower this value was, the more reliable the results were. P values were significant if <0.05.

A higher number of former smokers than controls had UC and a lower number of current smokers than controls had Ulcerative colitis. The risk of CD was increased with both current and former smoking, while the risk of UC was increased only in former smokers. Former smokers who had a high smoking load (smoked many cigarettes for a long period of time) were less likely to be at risk of developing UC than former light smokers. Former smokers had the highest "attributable cases of UC." The writers of this article concluded from the data they collected that ex-smokers had the highest risk of developing UC and that patients who never smoked had a higher risk of developing the disease than current smokers.

This study was relevant because it examined people who were recently diagnosed and was a prospective study. However, this study had many variables (including oral contraceptive use and cigarette smoking) and should have concentrated on one variable at a time to get the most detailed results. Studies that examine too many variables may have less time to concentrate on specifics about each topic in particular and may miss important details that can affect outcomes.

Some of the biases of this study were that the researchers could only obtain data from patients in a very limited geographic region and therefore, limited socioeconomic class. People from one specific socioeconomic class may have different smoking habits (i.e. increased load) when compared to wealthier people. It would be interesting to compare the smoking load from two different economic classes and determine how that affects IBD development. Also, it was difficult to assess the risk of breast-feeding and oral contraceptive use in females only while assessing the risk of smoking on both males and females. The definition of light and heavy smokers was not concrete. It is important to decipher how much smoking load delineates heavy from light smoking.

This article was published in the International Journal of Epidemiology, which is an Oxford Journal that is published six times a year. It is also a member of the COPE (Committee on Publication's Ethics), an organization whose board discusses moral judgment cases. Therefore, this journal would not be able to publish articles written based on opinion and not well-researched data ([7]).

STUDY 3

Another article about cigarette smoking and IBD was entitled, "Cigarette Smoking and its Relationship to IBD: a review" ([4]). The protocol for searching and selecting articles to include in this review were not mentioned. The author states that studies showed a decreased risk of developing UC while smoking and an increased risk once patients stop

smoking. One study conducted by Motley revealed that 52% of patients with UC were diagnosed within 3 years of quitting smoking. Another study found that former heavy smokers had a relative risk of developing UC of 4.4. Also, ex-smokers were found to have an increased rate of complications from UC such as colostomies and hospitalizations. The protective effect of current smoking for developing UC was studied by Castella. He found that current smokers had an increased risk of relapse while attempting to quit smoking. Rudid conducted a survey of 30 UC patients who restarted smoking after they quite and fifteen felt an improvement of their symptoms. Two hundred and nine UC patients were also questioned and revealed that hospitalizations were decreased in current smokers and there was a 17.9 higher rate of colostomy placement in former smokers when compared to current smokers.

Smoking and CD was found to have a very different relationship from smoking and UC. An age and sex-matched case control study revealed a relative risk of 4.8 for smokers to develop CD. Silverstein also examined this relationship and found that 115 CD patients were current smokers at time of diagnosis vs. 109 control patients; revealing a relative risk of 3.7 for current smokers. Another study included 109 cases of CD matched with age and sex equivalent controls. It found that smokers had a relative risk of 4.0 and that the risk increased with higher cigarette load. The concept of “dose dependency” was contradicted by another study that examined 144 CD patients. A study conducted in Sweden showed that there was an increased risk associated with both active and passive cigarette smoking. Increased relapses of CD have also been linked to smoking. Sutherland examined the need for recurrent surgery in 174 CD patients and discovered that patients who smoked had a higher need for recurrent surgery (relative risk of 2.2 at five years) than patients who didn't smoke.

This review also provides information regarding the possible mechanisms by which nicotine affect Inflammatory Bowel Disease. One theory to explain the protective effect of nicotine on patients with UC is that cigarette smoking reduces the immunological reaction in the colon by decreasing the amount of IgM, IgG, IgA and T cells. Smoking also normalizes the amount and quality of the protective mucus in the colon. A theory about why smoking increased the risk and exacerbation of CD deals with coagulability. CD has recently been linked with “multi-focal gastrointestinal infarcts” ($_{4}$). Smoking increased fibrinogen levels, damaged endothelium, inhibited platelet aggregation, increased plasma viscosity and decreased the amount of plasminogen which increased coagulability, which can lead to thrombi and eventually infarction. Also, smoking was associated with decreased circulation to the wall of the rectum for up to thirty minutes which could further exacerbate micro-infarcts.

This review did not explain the details of each study adequately, nor did it give the inclusion or exclusion criteria for inclusion in the review. Some of the studies the researchers used were well controlled by age- and sex-matching the cases and controls, while others were not. This makes the data difficult to compare. In order to know if the data is relevant and current, it is important to know what the inclusion and exclusion criteria were. Also, without knowing the method by which the studies were found, it is impossible to know if they were obtained from reputable sources. The researchers should have taken studies from a specific region of the world in order to minimize dietary and customary differences among cultures. The authors of this review only included the specific number of patients examined in certain studies. The same type of studies should have been examined to eliminate differences in mode of research. For example, a case-control study is very different from a questionnaire of UC or CD patients and can yield different outcomes.

STUDY 4

The last article examines the effect cigarette smoking has on the risk of developing Ulcerative colitis and is entitled, “A Population-Based Case Control Study of Potential Risk Factors for IBD” ($_{8}$). This study was written by Charles N. Berstein and compared the smoking habits of patients with IBD (364 with CD and 217 with UC) from the University of Manitoba IBD Research Registry with 433 sex, age and demographic origin equivalents from the Manitoba Health Registry. Cases consisted of patients that had documented diagnoses of UC or CD and were sent questionnaires via mail that examined use of analgesics (including acetaminophen and aspirin), a family history of IBD, and cigarette smoking status. Controls were sent the same questionnaire. It was not possible for the authors of this study to match cases and controls based on age and sex because only 10% of people approached to be controls were willing to participate. The data was adjusted for age and sex variation by “logistic regression modeling.” Each factor was compared by using either the two sample t-tests, Kruskal-Wallis tests or x2 analysis. The questionnaires were statistically analyzed and the p value was significant at

<0.05.

There was a higher incidence of men with IBD than controls. The researchers of this study felt that this reflected the willingness of males to respond to the surveys and not a sexual predominance for the disease. This study also found that those with UC were more likely to have been smokers at some point in their lives, when compared to controls of a similar age, sex and geographic origin with an OR of 1.66. This contrasts with the current theory of nicotine being protective against the development of UC. In addition, the study showed that UC patients were more likely to have quit smoking than controls with an OR of 2.07. Patients with CD were 1.78 times more likely to have smoked at some point in their life than the controls. Also, CD patients were more likely to be current smokers than controls (with an OR of 1.96). There was no difference in the aspirin usage (at least twice a week) of CD patients, UC patients or controls. The results for the association of examined variables with CD are as follows (Table 6):

Figure 1

Table 6: Multivariate Analysis in Crohn's Disease Adjusting for Age and Gender ()

Table 6. Mutlivariate Analysis in Crohn's Disease Adjusting for Age and Gender

	p Value	Odds Ratio, 95% CI
Jewish ethnicity *vs* all others	0.04	4.32, 1.10–16.9
First degree relative with IBD	0.0001	3.07, 1.73–5.46
Cigarette smoking ever	0.0251	1.54, 1.06–2.25
Longer years living with a smoker	0.004	1.03, 1.01–1.04
First generation Canadian	0.0006	0.33, 0.17–0.62
Living with pet cats before age 5	0.03	0.66, 0.46–0.96
Number of family members during childhood	0.006	0.87, 0.79–0.96

It was concluded that the factors associated with the highest risks of developing UC or CD among this population sample were associated with being Jewish, having a first degree relative with IBD or having smoked at some point in life.

This study was such a small sampling of the population, that its results cannot be extrapolated for world-wide significance. This study was well controlled in that the researchers of this study recognized that the predominance of male cases as compared to controls was not due to a larger amount of males having IBD.

If cases and controls had been interviewed by the same panel of researchers instead of filling out questionnaires at home, it would have eliminated the ability of patients to fabricate answers. Also, the questions would be asked in the same manner each time, decreasing the amount of patient misunderstandings. Also, those involved in the study were ages 18-50 years. This puts the study at a disadvantage because there is a bimodal distribution of diagnoses of UC. It peaks in early adulthood and over the age of 50. Therefore, a large percentage of people with UC were not evaluated.

This article was published in the American Journal of Gastroenterology, which is published by the American College of Gastroenterology. This organization was formed in 1932 and supports all medical and educational endeavors involving gastroenterology. The group consists of approximately 9800 members who are aware of the most current and relevant data in this field. The American Journal of Gastroenterology is held up to the same standards as its founding organization and prides itself on publishing the most “up-to-date” information as possible. It is likely that an organization such as the ACG would only allow studies to be published that were well-controlled and contained pertinent information ([9]).

CONCLUSION

Smoking has different effects on UC and CD. The cause of Ulcerative colitis is unknown and may not be discovered any time soon. However, the correlation between this disease process and environmental exposures will continue to be studied. It appears as though active smokers are less likely to develop the disease due to a protective effect on the mucosa layer of the large intestine from nicotine. However, ex-smokers with a genetic predisposition have the highest risk of developing UC because the withdrawal of the protective properties of nicotine injures the immune system of the mucosal layer and causes a cascade of improper immunological responses ([5]). Those who quit smoking also have a lower regression rate than those who actively smoke, which suggests that a history of smoking has long-term effects on the disease spectrum.

In addition, there was an increased risk of developing Crohn's Disease with any exposure to cigarette smoking. This suggests that the mechanism of insult and resulting injury for CD is different than in UC. It would be beneficial to study the histological effects of nicotine on the colon in UC patients versus CD patients ([1]). It has been found that

smoking increases the risk of developing CD with an OR of 4.0 and also, increases the severity of the illness. The mechanism of the effect of smoking on CD is not understood. It is hypothesized that cigarette smoking causes micro-infarcts to the bowel wall, which leads to CD ([4]).

The risks of cigarette smoking are very numerous and include developing both lung and cardiac diseases. Although nicotine may have a protective effect on developing UC, it would not be advisable for these patients to smoke cigarettes. Crohn's disease can be added to the list of illnesses associated with cigarettes. Once the mechanisms of both UC and CD are better understood, the reason why cigarette smoking has an inverse relationship with each disease may become clear.

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