How does the disease activity of Ulcerative Colitis relate to the incidence of Colon cancer?

A) Study Purpose and Rationale

Ulcerative colitis is a disease of the colon that affects 1:1000 individuals, with an increased incidence in Caucasians .It typically presents between the ages 10 and 19, with another lesser peak between 50 and 80 (1) .It is characterized by grossly bloody diarrhea, abdominal cramps, urgency and tenesmus. Ulcerative colitis (UC) may also have other manifestations including , but not limited to , erythema nodosum, pyoderma gangrenosum, apthous ulcers, arthritis, and most notably an increased risk of colon cancer.

Various aspects of patients with UC have been studied to predict which UC individuals would have a higher risk of colon cancer .Previous studies have shown that patients with pancolitis have a higher incidence of colon cancer than pts with less extensive disease. A population-based study in the United States estimated the risk was significantly increased in those with extensive or pancolitis (standardized incidence ratio (SIR) 2.4, 95% CI 0.6-6.0) (1).The approximate cumulative incidence of colon cancer is 5 to 10 percent after 20 years and 12 to 20 percent after 30 years of disease(2). L –sided colitis has also been shown to have an increased incidence of colon cancer, though it usually occurs after 15 to 20 years which is approximately one decade later than in pancolitis (3)

A population based cohort in Sweden showed that the standardized incidence ratio (rate of observed to expected cases) of colon cancer in pts with proctitis was 1.7 (.8-3.2) , L sided colitis 2.8 (1.6-4.4) and Pancolitis 14.8 (11.4- 18.9) (2)

In addition the age of onset of UC has been shown to be predictive of the risk of developing colon cancer. One study showed that for each increase in age group at diagnosis (less 15, 15-29, 30-39, 40-49, 50-59, and greater than or equal to 60 years), the relative risk of colorectal cancer , adjusted for the extent or disease at diagnosis , decreased by about 0.5 (2)

Duration of disease has also been shown to predict the likelihood of developing colon cancer. One retrospective study from Scandanavia showed that the cumulative risk of developing colon cancer in extensive disease was 12 % after 25 years (4). One source quoted a 1% increase in risk of developing colon cancer /year (5)

It is hard to use duration of disease as a predictor of risk of colon cancer because the disease course of ulcerative colitis is not the same for all individuals. Some patients have a relatively, benign disease free state. 80% of pts with UC have intermittent exacerbations, 10-15 % have continual active disease, and 5-10% have a severe initial attack. (5)

However despite the differences in the course of disease, the relation of the number of exacerbations or flares (disease severity) and how it relates to the incidence of colon cancer has not been studied thus far.
Given that duration and extent of ulcerative colitis increase the incidence of colon cancer, it stands to reason that an increased number of flares would also increase the incidence of colon cancer. You could explain this pathophysiologically by stating that duration and extent of UC all increase the inflammation . This chronic inflammation would then predispose to CA. The number of exacerbations that an individual has would also increase the inflammation and also the predisposition to colon cancer.
Given the increased risk of colon cancer patients with Ulcerative Colitis are screened for colon cancer at an earlier age. The current AGA (American Gastroenterological Association)recommend surveillance every one to two years after eight years of disease in patients with pancolitis or after 15 years in those with left-sided colitis .All patients should have surveillance colonoscopy beginning with 8 to 10 years of disease since the extent of disease cannot be accurately assessed. During each colonoscopy, biopsies are recommended every 10cm in all 4 quadrants (AGA guidelines). A study done in Gastroenterology in 1993 demonstrated a mortality benefit to this screening .The 5-year survival rate was 77.2% for the surveillance group and 36.3% for the no-surveillance group ($P = 0.026$). (6)
If indeed patients with increased exacerbations have a higher likelihood of colon cancer than screening practices could be targeted to this population, and patients with benign disease could be spared cololonoscopies at an earlier age.

(B) Study Design and Statistical Analysis

A retrospective case- control study was designed to test the hypothesis that patients with Ulcerative Colitis with an increased number of exacerbations are at higher risk for colon cancer than those patients with Ulcerative colitis that have a benign course with fewer exacerbations.
Patients with Ulcerative Colitis that have colon cancer (the outcome of interest) are defined as cases . Controls are defined as patients with Ulcerative Colitis without colon cancer. Each case will be matched with a control that had a similar age of onset, duration of disease and extent of disease to control for possible confounders. The number of exacerbations as defined by number of hospitalizations from 8/1/01 until 8/1/06 will then be recorded for each case and each control. The number of hospitalizations will then be divided by the number of years the patient had UC to obtain the number of hospitalizations/year. We expect the number of hospitalizations/year to be higher for cases (patients with UC and colon cancer) than the number of hospitalizations/ year of controls (patients only with UC).

Statistical Analysis

The data will then analyzed with the Wilcoxon variation of the t-test. Each case-control pair will be analyzed. A t- test cannot be used in this case because we cannot assume that the results will have a normal distribution. In fact it is quite possible that many patients with UC will not be hospitalized. Thus a Wilcoxon variance test will be used. A Wilcoxon variance model will rank the patients based on the number of

hospitalizations/year . For example 1 for the highest # hospitalizations/y, 2 for the second highest etc. A t- test will then be run on the ranks. The Wilcoxon test is helpful in that it enables us to analyze data that may not be normally distributed. However a downfall is that the Wilcoxon test loses the magnitude of the degree of difference between data points.

Sample Size

The total number of patients with UC in the actual study will be obtained from a mediated query in Data Warehouse selecting for patients with a IVD-9 code of 556 that meet inclusion and exclusion criteria. Prior to conducting the study, an estimation was done of the total amount of patients with Ulcerative Colitis. The estimation was based on the total amount of patients in the Datawarehouse from 8/1/01 till 8/1/06 which was 500,000. Given that Columbia serves primarily a Spanish population the incidence and prevalence of UC for a Spanish population were used.
The prevalence of UC in Spain is 43.4/100,000 and incidence is 3/100,000 (7)
If 43 /100,000 pts have UC then in 500,000 patients, **215 (43 x5) have UC.**
The incidence of Ulcerative Colitis is 3/ 100,000/year so in 500,000 people **15 (5x3) will get UC per year** , and over 5 years that would be **75 (15 x5**). The total number of patients with UC would then **be 75 + 215 = 290** patients with UC.
Then using the 10 % risk of colon cancer in pts with UC from the NIH website (7) A total number of 29 (290 x .10) was calculated. Though it should be noted that the % risk colon cancer can vary from 5-16%, given the factors previously mentioned but a lower percentage was used so that the value would not be overestimated.
Thus the number of cases (patients with ulcerative colitis and colon cancer) is **approximately 29, and the number of controls would be (roughly 290- 29)= 261**

The sample size has already been predetermined, however the effect size could be calculated as shown below:

Effect Size

Calculating effect size: Unpaired t-test was used
The sample size was a n of 29 but given that the ratio of controls to cases is 10:1 my n is roughly equivalent to 50
$N=50= 1+16\ (SD/effect)^2$
$49=16\ (SD/effect)^2$
$49/16=(SD/effect)^2$
$3=(SD/effect)^2$
Square root 3= SD/effect
1.75=SD/effect
.6(effect) =SD

(C) STUDY PROCEDURE

All information will be obtained from the Clinical data Warehouse at CUMC (https://webcis.cpmc.columbia.edu/webcis/wc_enter.cgi). The study period will be from 8/1/01 (when the datawarehouse first begins recording data) until 8/1/06

Both cases and controls will consist of patients with Ulcerative Colitis as defined by ICD 9 code 556. This ICD-9 code along with the dates of interest will be inputed into the website above as a mediated query. The list generated by this search will then be subject to chart review at which time the inclusion and exclusion criteria will be evaluated. Cases will be identified by having colon cancer (the out come if interest) with an ICD -9 code of 153. Once again the list generated by this search will be subject to chart review at which time the inclusion and exclusion criteria will be evaluated .For both cases and controls the number of exacerbations or flares will be recorded to obtain total number of exacerbations over five years. An exacerbation or flare is typically characterized frequent loose stools (greater than 10 per day) with severe cramps, fever up to 39.5ºC, rapid weight loss and bleeding often requiring blood transfusion. This constellation of symptoms would be hard to quantify in individual patients accurately so a hospitalization was used as a surrogate of an exacerbation. This was thought to be valid because usually patients that have a severe enough course to require transfusion require hospitalization.
The number of hospitalizations for cases and controls will also be obtained by the Datawarehouse of Columbia Presbyterian Hospital Medical Center by selecting for inpatient admissions. The number of hospitalizations/year will be calculated for each case and control. The data will then be analyzed by Wilcoxon analysis.

D)Study Drugs
N/A

E) Medical device
N/A

F)Subject selection
All patients with ulcerative colitis based on an ICD 9 code of 556 including 556.1-556.9 (defined by stage of disease) will be selected from the Columbia University Medical Center Datawarehouse from the dates 8/1/01 to 8/1/06 (the entire span that data is available from the warehouse). The list generated by this search will then be subject to chart review at which time the inclusion and exclusion criteria will be evaluated. Cases will be determined by searching for patients with ICD-9 codes for Ulcerative Colitis (556) and Colon Cancer (153). Once again the list generated by this search will be subject to chart review at which time the inclusion and exclusion criteria will be evaluated. Once it is determined who meets the inclusion and exclusion criteria, these pts will be asked to give informed consent to be part of the study. No identifiers will be used in processing the data, so the majority of individuals should have no contest to being used in the study. Efforts will be made to ensure that all ethnicities including minorities are represented. There will also be an equal number of men and women.

INCLUSION CRITERIA:

(1) Biopsy proven Ulcerative Colitis
(2) Patients between the ages 18-50

EXCLUSION CRITERIA:

(1) Patients with known colon cancer
(2) Patients with Familial Adenomatous Polyposis
(3) Patients with Hereditary Non-Polyposis colorectal Cancer
(4) Patients with known adenomatous disease of the colon
(5) Patients with other malignancies

H. Recruitment of Subjects

Participants will be determined first via ICD-9 code , and then if inclusion and exclusion criteria are met they will be considered eligible for the study. Eligible participants will then be contacted via phone and will be mailed a formal letter requesting participation in the study.

I. Confidentiality of study Data

All study data will be coded. A unique code number will be used for all study subjects. No identifiers will be used.

J. Potential Conflict of Interest

There are no potential conflicts of interest.

K. Location of the Study

The study will be conducted on the Columbia University Campus.

L. Potential Risks

There are no potential risks to the subjects in this study.

M. Potential Benefits

There are no potential benefits to the subjects in the study. However there are potential benefits to society. If it is shown that patients with ulcerative colitis with an increased number of exacerbations have an increased risk of colon cancer, screening practices could be changed to target that population. In addition patients that have benign courses may not need to be subjected to colonoscopies at an earlier age. This study could be a pilot study for further clinical trials.

N. Alternative Therapies

N/A

O. Compensation to subjects

No compensation will be given.

P. Costs to Subjects

There will not be any costs to the subjects.

Q. Minors as research subjects

All participants will be greater than 18 years old.

R. Radiation or Radioactive Substances

N/A

S. References:

(1) Rutter MD; Saunders BP; Wilkinson KH; Rumbles S; Schofield G; Kamm MA; Williams CB; Price AB; Talbot IC; Forbes A. *Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis*. Gastroenterology. 2006 Apr;130(4):1030-8.

(2)Helmick C; Zack M; Adami HO. *Ulcerative colitis and colorectal cancer. A population-based study*. N Engl J Med 1990 Nov 1;323(18):1228-33.

(3)Nugent FW; Haggitt RC; Gilpin PA *Cancer surveillance in ulcerative colitis.* Gastroenterology 1991 May;100(5 Pt 1):1241-8.

(4) Lofberg, R *Studies in long standing ulcerative colitis with special reference to malignant transformation of the colorectal mucosa.* Acta Chir Scandinavian Supplement .

(5) Ulcerative Colitis Colan'O Morain Library of congress 1991 page 175

(6) Choi PM; Nugent FW; Schoetz DJ Jr; Silverman ML; Haggitt RC .*Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis*. Gastroenterology 1993 Aug;105(2):418-24.

(7) Mate-Jiminez et al. *Incidence and prevalence of ulcerative colitis and Crohn's disease in urban and rural areas of Spain from 1981 to 1988.* J Clin Gastroenterol. 1994 Jan;18(1):27-31.

(8) http://digestive.niddk.nih.gov/ddiseases/pubs/colitis/index.htm