Chronic Hepatitis C as a Risk Factor for Colonic Neoplasia in a Community Setting

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Introduction

An estimated 3.5 million people have Chronic Hepatitis C (CHC) in the United States [1]. With the current opioid epidemic, the number of people who are injecting drugs in the US. Has substantially increased the incidence of CHC virus [2]. With an apparent second wave of CHC, it will be important to manage the sequelae of these chronically infected patients and recognize associated comorbidities. CHC has been shown to increase the risk of hepatocellular carcinoma and has been linked to such malignancies as Non-Hodgkin lymphoma, cholangiocarcinoma, breast, pancreatic, renal, skin/oral, thyroid, and colon cancer [3-6]. Colon cancer is the second leading cause of cancer-related death in men in developed countries and the third most prevalent cause of death from cancer for women [7]. Colorectal Cancer (CRC) screening has been shown to reduce the risk for the development of CRC and prevent the development of more advanced disease [8,9].

The risks for developing colorectal cancer are associated with increasing age, family history, history of adenomas or Inflammatory Bowel Diseases (IBD) and ethnicity. Other possible risk factors include a high fat, low-fiber diet, obesity, smoking, and excessive alcohol use. A possible link between colon cancer and CHC has not been extensively studied. However, previous studies have suggested that patients with CHC have a higher risk of colonic adenomas and more advanced lesions. Thus, the goal of this study was to determine if patients with CHC undergoing screening colonoscopies or surveillance colonoscopies in a community setting have an increased risk of colorectal cancer.

Methods

This was a retrospective, case-controlled study. The study population consisted of patients with HCV infection with HCV RNA >1,000 IU/ml undergoing either screening or surveillance colonoscopies from April 2008 to November 2015. The participants of the control group were average risk patients for colorectal cancer undergoing colonoscopies during the same time period and were matched with CHC patients according to age, sex, and race. A total of 370 patients were included in the study with 185 patients in each group respectively. Data from 126 patients was available for surveillance analysis.

The database for this study included colonoscopy, histopathology, age, sex, race, and BMI (calculated using height and weight). Other risk factors that were recorded were diabetes mellitus type 1 or 2, smoking history, alcohol history, family history, aspirin use, and statin use. Smoking history was defined as any history of smoking that was recorded in the patients charts, regardless of current status. Alcohol history was defined as any current or past alcohol usage. Family history was defined as diagnosed colon cancer in a first-degree or second-degree relative. Aspirin and statin use were defined as current everyday use of these medications at the time of their last colonoscopy. This data was collected for both the study population and the control population corresponding to the patients most recent colonoscopy.

Each participant had a screening colonoscopy (index colonoscopy) with results recorded along with the year the colonoscopy was performed. Surveillance colonoscopies, defined as any colonoscopy after the index colonoscopy, the number of years since the previous colonoscopy, and the subsequent result were also recorded. For each colonoscopy reported, the total number of polyps were recorded. In addition, the size of the polyps were also recorded based on two categories. The categories were less than 7.5 mm or greater than or equal to 7.5 mm. The polyps were further subdivided into tubular adenomas and advanced neoplasia. Advanced neoplasia was defined as villous histology, high-grade dysplasia, or adenocarcinoma on pathology.

The main outcomes of the study was the incidence of colorectal adenomas and advanced neoplasia. Collectively they are referred as polyps to form an indicator variable 1/0 (yes/no polyps). Logistic regression was performed on the data. A p-value of <0.05 was considered statistically significant. In this instance, a small p-value indicates that the chance of a research group reproducing results that are at least as strong as ours is highly possible. This would support our hypothesis of patients with CHC having an increased risk of developing colonic neoplasia. Logistic regression analysis was used to describe data and to explain the relationship between the dependent variable (yes/no polyps) and AGE, SEX, BMI, and the following indicator variables (yes/no) SMOKING, STATIN (statin use), DIABET (diabetes mellitus), FAM (family history), ASPIRIN (aspirin, nsaid use), CHC (hepatitis diagnosis) as systematic component was: In the logit model p=P (Polyp Present), probability of polyp present was:

\[ \log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_1 \text{AGE} + \beta_2 \text{SEX} + \beta_3 \text{BMI} + \beta_4 \text{SMOKING} + \beta_5 \text{STATIN} + \beta_6 \text{DIABET} + \beta_7 \text{FAM} + \beta_8 \text{ASPIRIN} + \beta_9 \text{CHC} \]

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Results

The screening data consisted of 185 patients with CHC and 185 non-hepatitis controls. The surveillance group had 67 CHC patients and 59 control group patients. Baseline characteristics of patients assessed are transcribed in (Table 1). The CHC group had a significantly higher number of adenomas detected on screening colonoscopy when compared to the control group (70.8% vs. 44.9%; p<0.001, respectively). The study group also had a significant number of larger polyps, defined as being larger than 7.5 mm (31.3% vs. 18.9%; p<0.05, respectively). A trend toward advanced neoplasia was noticed in the CHC group, however, it was not statistically significant (8% vs. 4%; p<0.15) (Table 2). Regression analysis was performed by taking age, sex, BMI, smoking history, statin use, diabetes mellitus, family history, aspirin use, and the hepatitis diagnosis into account. CHC and male sex were found to be the only independent risk factors for colonic neoplasia on regression analysis. The multivariate odds ratio of having polyps in CHC was 255% higher than in controls (odds ratio 3.55, 95% Confidence Interval (CI): 2.15, 5.94) (Table 3). In the surveillance data, the total number of patients with adenomas was higher in the CHC group than in controls (61% vs. 46%, p<0.12). The CHC group had a trend of having polyps larger than 0.75 cm in comparison to controls (25.3% vs. 18.6%, p=NS) (Table 2). Surveillance data regression analysis revealed CHC as an independent risk factor for the development of colonic neoplasia. The odds of having polyps for CHC patients were 228% higher than in controls (odds ratio 3.28, 95% CI: 1.37, 8.25) (Table 3).

Discussion

This study indicates an association between increased numbers of polyps and more advanced neoplasia in patients with CHC undergoing screening colonoscopy. We also demonstrate a higher rate of colorectal adenomas in surveillance colonoscopies of CHC patients. This study could have compelling implications for screening and surveillance colonoscopy in patients with CHC. Data was also collected on the established risk factors and protective factors for colorectal neoplasia. Known risk factors associated with colorectal adenomas are age, male sex, obesity, smoking, diabetes mellitus, and family history [10-16]. A healthy lifestyle is strongly associated with lower risk of all stages of colorectal neoplasm [17]. Aspirin and statin use are also associated with decreased incidence of colorectal adenomas [18-20]. In this study, the only determinants for higher risk of adenomatous polyps was male sex and chronic hepatitis C. Obesity and family history were also positive predictors, but did not reach significance in our study. We also found aspirin and statin use to be negative predictors in concordance with other known protective factors in research, but were not significant. Age, smoking, statin use, diabetes, and aspirin use did not appear to confer protection or risk for colonic neoplasia. The relatively small sample size may have impacted the detection of other existing risk factors for adenomatous polyps or

Table 1: Baseline characteristics of patients undergoing colorectal cancer screening and surveillance in patients with CHC and controls.

|                     | Screening |                     | Surveillance |                     |
|---------------------|-----------|---------------------|--------------|---------------------|
|                     | controls  | CHC                 | p-value      | controls  | CHC                 | p-value      |
| Age (n=185)         | 59.4      | 59.5                | 0.9393       | 61.8      | 62                  | 0.8116       |
| Male Sex (%)        | 110 (59.4)| 109 (59.8)          | >0.99        | 29 (49.1) | 40 (59.7)           | 0.3136       |
| BMI (%)             | 92 (49.7) | 68 (36.8)           | 0.0156**     | 27 (45.8) | 19 (28.4)           | 0.0659*      |
| Smoking (%)         | 88 (47.6) | 139 (74.1)          | <0.01***     | 28 (47.5) | 44 (65.7)           | 0.0599**     |
| Statin Use (%)      | 69 (37.3) | 26 (14.1)           | <0.01***     | 26 (44.1) | 10 (14.9)           | <0.01***     |
| Diabetes Mellitus (%)| 47 (25.4)| 53 (28.6)           | 0.5583       | 12 (20.3) | 29 (43.3)           | 0.0107*      |
| Family History of CRC (%) | 12 (6.5) | 25 (13.5)           | 0.0375**     | 8 (13.6)  | 12 (17.9)           | 0.6725       |
| Aspirin Use (%)     | 74 (40.0) | 51 (27.6)           | 0.0156**     | 27 (45.8) | 26 (38.8)           | 0.5429       |

Significance levels are denoted as: *0.05<p<0.10, **0.01<p<0.05, ***p<0.01

Table 2: Comparison of colorectal neoplasia in the CHC group and the control group.

|                     | Screening |                     | Surveillance |                     |
|---------------------|-----------|---------------------|--------------|---------------------|
|                     | CHC group | Control group       | p-value      | CHC group | Control group       | p-value      |
| Adenomas (%)        | 131 (70.8)| 85                  | <0.001       | 41        | 27                  | 0.016        |
| Advanced Neoplasia | 14        | 7                   |              |          |                     |              |
| (%)                 | -8        | -4                  | <0.015       |          |                     |              |
| Polyps              | 58 (31.3)| -18.9               | <0.05        | 23        | 16                  | NS           |
| >0.75cm (%)         | 37        |                     |              |          |                     |              |

Due to the small number of advanced neoplasia polyps observed (1 in control, 2 in CHC) in the surveillance groups, a meaningful statistical test could not be performed.
Further research is warranted to determine if CHC patients require colorectal cancer screening, shorter intervals of surveillance, and if CHC leads to a higher incidence of colorectal cancer.

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