

Establishing the link between hepatitis B virus infection and colorectal adenoma

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Background: Chronic hepatitis B (CHB) infection has been associated with malignancy, most notably hepatocellular carcinoma. Previous research has shown that hepatitis C is associated with increased colorectal adenomas and neoplasia. Currently, there are no studies on the association of CHB and colorectal adenomas. We aimed to identify a possible link between CHB and colorectal adenoma.

Methods: A retrospective chart review was performed on 588 consecutive patients undergoing screening or diagnostic colonoscopy that were previously screened or diagnosed with hepatitis B. Comparisons between categorical variables were analyzed with Chi Square test and t-test for continuous variables. Unconditional logistic regression was used to generate age-, gender- and race-adjusted odds ratios and their 95% confidence intervals (CI) comparing medication users with non-users. Statistical analyses were performed with SAS 9.3 software.

Results: A total of 487 patients were analyzed in the control group *vs.* 71 in the hepatitis B group. The adenoma detection rate was 23.9% in hepatitis B *vs.* 15.9% in the non-hepatitis B group for all cause colonoscopy; however this did not reach statistical significance. There was a significantly higher number of adenomas present in the distal colon compared to control (OR =2.16; 95% CI, 1.06-4.43; P=0.04). There were no significant findings between hepatitis B infection with size, multiplicity or presence of proximal adenomas. There was a significant difference noted in regards to smoking history, BMI and age between two groups.

Conclusions: Although the adenoma detection rate was higher in hepatitis B population *vs.* the non-hepatitis B group this did not reach statistical significance. However, we did find an association between CHB infection and the presence of distal colorectal adenomas. Larger prospective studies are needed to strengthen our findings along with future studies examining hepatitis B virus (HBV) and mechanisms inducing colorectal carcinogenesis.

Keywords: Colon cancer; colorectal adenomas; hepatitis B

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Introduction

Viruses and their relationship to malignancy is well understood, and has been established in those that chronically affect liver including hepatitis B virus (HBV) and hepatitis C virus (HCV) (1-3). Carcinogenesis in most cases is theorized to occur secondary to critical viral genes interfering with host genes, resulting in the activation of cellular proto-oncogenes and/or the inactivation of anti-oncogenes with their products subsequently leading to neoplastic processes.

Hepatitis B is a formidable health problem worldwide, with an estimated 1 million people dying annually from hepatitis B and its complications. About 90% of healthy adults will recover from acute hepatitis B infection; however, 5-10% worldwide (400 million people) still are infected with chronic hepatitis B (CHB) infection (4). HBV is a small enveloped, partially double-stranded DNA virus from the hepadna family, which integrates its DNA into the host genome (5). The proposed carcinogenic mechanism of HBV occurs through its direct integration of DNA into a host genome, causing production of transforming proteins, mainly protein X and pre S-S proteins (6-9). The progression to hepatocellular carcinoma occurs through chronic inflammation and repeated cellular regeneration of hepatocytes leading to cirrhosis and then malignancy, typically occurring after 25-30 years of infection (10). Chronic HBV infection has also been linked to other malignancies including pancreatic cancer, and hematological malignancies such as non-Hodgkin's lymphoma and chronic lymphocytic leukemia (11-13).

Colorectal adenocarcinoma is the third most common cancer and the third leading cause of cancer-related deaths in both men and woman. In 2011, there were 141,210 new cases of colorectal cancer and 49,380 colorectal cancer-related deaths (14). American Cancer Society recently found the rate people are diagnosed with colorectal cancer in the US has dropped 30% in the last 10 years for those 50 years and older, which is credited to more people following the recommended screening guidelines. Establishing a link with early detection of colorectal adenomas in chronically infected HBV patients can potentially prevent future development of CRC. Recently Rustagi *et al.* suggested a link between chronic hepatitis C (CHC) and higher incidence of colorectal adenoma occurring through a T cell mediated process (15). They proposed the mechanism via T cells mediated cascade of unopposed B cell induction initiated by the HCV envelope

protein E2 binding to CD81 molecule on B cells, lowering the threshold for B cell proliferation (16). In addition, they suggested the HCV core protein may also function as a gene regulator, with the ability to inhibit the tumor suppressor gene p53 and induce the growth factor NF- κ B (17). To our knowledge, a link between chronic HBV and colorectal adenomas has yet to be explored. We aimed to identify the incidence of colorectal adenomas in HBV patients and whether chronic HBV infection is an independent risk factor for colorectal adenomas.

Methods

Patients

Institutional Review Board (IRB) approval was obtained from Nassau University Medical Center in East Meadow, New York. This is a 1,200-bed tertiary care teaching hospital in East Meadow, New York affiliated with North Shore Long Island Jewish Health System. A retrospective chart review was performed between July 1, 2009 to March 21, 2011. We established a database of 558 consecutive patients undergoing screening or diagnostic colonoscopy that had previously been screened or diagnosed with hepatitis B. Data were collected including age, sex, race, smoking, alcohol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hypertension, diabetes mellitus, and dyslipidemia. Patients with incomplete chart records or with colon cancer, inflammatory bowel disease, incomplete colonoscopies were excluded from our study. Information regarding whether the colonoscopy was screening or diagnostic was based on United States Preventative Services Task Force (USPSTF) guidelines. We recorded colonoscopy findings included presence of adenoma, adenoma >9 mm, two or more adenomas. In addition we also distinguished adenoma depending on location whether proximal/distal colon, size, largest adenoma location.

Statistical analysis

Comparisons between categorical variables were made using a Chi Square test and a *t*-test was used for comparisons between continuous variables. Unconditional logistic regression was used to generate age-, gender- and race-adjusted odds ratios and their 95% confidence intervals (CI) comparing hepatitis B group with control. Statistical analyses were performed with SAS 9.3 software.

Table 1 Demographics of hepatitis B and control patients undergoing all cause colonoscopies

Characteristics	No hepatitis B, n=487 (%)	Hepatitis B, n=71 (%)	P value*
Age	53.5±10.5	56.1±8.0	0.02
BMI	29.4±6.4	28.0±6.6	0.10
Sex, female	252 (51.8)	24 (33.8)	0.005
Race			
White	94 (19.3)	18 (25.4)	0.003
Black	150 (30.9)	33 (46.5)	0.003
Hispanic	223 (45.9)	16 (22.5)	0.003
Other	19 (3.9)	4 (5.6)	0.003
Smoking, yes	118 (24.2)	34 (47.9)	<0.0001
Alcohol, yes	89 (18.3)	17 (23.9)	0.26
Diabetes, yes	97 (19.9)	22 (31.0)	0.03
Hypertension, yes	235 (48.3)	35 (49.3)	0.87
Dyslipidemia, yes	125 (25.7)	19 (26.8)	0.84
Family history of colorectal cancer	45 (9.2)	7 (9.9)	0.92

*, use χ^2 test for categorical variables, and *t*-test for continuous variables.

Table 2 The number, size, and location of adenoma encountered during all cause colonoscopies in hepatitis B *vs.* control

Colorectal adenomas	No hepatitis B, n=487 (%)	Hepatitis B, n=71 (%)	P value*	OR (95% CI)*
Adenoma	80 (16.4)	17 (23.9)	0.38	1.33 (0.70-2.51)
Adenoma ≥10 mm	13 (2.7)	2 (2.8)	0.89	1.12 (0.23-5.53)
Adenoma ≥2	27 (5.5)	4 (5.6)	0.94	0.96 (0.30-3.06)
Adenoma present in proximal colon	51 (10.5)	7 (9.9)	0.47	0.72 (0.30-1.75)
Adenoma present in distal colon	44 (9.0)	13 (18.3)	0.05	2.03 (0.99-4.14)
Largest adenoma in proximal colon	38 (7.8)	5 (7.0)	0.33	0.60 (0.22-1.67)
Largest adenoma in distal colon	44 (9.0)	12 (16.9)	0.09	1.88 (0.90-3.90)

*, use logistic model controlling age, sex, BMI, race, alcohol, tobacco, and history of diabetes. CI, confidence interval.

Results

When examining patient demographics in *Table 1*, there were a total of 487 individuals in the control group *vs.* 71 in the CHB group. There was a significant age difference between HBV group and control group ($P<0.05$) with HBV infected patients significantly older 53.5±10.6 *vs.* 56.1±8.0, $P=0.048$. In addition, there was a higher occurrence of HBV in blacks compared to whites, Hispanics, and others (46%, 25%, 22%) respectively. Females were less likely to have hepatitis B at 51.8% compare to 33% with hepatitis B ($P=0.005$). Smoking was more prevalent in HBV group compared to control

group ($P=0.0001$). There was no significant difference between hypertension, dyslipidemia or family history of colon cancer, however there was a significantly increased rate of diabetes 31.0% *vs.* 19.9% seen in the hepatitis B group ($P=0.03$). Similarly, there was no significant difference in alcohol consumption between HBV group and control group. There was significant difference in BMI between control and HBV group (28.8±7.5 *vs.* 26.4±9.1, $P=0.02$).

Table 2 shows the number, size, and location of adenoma encountered during either screening or diagnostic colonoscopy after adjusting for age, sex, race, BMI, diabetes, smoking, and alcohol use. There was a higher

incidence of adenoma presence found in the HBV group compared to control (23.9% *vs.* 16.4%), however this did not reach statistical significance ($P=0.38$). There was a statistically significant higher number of adenomas present in the distal colon compared to control (OR =2.16; 95% CI, 1.06–4.43; $P=0.04$). We found no association with the presence of colorectal adenomas in CHB patients with regard to multiplicity, size, or presence in the proximal colon. There was a significantly higher number of HBV patients with elevated AST and ALT compare to the control group (59% *vs.* 35%, $P<0.0001$).

Discussion

This article presents one of the first studies looking for an association between hepatitis B and colorectal adenomas. Our data shows evidence for an association between HBV infected individuals and a higher detected rate of adenomas located in the distal colon. The carcinogenic properties of HBV infection is likely multi-factorial and remains a heavily studied area of interest. One hypothesis that is suggested which highlights the carcinogenesis process is through the chromosomal segments containing P53, PB Wnt/ β -catenin, transforming growth factor β (TGF- β) and Ras signaling pathways. HBV X protein (HBx) can bind to the p53 tumor-suppressor protein, interfering with the role p53 plays in the cellular response to repair DNA damage. The role of p53 as a key player in the colorectal tumor progression has previously been demonstrated in the adenoma-carcinoma time sequence occurring in the transformation of colorectal adenomas into carcinomas (18), and may serve as a link between HBV and colorectal cancer. Hepatitis B presents with extra-hepatic manifestations including polyarteritis nodosa and glomerular disease, which are thought to be mediated by circulating immune complexes, occurring in ~10% to 20% of patients with chronic HBV infection (19–22). Fahal *et al.* looked at the detection rate of hepatitis B surface antigen (HBsAg) and gastrointestinal tract tumors. The data did not find a significant relationship although they were able to detect HBsAg in primary hepatocellular (25%), gastric (12%), rectal (10%) and colonic carcinoma (8%) (23). Previously other viruses (CMV, HPV, and EBV) were investigated by Boguszaková *et al.* although no viral antigen was detected in 13 patients with adenocarcinoma of colon and 10 patients with endoscopic polypectomies

for colon adenoma using a DNA probe (24). Future studies are warranted looking specifically at HBV and mechanisms inducing carcinogenesis, specifically colorectal adenocarcinoma.

African Americans currently have 20% higher incidence of colon cancer when compared to whites (25). Whether this is genetic, environmental, ability to access health care, or a combination is unknown. In 2010, African-Americans had the highest rate of acute or recent HBV infection, at 1.7 cases per 100,000 persons, 4-fold higher than the rate for whites (26). Similarly, our findings show the highest percentage of the HBV population was African American compared to whites or other groups. It would be of potential interest for future studies to examine if African Americans with HBV have a higher incidence of adenoma compared to the other races with HBV infection through a different mechanism of genetic susceptibility. In addition, other independent risk factors have been identified that increases the risk for CRC such as smoking, metabolic syndrome, increasing age and family history of colorectal cancer to name many of the few (27). Based on evidence identifying African Americans as having a higher colorectal cancer incidence and mortality, a younger mean age of diagnosis, and evidence for more proximal colonic cancer distribution in comparison to whites (28), the American College of Gastroenterology recommends earlier screening at age 45 instead of age 50 recommended for other races (29). This demonstrates the necessity of large scale studies to delineate higher risk patient populations such as ones with HBV infection and the importance of implementing new guidelines for screening and prevention. Given that African American population have a higher incidence of HBV infection and are at higher risk of colorectal adenomas, future large scale studies are recommended for this population.

Strengths of this article include adding data to a topic that is currently limited and unavailable. We hope through our study to encourage further interest for future large scale, prospectively collected data that can answer many of the questions created from our study, and can promote campaigns for HBV vaccination and HBV infection prevention, ultimately decreasing the risk of CRC especially in high risk populations. Limitations include a retrospective design, small sample size, and unknown length of HBV diagnosis. Additionally, the HBV groups were not analyzed in regards to their viral load or genotype. Despite these limitations HBV remains a difficult disease to treat and

many of the patients face a chronic disease, therefore risk factors for other malignancies and complications should be understood to further advance longevity of life in these patients.

Conclusions

In conclusion, we have demonstrated that there is a statistically significant association between CHB infection and the presence of colorectal adenomas in the distal colon. Future large scale prospective studies are needed with specific focus on duration of disease, viral load, and genotype are needed to further delineate our findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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