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Opportunistic Intestinal Infections and Risk of Colorectal Cancer Among People with AIDS

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Abstract

Because mucosal inflammation contributes to colorectal carcinogenesis, we studied the impact of intestinal infections on risk of this malignancy among people with AIDS (PWA). Using the population-based HIV/AIDS Cancer Match, which includes approximately half of all PWA in the United States, the cancer registries ascertained colorectal cancers (ICD-O3 codes C180-C189, C199, C209, and C260). During 4–120 months after AIDS onset, risk of cancer occurring after AIDS-defining intestinal infections (considered as time-dependent exposures) was estimated with hazard ratios (HR) and 95% confidence intervals (CI) calculated by Cox regression. Analyses included cancers overall and by histology and anatomic site. After excluding 118 squamous cell rectal cancers (possible anal cancers), we analyzed 320 incident colorectal cancer cases that occurred among 471,909 PWA. Colorectal cancer risk was marginally elevated following cryptosporidiosis (HR = 2.08, 95% CI = 0.93–4.70, $p = 0.08$) and mucocutaneous herpes (HR = 1.69, 95% CI = 0.97–2.95, $p = 0.07$) but not with *Pneumocystis* pneumonia (HR = 0.79, 95% CI = 0.57–1.10). Cryptosporidiosis was associated with rare colon squamous cell carcinoma [$N = 8$, HR = 13, 95% CI = 1.5–110] and uncommon histologies [HR = 4.4, 95% CI = 1.1–18, $p = 0.04$], but it was not associated with colorectal adenocarcinoma ($N = 269$, HR = 1.3, 95% CI = 0.4–3.9, $p = 0.70$). Mucocutaneous herpes was associated with colon squamous cell carcinoma (HR = 13, 95% CI = 2.4–67, $p = 0.003$) but not with colorectal adenocarcinoma (HR = 1.3, 95% CI = 0.6–2.6, $p = 0.52$) or uncommon histologies (HR = 2.5, 95% CI = 0.8–8.2, $p = 0.13$). Colon squamous cell carcinoma risk was significantly elevated among PWA who had cryptosporidiosis or mucocutaneous herpes. These findings might suggest that HPV or inflammation from other infection may contribute to carcinogenesis.

Introduction

In people infected with human immunodeficiency virus (HIV) there has been an increasing number of non-AIDS-defining cancers, including colon cancer, with the introduction of highly active antiretroviral therapy (HAART). This increase can be attributed to increased longevity, which translates into a growing number of HIV-infected people, aging of the HIV population, longer duration of immune perturbation, longer persistence of oncogenic infections, and more opportunity for carcinogenic exposures.[1] For colorectal cancer, there is mounting evidence of an important role for intestinal microbial organisms in triggering and sustaining inflammation of the colon.[2–4] Recently, two independent groups have discovered that colon cancer tissue, compared to normal colon tissue, was strongly associated with a specific bacterium, *Fusobacterium nucleatum*.[5,6] Beyond common bacterial and protozoan pathogens, such as *Escherichia coli* O157:H7, *Clostridium difficile*, and *Entamoeba histolytica* (amebiasis), AIDS-defining opportunistic infections of the large and small intestine could be exceptionally effective at causing sustained perturbation and inflammation of the colonic mucosa, thereby increasing the risk of malignancy. The possibility that intestinal opportunistic infections may be related to colon cancer has never been investigated. Most population-based studies of HIV-infected people demonstrate that they do not have an elevated risk of colorectal cancer.[7–10] In contrast, Patel *et al*. reported a 2-fold increased risk for colorectal cancer with HIV.[11] Furthermore, a few studies suggest that colorectal cancers may present with more aggressive behavior with HIV.[12–14]

Thus, it is possible that the risk of cancer is elevated with an AIDS-defining opportunistic intestinal infection, due to the infection's associated sustained inflammatory response. Therefore, we analyzed the impact of AIDS-defining intestinal infections on risk of colon cancer using the HIV/AIDS Cancer Match Study data.

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Materials and Methods

Study subjects and exposure ascertainment

We investigated the risk of colorectal cancer in people with AIDS (PWA) and its association with infections, utilizing updated data from the HIV/AIDS Cancer Match Study (http://hivmatch.cancer.gov/).[7] This study links population-based HIV/AIDS and cancer registry databases in 16 U.S. states and metropolitan areas. Colorectal cancer was identified using data from the cancer registries (ICD-O3 topography codes C180-C189, C199, C209, and C260). We excluded non-specific histologies, Kaposi sarcoma, non-Hodgkin lymphoma, and mesothelioma (codes 8000–8005, 9050–9055, 9140, 9590–9998). For rectal cancers, we excluded squamous carcinoma (codes 8050–8084, 8094, 8123, and 8124), which is usually of anal origin rather than colorectal origin.

The AIDS registries collect data on AIDS-defining infections, including cryptosporidiosis, cryptococcosis, cytomegalovirus, esophageal candidiasis, extrapulmonary tuberculosis, *Mycobacterium avium*, and chronic mucocutaneous herpes. All of these particular infections are often accompanied by disseminated infection of the mucosae of the large and/or small intestine, in addition to the primary site of infection. For comparison, *Pneumocystis jirovecii* pneumonia (PCP) was included. Each of these "exposures" was considered if they occurred at AIDS onset (defined as the 0–3 months after the AIDS registration date with an AIDS-defining condition or CD4 <200 cell/mm^3) or subsequent to AIDS onset. Follow-up for cancer started in month 4 or beginning of cancer registry coverage, whichever occurred later.

Statistical analysis

We assessed colorectal cancer risk over a 10-year period, spanning 4–120 months after AIDS onset. We used Cox regression to assess the relationship between infections (considered as time-dependent exposures) with subsequent colorectal cancer risk. These analyses were conducted for all cancers and separately for the colon and rectum/rectosigmoid junction. Additionally, we assessed the relationship by time interval between infection and cancer diagnosis (i.e., latency). We assessed cancer risk with intestinal infections individually and collectively, and PCP as negative control. All statistical tests were two-sided and statistical significance was assessed at $p<0.05$.

Results

The study included 471,909 PWA, of whom 79.5% were male, with a median age at AIDS onset of 37 [interquartile range (IQR) 32–43] years and median CD4 T cell count at AIDS onset of 118 (IQR 40–183) cells/mm^3 (Table 1). There were 438 colorectal cancers (269 adenocarcinoma, 126 squamous cell carcinoma, and 43 other cancers). After excluding 118 squamous cell rectal cancers (possibly miscategorized anal cancers), we analyzed 320 colorectal cancers [269 adenocarcinomas, 8 squamous cell carcinomas, and 43 other cancers including undifferentiated carcinoma (1 case), leiomyosarcoma (3), small cell carcinoma (5), and carcinoma not otherwise specified (NOS, 34)] that were diagnosed within the risk period of 4 to 120 months after AIDS onset. We observed an adenocarcinoma incidence rate of 14.4, 95% CI 12.7–16.2 per 100,000 person-years, and a squamous cell carcinoma incidence rate of 0.43, 95% CI 0.18–0.84 per 100,000 person-years.

Table 1. Characteristics of Individuals Registered with AIDS in the United States Who Were at Risk for Colorectal Cancer

Characteristics	N *(%)*
AIDS diagnosis year	
<1980	18 (0.00)
1980–1989	64,685 (13.71)
1990–1995	210,738 (44.66)
1996+	196,468 (41.63)
Sex	
Male	374,959 (79.46)
Female	96,950 (20.54)
Age at AIDS onset (years)	
0–14	5,434 (1.15)
15–29	75,500 (16.00)
30–39	206,900 (43.84)
40–49	132,416 (28.06)
50+	51,659 (10.95)
Race/ethnicity	
White	175,179 (37.12)
Black	202,889 (42.99)
Hispanic	93,841 (19.89)
CD4 count	
0–49	78,815 (16.70)
50–99	44,451 (9.42)
100–149	46,199 (9.79)
150–199	64,204 (13.61)
200+	45,728 (9.69)
Missing	192,512 (40.79)
Mode of HIV acquisition	
MSM	202,688 (42.95)
IDU	119,019 (25.22)
MSM+IDU	27,118 (5.75)
Heterosexual	62,347 (13.21)
Other categories	60,737 (12.87)
Registry	
Colorado	7,815 (1.66)
Connecticut	12,723 (2.70)
Florida	73,999 (15.68)
Georgia	23,380 (4.95)
Illinois	26,514 (5.62)
Los Angles	50,624 (10.73)
Maryland	26,291 (5.57)
Massachusetts	16,055 (3.40)
Michigan	11,101 (2.35)
New Jersey	41,080 (8.71)
New York city	93,691 (19.85)
San Diego	9,112 (1.93)
San Francisco	23,671 (5.02)
Seattle	6,414 (1.36)
Texas	38,493 (8.16)
Washington, DC	10,946 (2.32)

Subjects were evaluated for colorectal cancer within a risk period of 4 to 120 months after AIDS diagnosis.

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus infection; MSM, men who have sex with men; IDU, injection drug users.

At or after AIDS onset, the following 10 infections postulated to possibly affect colorectal cancer risk were recorded: esophageal candidiasis (42,216; 9.0%), disseminated *Mycobacterium avium* complex infection (22,351; 4.7%), mucocutaneous herpes

Table 2. Risk of Colorectal Cancer by Exposure to Selected Infections

Infection	*Infection* N[a]	*Cancer* N *(%)*	*Hazard ratio (95% CI)*[b]	p *value*
No selected infection[c]	364,324	258 (0.07)	1.00	
Any selected infection[c]	107,426	62 (0.06)	1.23 (0.92–1.64)	0.168
Esophageal candidiasis	42,216	28 (0.07)	1.34 (0.90–1.98)	0.147
Mycobacterium avium complex	22,351	6 (0.03)	0.77 (0.29–2.07)	0.603
Mucocutaneous herpes	14,351	15 (0.10)	1.69 (0.97–2.95)	0.066
Cytomegalovirus, systemic	14,127	5 (0.04)	1.03 (0.42–2.49)	0.952
Cryptococcosis, extrapulmonary	13,884	4 (0.03)	0.74 (0.27–1.98)	0.542
Extrapulmonary tuberculosis	8,737	7 (0.08)	1.60 (0.75–3.40)	0.222
Cryptosporidiosis	7,978	7 (0.09)	2.08 (0.93–4.70)	0.077
Atypical mycobacterium	4,633	2 (0.04)	1.03 (0.26–4.15)	0.965
Salmonella septicemia	933	1 (0.11)	2.10 (0.29–14.96)	0.461
Coccidioidomycosis	587	0 (0.00)	—	0.958
Pneumocystis pneumonia	117,373	48 (0.04)	0.79 (0.57–1.10)	0.167

Cancers occurred within risk period of 4 to 120 months after AIDS diagnosis.
[a]Infections are not mutually exclusive.
[b]Models were run separately for each condition and adjusted for age, sex, race, mode of HIV acquisition, CD4 count, and AIDS diagnosis year.
[c]Selected infections are listed as those that may involve the colorectum, excluding *pneumocystis* pneumonia.

(14,351; 3.0%), systemic cytomegalovirus (14,127; 3.0%), extrapulmonary cryptococcosis (13,884; 2.9%), extrapulmonary tuberculosis (8737; 1.9%), cryptosporidiosis (7978; 1.7%), atypical mycobacteria (4633; 1.0%), salmonella septicemia (933; 0.2%), and coccidioidomycosis (587; 0.1%). *Pneumocystis* pneumonia (PCP), the negative comparison infection, occurred in 117,373 (24.9%) of the PWA.

As shown in Table 2, colorectal cancer risk was not significantly elevated following the first diagnosis of an intestinal infection when considered together (HR = 1.23, 95% CI = 0.92–1.64, $p = 0.17$). Considering the infections individually, PWA with cryptosporidiosis and mucocutaneous herpes were at borderline higher colorectal cancer risk than those without (HR = 2.08, 95% CI = 0.93–4.70, $p = 0.08$ and HR = 1.69, 95% CI = 0.97–2.95, $p = 0.07$, respectively). We did not detect any significant difference in cancer risk for the remaining infections.

The colorectal cancer risk associations did not differ for infections that occurred at AIDS onset versus after AIDS onset (cryptosporidiosis $p = 0.26$, mucocutaneous herpes $p = 0.59$), nor did the risk of colorectal cancer vary with time since cryptosporidiosis ($P_{trend} = 0.76$) or time since mucocutaneous herpes ($P_{trend} = 0.57$). Colorectal cancer risk did not differ significantly among PWA diagnosed with cryptosporidiosis or mucocutaneous herpes in the pre-HAART era compared to PWA diagnosed with cryptosporidiosis or mucocutaneous herpes in the HAART era ($p = 0.62$ and 0.45, respectively). Similarly, the cancer associations with cryptosporidiosis or mucocutaneous herpes did not vary by age, sex, race/ethnicity, risk group, or CD4 count ($P_{interaction} \geq 0.40$ for all).

As shown in Table 3, cryptosporidiosis was associated with excess risk for rare squamous cell colon carcinoma (HR = 13) and colorectal cancers of uncommon histologies (HR = 4.4). Mucocutaneous herpes was associated with excess risk for squamous cell colon carcinoma (HR = 13) and nonsignificantly with colorectal cancers of uncommon histologies (HR = 2.5). One squamous cell carcinoma case had been

Table 3. Risk of Colorectal Cancer Following Cryptosporidiosis and Mucocutaneous Herpes by Histology and Anatomic Site

		Cryptosporidiosis				*Mucocutaneous herpes*			
	Cancer N	N	*Unadjusted HR (95% CI)*[a]	*Adjusted HR (95% CI)*[a,b]	p *value*[a,b]	N	*Unadjusted HR (95% CI)*[a]	*Adjusted HR (95% CI)*	*p value*[a,b]
Cancer histology									
Adenocarcinoma	269	3	1.0 (0.3–3.1)	1.3 (0.4–3.9)	0.70	10	1.0 (0.5–2.1)	1.3 (0.6–2.6)	0.52
Squamous cell carcinoma	8	1	13 (1.6–100)	13 (1.5–110)	0.02	2	11 (2.2–54)	13 (2.4–67)	0.003
Other[c]	43	3	4.3 (1.0–18)	4.4 (1.1–18)	0.04	3	2.4 (0.7–7.8)	2.5 (0.8–8.2)	0.13
Cancer site									
Proximal to rectosigmoid junction	176	4	2.1 (0.8–5.6)	2.3 (0.9–6.3)	0.13	9	1.6 (0.8–3.2)	1.9 (0.9–3.8)	0.08
Rectum/rectosigmoid junction	144	3	1.2 (0.3–5.0)	1.6 (0.4–6.6)	0.50	6	1.2 (0.5–2.9)	1.5 (0.6–3.6)	0.42

[a]Analyses were run separately for each intestinal infection condition and by each cancer subtype.
[b]Models were adjusted for age, sex, race, mode of AIDS acquisition, CD4 count, and AIDS diagnosis year.
[c]Other cancers include small cell carcinoma, leiomyosarcoma, and undifferentiated carcinoma.

diagnosed with both cryptosporidiosis and herpes. Colorectal adenocarcinoma risk was not associated with cryptosporidiosis (HR = 1.3) or mucocutaneous herpes (HR = 1.3). The risk of colorectal cancer in association with cryptosporidiosis or mucocutaneous herpes did not differ by anatomic site [colon (HR = 2.3 and 1.9, respectively); and rectum/rectosigmoid junction (HR = 1.6 and 1.5, respectively)].

Discussion

Intestinal infections with nontyphoidal salmonella, campylobacter, shigella, *Clostridium difficile,* and *E. coli*, as well as mucocutaneous candidiasis, are common among PWA.[15–19] *Fusobacterium nucleatum*, which contributes to periodontitis and was recently discovered in close association with colon cancer, can be highly invasive.[5,6] The prevalence of *F. nucleatum* among PWA is unknown. Given accumulating evidence that infection and especially inflammation might contribute to colorectal cancer pathogenesis among individuals in the general population,[3,4,20] we evaluated whether the diverse and severe intestinal infections that are diagnostic of AIDS could provide a different perspective and insight on the association. In agreement with this hypothesis, we found that colorectal cancer risk was increased approximately 2-fold with cryptosporidiosis and approximately 1.7-fold with mucocutaneous herpes, although neither of these met the conventional criterion for statistical significance. The associations with cryptosporidiosis and mucocutaneous herpes did not appear to vary in subgroups defined by demographic and HIV-related variables, including availability of HAART. Importantly, colorectal cancer risk with cryptosporidiosis or mucocutaneous herpes was not increased for adenocarcinomas; although our estimates were based on few cases, risk was significantly increased only for squamous cell carcinoma of the colon.

A role for *Cryptosporidium* and herpes simplex virus in colorectal cancer may be plausible. Chronic intestinal *Cryptosporidium parvum* infection is not rare in people with advanced HIV infection, and the organism has been observed in malignant colon tissue.[19,21–27] Using a mouse model, Sasahara *et al*. demonstrated the loss of absorptive cells and goblet cells, and the apoptosis of intestinal epithelial cells following *Cryptosporidium parvum* infection.[28] This protozoan is usually an intracellular parasite of the small intestine epithelium. However, it also is seen on the surface of epithelial cells in histological examinations of colon biopsies of PWA.[29] In addition, *Cryptosporidium parvum* infection was associated with the formation of polyps and high-grade neoplasia in the cecum and proximal gut of corticosteroid-treated immune deficient mice.[2]

In addition to being an AIDS-defining condition,[30] herpes simplex virus, like HIV, is often acquired sexually.[31] In addition, PWA are at higher risk for reactivated and severe herpes infections due to AIDS-related immunosuppression. Among PWA, herpes simplex often manifests as proctitis, esophagitis, and perianal lesions.[19,32–34] Herpes simplex virus has been implicated as a possible cofactor for anal and cervical cancers.[35–37]

The majority of colorectal malignancies both in the general population and among PWA are adenocarcinomas. However, unlike the general population, we identified higher proportions of other cancer histologies.[38,39] For example, compared to the general population, more PWA cases were classified as squamous cell carcinoma (2.5% vs. 0.04%), small cell carcinoma (1.6% vs. 0.08%, respectively), and leiomyosarcoma (0.9% vs. 0.04%, respectively).[39] Notably, the associations that we observed with cryptosporidiosis and mucocutaneous herpes were with rare subtypes. We observed a significant excess risk of squamous cell colon carcinoma in association with cryptosporidiosis and mucocutaneous herpes, although these associations were based on only one to two cancer cases in PWA with these infections. In addition, risk of other uncommon colorectal cancers (including small cell carcinoma, leiomyosarcoma, and carcinoma NOS) was significantly elevated in association with cryptosporidiosis and nonsignificantly with mucocutaneous herpes.

An excess risk of these uncommon and aggressive cancers might reflect concomitant HIV-associated conditions, particularly human papillomavirus virus (HPV),[40] which shares the same transmission route with mucocutaneous herpes. In support of this notion, HPV DNA has been detected in primary squamous cell carcinoma of the rectum,[41–43] malignancies that we excluded from our analyses to reduce misclassification of anal cancer. Importantly, squamous cell carcinoma, not only of the rectum but also of the cecum and right colon, has been associated with inflammatory bowel disease, especially ulcerative colitis, and with HPV, schistosomiasis, and *Entamoeba histolytica* infections.[44,45]

Ascertainment and reporting of AIDS-defining intestinal infections may have varied across both calendar time and between the AIDS-onset period and the subsequent follow-up periods, which could have biased our results. Arguing against ascertainment bias, the associations of cryptosporidiosis and mucocutaneous herpes with colorectal cancer did not differ by calendar time or AIDS-relative time. The lack of a significant trend in colorectal cancer by time since cryptosporidiosis or mucocutaneous herpes diagnosis reduces the possibility of reverse causality, i.e., that subclinical colorectal cancer facilitated the establishment of cryptosporidiosis or mucocutaneous herpes. Nonetheless, our ability to test for interactions of these infections with time was limited by the small number of exposed colorectal cancer cases. Importantly, the tumors with cryptosporidiosis, mucocutaneous herpes, or both were located in the large intestine proximal to the rectum, but the exact site was unspecified. Thus, misclassification of anal cancer cannot be completely excluded.

Our study has several strengths, such as the use of population-based data and the ability to assess the temporal association of infections with colorectal cancer. Although we had a very large population, with nearly half of all PWA in the United States, some of our analyses of particular infections and subgroups suffered from sparse data resulting in low statistical power. An additional limitation was our inability to accurately define the anatomic location of infections, given that our assessment of intestinal infections was based on AIDS registry data.

In summary, PWA with chronic cryptosporidiosis or mucocutaneous herpes had an increased risk for colorectal cancer of borderline statistical significance, and they had a statistically significant, 12-fold increased risk for colon squamous cell carcinoma. As noted previously for inflammatory bowel disease, these findings suggest that severe intestinal infections can contribute to colon carcinogenesis.

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F.M.S. participated in the design of the study, carried out the analysis, and drafted the manuscript. E.A.E. and J.J.G. participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Author Disclosure Statement

No competing financial interests exist.

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