

REVIEW ARTICLE

Infection and Colorectal Neoplasm

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ABSTRACT

Colorectal cancer is a major cause of cancer-related morbidity and mortality. Colorectal cancer is the third most common malignancy and the 4th most common cause of cancer mortality worldwide. A number of infectious agents are considered to be cancer risk factors due to the hypothesis-generating and supportive evidence accumulated to date. It has been estimated that one fifth of all cancer is caused by some infectious agent(s). Infections from certain bacteria, such as *Helicobacter pylori* (*H. pylori*), *Streptococcus bovis* (*S. Bovis*), viruses, such as human papillomavirus (HPV), human cytomegalovirus (HCMV), and parasites may increase the risk of colorectal cancer. More studies are needed to learn the association of infectious agents with the incidence of colorectal cancer.

Keywords: colorectal cancer, infectious agents, malignancy, neoplasms

ABSTRAK

Kanker kolorektal merupakan penyebab utama morbiditas dan mortalitas terkait kanker dan merupakan kanker nomor tiga tersering serta penyebab nomor empat dari kematian kanker di seluruh dunia. Sejumlah agen infeksius dianggap faktor risiko kanker terkait hipotesis dan bukti yang ditemukan dan mendukung fakta terkini. Diperkirakan bahwa seperlima dari semua kanker disebabkan oleh beberapa agen infeksi. Infeksi dari bakteri tertentu, seperti *Helicobacter pylori* (*H. pylori*), *Streptococcus bovis* (*S. Bovis*), virus, seperti Human papillomavirus (HPV), Human cytomegalovirus (HCMV), dan parasit dapat meningkatkan risiko kanker kolorektal. Penelitian lebih lanjut diperlukan untuk mengetahui asosiasi agen infeksi dengan kejadian kanker kolorektal.

Kata kunci: kanker kolorektal, agen infeksi, ganas, neoplasma

INTRODUCTION

Colorectal cancer (CRC) is a major cause of cancer-related morbidity and mortality. Colorectal cancer is the third most common malignancy and the 4th most common cause of cancer mortality worldwide. Colorectal cancer can be classified as inherited (due to

genetic instability), inflammatory (due to the presence of chronic inflammation of the gastrointestinal tract, e.g., Crohn's disease) or sporadic, which accounts for more than 80% of all CRC.¹

High-fat diet, living in Western Countries (which can be related to the diet of the Western Civilizations,

diets higher in red meat and fats) and obesity are risk factors for CRC. On the other hand, vitamin D, high fiber diet and fish intake are associated with decreased risk of CRC. The long list of cancer risk factors continues to evolve, and in the past few decades has expanded to include infectious agents.¹

A number of infectious agents are considered to be cancer risk factors due to the hypothesis-generating and supportive evidence accumulated to date. It has been estimated that one fifth of all cancer is caused by some infectious agent(s). In the case of CRC, the most recent list of acknowledged risk factors still does not include infectious agents, despite the current trend in the literature that supports this association. As our understanding of the underlying molecular processes in colorectal-cancer develops, the concept of microbial–epithelial interactions as an oncogenic trigger might provide a plausible hypothesis for the pathogenesis of colorectal cancer.² It is reported that viruses and bacteria can cause CRC through direct mutagenesis, secretion of mutagenic products and/or prolonged infection and accompanying inflammation that leads to increased epithelial cell proliferation. This increased cell proliferation, on the other hand, has the potential to preferentially select carcinogenic clones. Data available that addresses specific mechanisms remain limited and well-designed clinical trials with large patient populations to provide adequate statistical power are needed in order to adequately evaluate this hypothesis.¹

Helicobacter pylori

Helicobacter pylori is classified as a class I carcinogen by the International Agency for Research in Cancer due to the strong correlation between *H. pylori* infection and gastric cancer. *H. pylori*, a gram negative rod, is well adapted for life within the human stomach. It invades through a pH neutral niche between the mucus layer of the stomach and the gastric epithelium; it further has a set of adaptations which allows it to survive and modify innate immune responses. Interestingly, *H. pylori* does not invade tissues. Also, it does not enter epithelial cells nor does it penetrate the basal membrane; however, *H. pylori*

does cause prolonged inflammation which is one of its proposed mechanisms for the development of neoplastic changes.³

Brim et al found that there is correlation between *H. pylori* and colorectal neoplasm. Prevalence of colorectal polyps and adenomas were 456 (36%) and 300 (24%) respectively. Colorectal polyps were more prevalent in gastric *H. pylori* infected than non-infected subjects [43% vs. 34%; (95% CI = 1.2-1.9; OR = 1.5; p = 0.001)]. Patients with *H. pylori*-associated chronic active gastritis were at high risk to have adenomas (95% CI = 1.0-1.8; unadjusted OR = 1.3; p = 0.04). Gastric *H. pylori* infection, age, and male gender were independent risk factors for colorectal polyps. Serological testing also revealed a higher prevalence of *H. pylori* and its toxin Cag-A in polyp patients vs. non polyp patients' sera, although in a non-statistically significant manner.⁴

Recent studies based on large databases with careful control for confounding variables have clearly demonstrated an increased risk of colorectal neoplasm associated with *H. pylori* infection. *H. pylori*-related chronic active gastritis confers an increased risk of colorectal neoplasm, and more extensive atrophic gastritis will probably be associated with even higher risk of neoplasm. The activity of *H. pylori*-related chronic gastritis is correlated with colorectal neoplasm risk. *H. pylori*-related chronic gastritis could be involved in an increased risk of colorectal neoplasm that appears to be enhanced by the progression of gastric atrophy and the presence of active inflammation.⁵

Meta-analysis was obtained from 22 studies of 86,880 cases and 93,760 controls, of which 13,318 cases and 10738 controls were *H. pylori* positive. As shown in Figure 1, the overall OR was 1.49 (95% CI = 1.30-1.72), and the test for the overall effect Z value was 5.57 (p < 0.05).⁶ Wu et al, also have reported the same result (95% CI = 1.18-1.64; OR = 1.39).⁷

Shmueli et al reported 10-fold increase in colorectal cancer risk with CagA(+) strains compared to CagA(-) strains (95% CI = 2.7– 41.3; OR = 10.5; p = 0.001).⁸ Meucci et al found a significant relationship between seroprevalence of *H. pylori* and the risk of developing colorectal adenomas (CRA) but not CRC.⁹

Table 1. Studies investigating correlations between *Helicobacter pylori* and risk of colorectal neoplasm⁵

Country	Year of publication	Type of study design	No. of subjects	Measure of <i>H.pylori</i> status	Outcome	Crude OR (95% CI)	Adjusted OR (95% CI)
Taiwan	2010	Cross sectional	9311	Urease test	Adenoma	-	1.37 (1.23-1.52)
South Korea	2012	Cross sectional	2195	IgG	Adenoma	1.35(1.10-1.66)	1.36 (1.10-1.68)
					Advance-adenoma	2.19 (1.40-3.42)	2.21 (1.41-3.48)
Japan	2011	Population-based case control	478	IgG	Adenoma	2.26 (1.44-3.55)	2.52 (1.57-4.05)
Germany	2012	Population-based case control	3381	IgG	Cancer	-	1.3 (1.14-1.50)
				CagA	Cancer		1.35 (1.15-1.59)

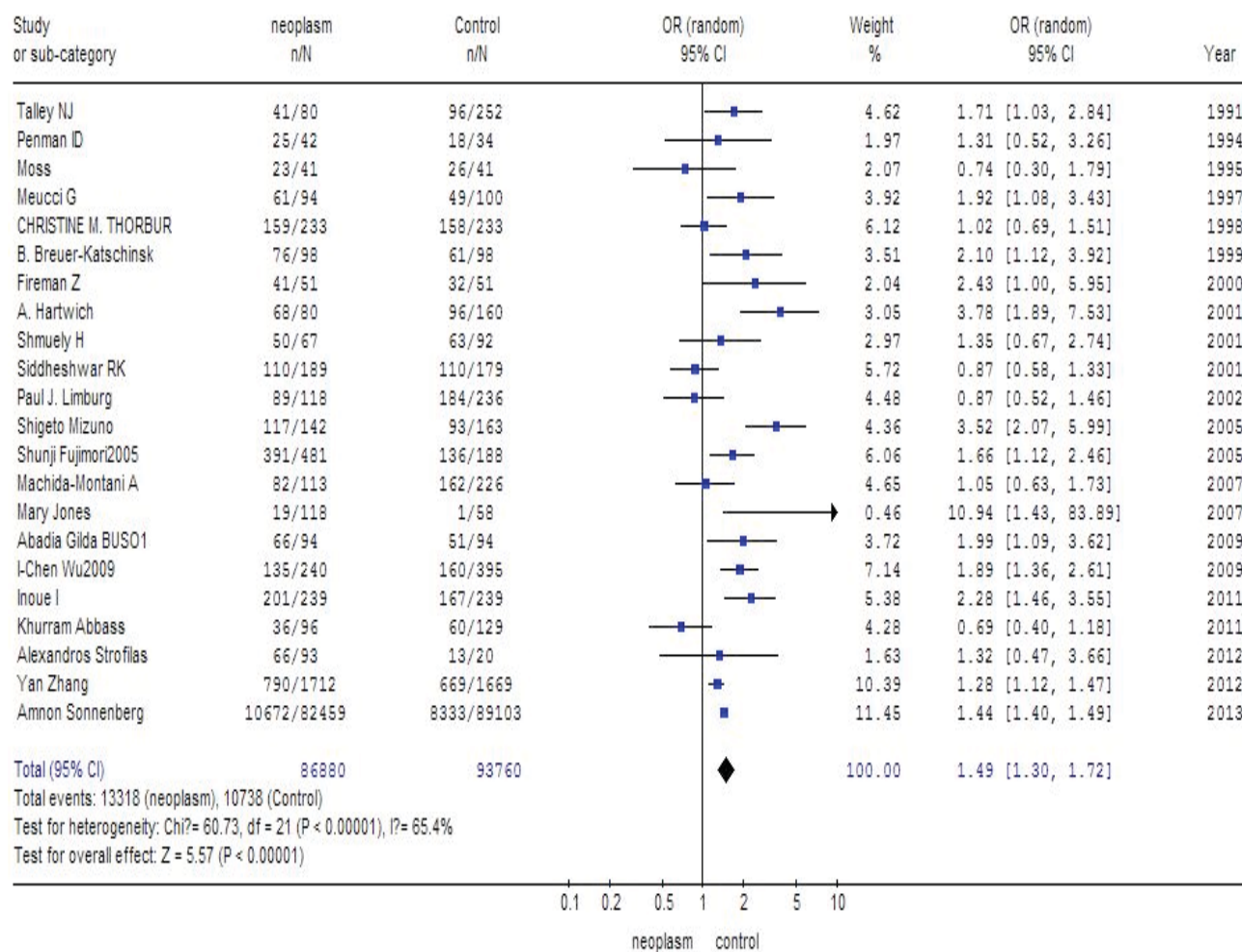


Figure 1. Association between *H. pylori* infection and colorectal adenoma and adenocarcinoma⁶

Various mechanisms have been suggested to underlie the correlation between *H. pylori* infection and colorectal neoplasm. *H. pylori* infection increases gastrin secretion, which could contribute to colorectal carcinogenesis by inducing mucosal cell proliferation in the colon. An epidemiological study of patients with *H. pylori* infection showed that mild hypergastrinemia was associated with about a 4-fold increase in the risk of colorectal neoplasm.⁵ Gastrin is a candidate trophic factor that can possibly mediate the effects of *H. pylori* on tumors. Patients with *H. pylori* infection have increased basal and postprandial serum levels of gastrin. Thus, a plausible hypothesis is that *H. pylori* infection promotes colonic neoplasia by inducing hypergastrinaemia. Then, gastrin increases the expression of cyclooxygenase 2, a pro-inflammatory enzyme that releases excessive amounts of prostaglandin E2, leading to further mucosal proliferation, reduction of apoptosis, angiogenesis and tumor growth.⁹

H. pylori infection might result in damage to the colorectal epithelium through inflammatory responses, such as those mediated by interleukin (IL)-8, which is associated colorectal cancer.⁵

Streptococcus bovis

S. bovis, a non-enterococcal group D Streptococcus, is a bacterium that is found among the normal flora of the human gastrointestinal (GI) tract in 5% to 16% of adults. In addition, *S. bovis* is commonly detected as a contaminant in packaged meat. If *S. bovis* enters the blood stream, it can cause bacteremia and endocarditis. *S. bovis* type I, recently reclassified as *Streptococcus gallolyticus*, have an increased risk of prevalent colorectal neoplasia. Studies of *S. bovis* reveal that this bacterium releases proteins that stimulate inflammation. In addition, *S. bovis* proteins were associated with an in vitro overexpression of cyclooxygenase-2, which is known to be frequently over expressed in human colorectal cancers and which can inhibit apoptosis and increase angiogenesis.¹⁰

Sanchez et al reported one hundred nine cases of SGG (*S. gallolyticus* subsp. *gallolyticus*) bacteremia were detected (mean age, 66 years; 87% male). Colonoscopy was performed in 98 cases, diagnosing 69 cases of CRN: 57 adenomas (39 advanced adenomas) and 12 invasive carcinomas. Only 4 cases had suspected CRN before the blood culture. The

Table 2. Comparison of colorectal pathology in patients with bacteremia due to *Streptococcus gallolyticus* subs *gallolyticus* and control group¹¹

	S. gallolyticus subsp. Gallolyticus Bacteremia (n=96)^a	Control Group (n = 196)	OR (95% CI)	p Value
Age, mean ± SD	66.2 ± 11.7	66.3 ± 11.9		NS
Sex, % male	89 (91%)	178 (91%)	1.0 (.4 – 2.3)	NS
Born in Spain	98 (100%)	192 (98%)	4.6 (.2-86.4)	NS
Symptoms^b	11 (11%)	143 (73%)	0.05 (.02-1)	.0001
Colorectal neoplasia^c	69 (70%)	62 (32%)	5.1 (3.0-8.6)	.0001
Nonadvanced adenoma	18 (19%)	23 (12%)	1.7 (.9-3.3)	NS
Advanced adenoma	39 (40%)	31 (16%)	3.5 (2.0-6.1)	.0001
Invasive carcinoma	12 (12.5%)	9 (5%)	2.9 (1.2-6.9)	.03

prevalence of CRN was higher in patients with SGG bacteremia than in the 196 control patients (70% vs. 32%; 95% CI = 3.0–8.6; OR = 5.1; 95%).¹¹

Boleij et al reported among the *S. bovis*-infected patients who underwent colonic evaluation, the median percentage of patients who had concomitant adenomas/carcinomas was 60% (interquartile range, 22%), which largely exceeds the disease rate reported in the general asymptomatic population. Meta-analysis showed that patients with *S. bovis* biotype I infection had a strongly increased risk of having CRC (95% CI = 3.94–13.36; pooled OR = 7.26) compared with *S. bovis* biotype II-infected patients. Notably, CRC occurred more often among patients with *S. bovis* IE than among patients with *S. bovis* infection at other sites (95% CI = 2.03–6.81; pooled OR = 3.72).¹²

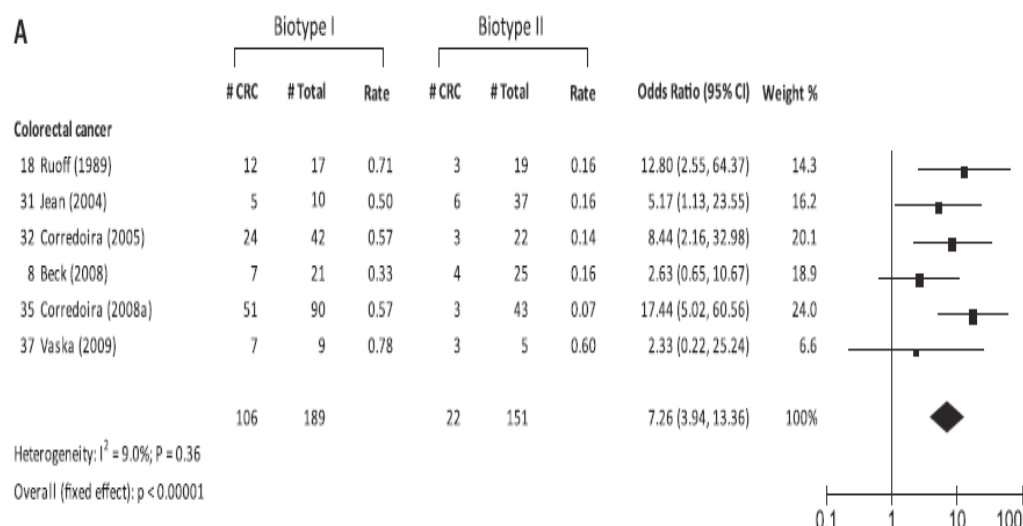
Klebsiella pneumoniae

Klebsiella pneumoniae is a gram-negative, non-motile, encapsulated, lactose fermenting, facultative anaerobic, rod shaped bacterium found in the normal flora of the mouth, skin, and intestines. It is most commonly associated with pneumonia and is a common cause of infections in the urinary tract, lower

biliary tract, and surgical wound sites. Pyogenic liver abscess (PLA) is caused by bacteria and depending on the geographical data, most commonly isolated bacteria from pyogenic liver abscesses are *E. coli* for the Western Countries and *K. pneumoniae* for the eastern populations.¹

There are a number of case reports showing a positive correlation between PLA caused by *K. pneumoniae* and CRC. In one meta-analysis, 30 case reports were identified and analyzed along with two case-controlled studies. Researchers found strong correlation between *K. pneumoniae*-caused PLA and CRC and they reported isolation of these bacteria from 50% of this patient population.¹³

A retrospective study was conducted on 2,294 patients of which 1,194 (52%) had *K. pneumoniae* infection. During a 10-year follow-up period, 54 (2.3%) patients were diagnosed with CRC, corresponding to an overall incidence rate of 669.1 (95% CI = 490.7–847.6) per 100,000 person-years. The adjusted hazard ratio of CRC was 2.68 times greater for patients with *K. pneumoniae* PLA than for those with non-*K. pneumoniae* PLA (95% CI = 1.40–5.11). There is very limited mechanistic data to support these findings,

**Figure 2. The relationship between biotype and colorectal cancer¹²**

even though there is an increasing body of evidence about the positive correlation between *K. pneumoniae* PLA and CRC.¹⁴

Fusobacterium

Fusobacterium is the genus of anaerobic, gram-negative bacteria rod-shaped bacilli with pointed ends. Strains of Fusobacterium contribute to several human diseases, including periodontal diseases, Lemierre's syndrome, and topical skin ulcers. In 2011, researchers discovered that this bacteria flourishes in colon cancer cells, and is often also associated with ulcerative colitis.¹

Flanagan et al reported that relative quantification of Fusobacterium is significantly higher in colorectal tumor tissue than in matched normal colorectal epithelium tissue, in all CRC cohorts (Czech $p = 0.0016$; Germany $p = 0.0001$; Ireland $p = 0.0063$). There is a significant difference between quantification in tumor tissue and tissue of less advanced forms of adenoma (CRC vs. TA $p = 0.0287$; CRC vs. TVA $p = 0.0013$). As in CRC, high grade dysplasia shows elevated *Fusobacterium nucleatum* quantification in disease tissue compared to matched normal colorectal epithelium tissue ($p = 0.0148$).¹⁵

Fusobacterium contributes to CRC development through several mechanisms: invade colonic mucosa (highly invasive), induce local inflammation, and increase the expression of cytokines.¹⁵

Human Polyoma Virus

Human infection with the polyomavirus, JCV, is extremely common, affecting up to 80% of the population. Although the route of transmission for JCV is unknown, primary infection generally occurs in early childhood. The vast majority of those infected with JCV have no symptoms, and the virus travels to the kidneys, where it remains latent. However, severe immunosuppression, as seen in transplant patients and those with advanced HIV disease, can trigger reactivation of the virus causing a serious demyelinating disease known as progressive multifocal leukoencephalopathy. The oncogenic properties of JCV are well described in the literature and attributed to the viral protein, large T-antigen. Laboratory studies of this viral protein have shown that the large T-antigen has the ability to immortalize cells in culture. The mechanism for this cellular transformation has been studied: the large T-antigen binds p53 and members of the pRb family of proteins, thereby blocking tumor suppression and inducing unchecked cellular replication. This is

hypothesized to result in chromosomal instability, which is common in colon carcinogenesis.¹⁰

Casini et al reported that 16 out of 18 patients (88.9%) have been positive for the presence of viral DNA, assessed with three techniques, PCR, Northern blot and *in situ* hybridization, within the primary tumor mass and peri-tumoral tissue.¹⁶

Theodoropoulos et al reported that 61% of 80 patients with carcinomas, 60% of 25 patients with adenomas, and 30% of controls were PCR positive for JC virus. Statistically higher number of JCV copies in adenoma and adenocarcinoma than normal tissues with a much higher relative number of copies/ μg of DNA (9-20x10³ copies/ μg DNA vs 50-450 copies/ μg DNA).¹⁷

Human papillomavirus (HPV)

HPV is a double-stranded DNA virus that infects basal layer epithelial cells through microscopic abrasions or tears. There are more than 100 types of HPV, and about 40 of these types are known to infect genital epithelial cells. Not all types of HPV are associated with cancer. Currently, types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 are classified as "high-risk" oncogenic infections. Of these, types 16 and 18 are the most common types found in cervical cancer tumors, with one review finding that 70% of cases were positive for HPV-16, HPV-18, or both. HPV infection is a necessary cause of cervical cancer and is associated with other epithelial malignancies, such as oropharyngeal, penile, vaginal, vulvar, and anal cancers.¹⁰

Oncogenic HPV allows for the growth of cancerous cells through the expression of viral proteins E6 and E7. These interfere with tumor suppressor proteins, p53 and pRb, and induce telomerase, thereby immortalizing cells. Thus, HPV-related tumors infrequently contain p53 mutations. In a meta-analysis of nine case controlled-studies OR associated with HPV in CRC ranged from 2.7 to 9.1 (95% CI = 1.1-6.2 and 95% CI = 3.7-22.3).¹⁰

Damin et al reported HPV DNA was detected in colorectal specimens of 60 patients with cancer (83.3%), but in none of the tissues from the control group ($p < 0.001$). HPV16 was the viral type most frequently detected, being present in 41 out of 60 positive cases (68.3%).¹⁸

Bodaghi et al found that colorectal tissues from 28 of 55 (51%) patients with colorectal cancer were positive for HPV DNA. Colorectal tissues from all 10 control individuals were negative for HPV DNA ($P = 0.0034$). HPV 16 being the most prevalent type. The HPV infection may play a role in colorectal carcinogenesis.¹⁹

Table 3. Summary of evidence linking gastrointestinal parasites and neoplasia²¹

Parasite	Cancer type	Site	Types of studies	Probability of causation of neoplasia
S. japonicum	Adenocarcinoma	Colon and rectum	Case-control studies, epidemiological studies, case series, and many case reports	Probable
S. mansoni	Adenocarcinoma	Colon and rectum	Case control studies, case reports	Equivocal, weak association
E. histolytica	Adenocarcinoma	Colon	Rare case reports	Unlikely
A. lumbricoides	Adenocarcinoma	Biliary tract and ampulla	Rare case reports	Unlikely
Anisakis	Adenocarcinoma	Colon	Rare case reports	Unlikely
G. lamblia	Ductal adenocarcinoma	Pancreas	Rare case reports	Unlikely

Human cytomegalovirus (HCMV)

HCMV can induce genes that are contributing to cancer progression (Bcl-2 and COX2). A larger study of 163 CRC tissues and non-neoplastic adjacent tissues as controls were tested for the presence of HCMV. The results showed HCMV DNA (PCR), was detected in 42.3% (69/163) of the tumor specimens, while only 5.6% (14/163) of samples of adjacent non-neoplastic tissue were positive for HCMV ($p < 0.0001$). Quantitative real-time PCR in 54 sample pairs revealed significantly higher viral copies in the tumor specimens than the adjacent non-neoplastic tissue specimens ($p < 0.001$).²⁰

Parasites

A link between *S. japonicum* and colorectal neoplasia has been debated for decades. The first reports on this topic began to appear in the English literature in the late 1950's. Since this time, there have been a large number of patients reported individually or in groups with both colorectal carcinoma and evidence of infection by *S. japonicum*. *S. japonicum* associated colorectal cancers. It appears that the chronic inflammatory response due to deposited schistosome ova plays an etiologic role. No evidence was found to suggest that ova release a mutagenic factor.²¹

Qiu et al reported 142 colon cancer patients were compared to 285 matched control patients in Sichuan, China. Out of 142 colon cancer patients, 42 (30%) gave a history of previous *S. japonicum* infection, as compared to 14% of control patients. From this data, the authors reported a statistically significant association between *S. japonicum* infection and colon cancer (OR = 3.3, $p < 0.01$).²²

CONCLUSION

Infections from certain bacteria (*H. Pylori*, *S. Bovis*, etc) viruses (HPV, HCMV, etc) and parasites may increase the risk of CRC. More research is needed to learn the pathogenesis of infectious agents with the incidence of CRC.

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