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Review Article

Schistosoma japonicum–Associated Colorectal Cancer: A Review

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Abstract. *Schistosoma japonicum* is a digenetic blood fluke that has been implicated in the carcinogenesis of several human malignancies, notably liver and colorectal cancer (CRC). *Schistosoma japonicum*–associated colorectal cancer (SACC) is a distinct subtype with biological behavior analogous to colitis-induced CRC. The clinicopathological characteristics of SACC include young age at diagnosis, predominance among males, a strong predilection for the sigmoid colon and rectum, multifocal distribution, frequent mucinous histology, and poor prognosis. In addition to chronic inflammation, immunomodulation, and schistosomal toxins, bacterial coinfection appears to play an important role in the carcinogenic process. The present review provides the most recent updates on epidemiology, pathobiology, and clinical and prognostic features pertaining to SACC.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer death worldwide, accounting for nearly 10% of the total newly diagnosed cancer cases and 8.5% of the total cancer deaths.[1] Multiple genetic and environmental factors have been implicated in colorectal carcinogenesis, including inflammatory bowel disease, tobacco smoking, excessive alcohol consumption, and high consumption of red and processed meats.[2] However, most of these factors confer a moderate risk. Recently, several pathogens with oncogenic potential have been associated with increased risk of CRC, although direct causal inference has not been established.[3]

On a global scale, around 2.2 million new cancer cases are attributable to carcinogenic infections, representing 15.4% of the total new cancer cases. This fraction is higher in developing countries, with more than 22% in East Asia.[4] Most of these infection-related cancers are caused by viral and bacterial agents. Meanwhile, human helminths are less appreciated. Among these, *Schistosoma japonicum*, a zoonotic trematode that is endemic in Indonesia, the Philippines, and mainland China, has been classified by the International Agency for Research on Cancer as a probable carcinogen in humans (class 2B) causing liver cancer.[5] In parallel, a growing body of epidemiological and pathological evidence is implicating *S. japonicum* infection in colorectal carcinogenesis, leading to tumors with a distinct biological behavior.[6] Nonetheless, the experimental evidence supporting this association is meager. This may be ascribable to the difficulty in maintaining *S. japonicum* infection in experimental animals, poor multiplication of the intermediate *Oncomelania* snails in artificial conditions, and the relatively lengthy life cycle of the parasite system.[7,8]

The purpose of this review is to provide updates on the epidemiology and clinicopathology of *S. japonicum*–associated colorectal cancer (SACC), with special consideration placed on the etiopathogenesis of this clinical entity.

ASSOCIATION BETWEEN *S. JAPONICUM* AND CRC

Epidemiological studies. The evidence associating chronic *S. japonicum* infestation with CRC has emerged from several population-based ecological studies that correlated the incidence and mortality of cancer with prevalence of infection in various geographical areas, and a few case–control studies. In the early 1970s, an epidemiologic parallel between the distribution of large bowel cancer and schistosomiasis japonica endemicity was noted in the eastern Chinese provinces.[9] Ecological studies in the same endemic areas showed a strong geographical correlation between the prevalence of schistosomiasis japonica and CRC incidence and mortality.[10] Likewise, large-scale analyses demonstrated a parallel correlation between CRC-associated mortality and schistosomiasis japonica endemicity and mortality in rural China, even after adjustment for dietary factors.[11–13] The continuing high incidence of CRC in endemic regions was attributed to the high prevalence of chronically infected individuals. This conclusion was further bolstered by a retrospective cohort study conducted in an endemic area in Japan, where the standardized mortality ratio for colonic cancer was significantly high in females who lived in the area for 50 years or more.[14]

More importantly, a case–control study carried out in the endemic area of Jiangsu Province, China, demonstrated that the risk of rectal cancer was increased among subjects with a previous diagnosis of *S. japonicum* infection with odds ratios of 4.5 and 8.3 (depending on the type of controls used), but the risk of colon cancer was not significantly increased in the same patient group.[10] In a similar investigation in the same endemic area, Guo et al. confirmed strong associations between colon cancer and early- and late-stage *S. japonicum* infection, regardless of the type of control used for comparison. When the results were adjusted for smoking and family history of colon cancer, statistically significant associations were still noted. In addition, the estimated relative risk increased with the duration of exposure to *S. japonicum* infection.[15] Of interest also is a recent matched case–control study which reported that patients with chronic schistosomiasis japonica have more than three times risk of developing colon cancer than those with no previous exposure to schistosomal infection. Moreover, the authors attributed 24% of colon cancer cases to long-standing schistosomal infection.[16]

Pathological studies. Pathological consequences of *S. japonicum* infection are primarily due to host reaction to the deposited eggs, which are characteristically retained in clusters in the gut wall, particularly the large intestine, or flow

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backward and cause egg embolism in the liver or other organs.[8,17] In the colorectum, the sequestered eggs in the mucosa and submucosa incite a severe focal inflammatory reaction with cellular infiltration and consequent minute mucosal ulcerations, and microabscesses and granuloma formation. The continuous irritation produced by the egg nests eventually leads to fibrosis, mucosal hyperplasia, polyposis, and pseudopolyposis.[18–20]

The transition from schistosomal colitis to cancer development has been investigated by Chen et al.,[21] who examined 90 specimens from patients with SACC and proposed that *S. japonicum* colitis, in its late phases, is a premalignant condition not infrequently leading to cancer. Supporting their previous results and giving better insight into the pathogenesis of SACC, the same authors examined the mucosal changes in the immediate vicinity of the tumors in 289 colectomy specimens of patients with SACC and referred to the close similarity between certain schistosome-induced lesions and those associated with long-standing ulcerative colitis. Pointing to the mimicry of cancer evolution in these two clinical entities, they described the presence of pseudopolyps, multiple ulcers, and hyperplastic ectopic submucosal glands, with evidence of oviposition and precancerous and cancerous transformation in these lesions.[22] In addition, it was demonstrated that the closer to the tumor the area is, the more the ova tend to be detected.[23] In a separate study, Chen et al.[24] observed variable degrees of colonic epithelial dysplasia in 60% of cases with *S. japonicum* colitis and regarded these changes as the transition to cancer development in schistosomal colonic disease. A similar conclusion was drawn by Yu et al.[25] from their studies on different types of schistosomal egg polyps.

Generally, SACC develops in patients who had a history of schistosomiasis for 10 years or more and in whom the large bowel is wholly involved.[22,26] The prevalence of CRC in patients with colonic schistosomiasis japonica runs between 6.3% and 37.1%, depending on the diligence with which the diagnosis was sought and the patient group among which the disease was described.[22,27–29] Tumors are mostly adenocarcinomas and are found at varying stages of differentiation.[22,30] Mucinous histology has been reported in 3–31% of patients.[27,30–32] Seventy to eighty percent of SACCs are located in the rectosigmoid region, figures that are higher than those reported (40–65%) for CRC without schistosomiasis.[11,22,26,27] The lesions not uncommonly exhibit multicentric and multifocal distribution, and are significantly larger in size relative to non-schistosomal CRC.[27,30,31,33,34]

Age and gender ratios. Worldwide, the peak incidence of sporadic CRC occurs in the sixth and seventh decades of life; only 2–8% of CRC cases occur in people younger than 40 years.[35] On the contrary, and possibly due to the early environmental exposure to schistosomal infection in childhood, SACC was notably shown to occur in the younger age group with a maximum age incidence 6–16 years earlier than ordinary CRC[21,22,26,27]; more than half of SACC patients are less than 40 years of age at diagnosis.[22,26,34] The gender ratio of male to female in SACC ranges between 1.4:1 and 3:1 and is consistently higher than that in non-schistosomal CRC.[22,27,26,31] This can be attributed to the fact that men are more prone to schistosomal infection through contact with cercariae-infested waters during agricultural activities.

Mechanisms of carcinogenesis. The pathogenesis of SACC is a complex process that probably involves multiple mechanisms. From the existing evidence, the following mechanisms may be suggested.

Inflammatory cells. Although several factors may interact to induce carcinogenesis, chronic inflammation appears to play a pivotal role in the initiation and promotion of SACC. Chronic inflammatory reaction provoked by schistosome antigens results in hyperplasia and adenomatous changes of the colonic epithelium, rendering the epithelium vulnerable to genotoxic agents,[36] and provides the proliferative stimulus necessary to promote cancer growth from potentially malignant foci produced by exogenous carcinogens.[22] Moreover, activated macrophage and other inflammatory cells at the sites of inflammation are implicated in the generation of genotoxic mediators, such as reactive oxygen and nitrogen species and pro-inflammatory cytokines, that lead to DNA damage and subsequently to events such as mutations, DNA strand breaks, sister chromatid exchanges, and dysregulation of oncogenes and oncosuppressor genes.[37–39]

Schistosomal toxins. Further explanation for the carcinogenic process of SACC is a possible mutagenic effect of schistosomal toxins. In support of this hypothesis is the presence of inducible nitric oxide synthase (iNOS) in *S. japonicum* eggs, larval stages, and adult worms.[40] In both clinical and experimental CRC studies, iNOS activity has been implicated in p53 mutation and tumor angiogenesis through generation of high concentrations of nitric oxide, thereby playing a role in tumor initiation and progression.[41,42] The mutagenicity of *S. japonicum* soluble egg antigens (SEA) has also been evaluated using the Ames *Salmonella/Escherichia coli* test in the presence and absence of rat liver S9 mixture. Although no mutagenic activity for the soluble extracts of both eggs and adult worms was identified, a weak but significant tumor-promoting activity was noted for the *S. japonicum* SEA when tested using cultured viral genome–carrying human lymphoblastoid cells.[43]

Bacterial coinfection. Prolonged *Enterobacteriaceae* infections, particularly *Salmonella* sp., have been reported concurrently with *S. japonicum* infestation, which confers a survival advantage to bacteria by inducing immunosuppression.[44–50] Both severe clinical infection and chronic carrier state of *Salmonella enterica* subsp. (serovars Typhi/Paratyphi, *Typhimurium*, and Enteritidis) are associated with increased risk of developing CRC, suggesting a contribution of these pathogens to the multistep process of colorectal carcinogenesis.[51,52] In a recent experiment testing whether *Salmonella* could lead to cancer formation in pretransformed host cells, *S. typhimurium* induced CRC in genetically predisposed (adenomatous polyposis coli ±) mice.[53] In addition, *S. enterica* AvrA, an effector protein detectable in *Salmonella*-infected mice with colon cancer and human colorectal tumor specimens, can promote tumorigenesis in the intestinal mucosa through various epigenetic mechanisms: upregulation of the *Wnt/β-catenin* signaling pathway, c-Jun N-terminal kinase pathway inhibition with consequent apoptosis suppression, and p53 acetylation.[54,55] Other mechanisms of *Salmonella*-mediated carcinogenesis include chronic inflammation, activation of environmental procarcinogens, and alteration of the host transcriptome.[56]

Immunomodulation. Helminth parasites may promote carcinogenesis through downregulation of immune surveillance and antitumor immunity, leading to escape of mutated host cells and accelerating tumor growth.[57] Several types of

immunosuppressive cells are involved in this process: myeloid-derived suppressor cells (MDSCs), type 2 natural killer T cells, regulatory T cells (Tregs), and tumor-associated macrophages. Experimental evidence indicated that SEA and schistosome worm antigen enhance the accumulation of MDSCs in lymphoid organs and tumor microenvironment via activation of JAK/STAT3 signaling pathway.[58] *Schistosoma japonicum* infection–induced MDSCs, a procarcinogenenic heterogeneous group of immature myeloid cells, inhibit T cell functions and proliferation, especially $CD8^+$ T cells via secretion of inhibitory cytokine interleukin (IL)-10 and alteration of L-arginine pathways. The latter mechanism comprises an increase in arginase 1 expression, induction of iNOS activity, and production of reactive oxygen species.[58,59] Furthermore, MDSCs exert non-immunological functions, including the promotion of angiogenesis, tumor invasion, and metastasis.[60] In a separate experiment, *S. japonicum* infection expanded $CD4^+CD25^+$ Tregs in mice.[61] Besides modulating IL-17–driven immune procarcinogenesis, $CD4^+CD25^+$ Tregs can suppress the activation and proliferation of $CD4^+$ T and $CD8^+$ T cells by mechanisms of direct contact or secretion of suppressive factors IL-10 and transforming growth factor-β, thereby favoring CRC progression.[62,63]

Molecular alterations. Recent studies have shed light on the molecular events associated with SACC, taking the latter as a separate clinical entity. Zhang et al.[64] investigated the mutation pattern in the p53 gene in *S. japonicum*–associated rectal carcinomas. They observed a higher proportion of base pair substitutions at 5′-cytosine-phosphate-guanine-3′ dinucleotides and arginine missense mutations among schistosomal rectal cancer patients than in patients with ordinary CRC, albeit the differences were of marginal significance. Their results also indicated that most mutations in *p*53 gene were in exon 7 in the schistosomal group compared with exon 5 in the non-schistosomal group. Borrowing from the ulcerative colitis example, nitric oxide, an endogenously produced genotoxic agent, is capable of inducing similar transition mutations and activation of p53 gene in the inflamed colonic mucosa.[65] Conceivably, therefore, chronic colonic inflammation induced by schistosomal infection may follow a similar pathway.

Prognosis. *Schistosoma japonicum* infestation may exercise some influence on the prognosis of CRC patients. It has been reported that the 5-year survival rate for patients with CRC complicated with schistosomiasis japonica was 45.6% of 430, which was significantly lower than that in those without schistosomiasis (50.9% of 2,717).[11] Wang et al.[33] reviewed 30 patients with *S. japonicum*–associated rectal cancer and concluded that schistosomiasis was the only independent prognostic factor for worse disease-free survival and overall survival. In a subsequent analysis of 74 SACC patients by the same authors, it was demonstrated that the site of deposition of *S. japonicum* eggs in the colonic wall significantly correlated with the overall survival, although it did not independently predict survival. Of note, the presence of schistosome eggs at the resection margin did not correlate with the overall survival nor affected the risk of anastomotic leakage. The authors indicated that the current standard surgical resection of CRC appears to be sufficient and there is no evidence that the scope of surgical resection should be expanded.[34]

CONCLUSION

Even though experimental evidence is currently lacking, the consensus of available epidemiological and pathological data strongly implicates an association between *S. japonicum* infestation and induction of CRC. Some unique characteristics of SACC seem to already be emerging from the existing literature, including young age at diagnosis, male predominance, distal colonic location, multifocal distribution, and poor prognosis. Multiple genetic and epigenetic changes occur during the development of SACC. Although some of these changes may play an integral role in tumor progression, others appear to have a significant impact on the prognosis. Further epidemiological and experimental studies are warranted to investigate the causal relationship between *S. japonicum* and colorectal malignancy. We believe that control of schistosomiasis japonica in these endemic areas and more frequent treatment as part of mass drug administration programs may play a key role in decreasing the disease morbidity and CRC incidence.

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