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REVIEW ARTICLE

A Current Perspective of *Schistosomiasis* in Association with Colorectal Carcinogenesis

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Abstract:

Background:

Schistosomiasis is one of the parasitic infections that are often found in humans. More than approximately 200 million people are infected with *Schistosomiasis* in tropical and subtropical areas of Africa, South America and Asian countries. Literature has long been suggesting the correlation between *Schistosomiasis* and colorectal malignancy. There is a considerable directory supporting the etiological relation between *Schistosoma japonicum* infection and colorectal cancer in the Far East, however, the available data about the role of *Schistosoma mansoni* that can initiate the carcinogenesis of colorectal remain insignificant.

Objective:

As such, more studies of this disease should be conducted comprehensively for corporate social responsibility internationally.

Methods:

The present study reviewed the available data about the role of *Schistosoma*, including *S. mansoni* in association with the carcinogenesis of colorectal.

Results:

The study shows the possible evidence of epidemiology, pathology, molecules and immunopathology associated with Schistosomal infections and colorectal cancer. The infections are apparently getting little attention nor support worldwide due to the geographical barriers and some political issues because it mainly occurs in the people living in the bottom billion and happens in the endemic regions only.

Conclusion:

The in-depth study of this infectious disease will tailor early diagnosis, novel prescription drugs and cost-effective strategies for the treatment of infectious disease colorectal cancer, and hence eradicate the disease in the endemic regions.

Keywords: *Schistosomiasis*, Colorectal cancer, Neglected infectious disease, *Schistosoma mansoni*, *Schistosoma japonicum*, Disease eradication.

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1. INTRODUCTION

Schistosomiasis is a fairly predominant infectious disease that is caused by trematode of the Schistosoma genus in tropical and subtropical areas [1, 2]. It is the second most common parasitic infections for human after Malaria in the world. The diseases affect the health of more than 200 million people worldwide, particularly to the people living under poor and transmission-favourable conditions [1, 3]. *Schistosomiasis* that occurs in humans is mostly caused by three main species of Schistosoma; *Schistosoma mansoni* (*S. mansoni*) that constantly occurs in the endemic areas of South America, the Middle East and Africa, whereas *Schistosoma japonicum* (*S. japonicum*) commonly occurs in Southeast Asia, the Philippines, Southern China and Laos [4, 5]. On the other hand, *Schistosoma haematobium* (*S. haematobium*) is prevalent in the Middle East and Africa [1, 6].

The development of molecular biology has provided guidelines to clarify the relationship between the agents of the

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infection of this disease in the development of cancers. Studies of the development of cancers have delivered a great deal of valuable information on the molecular basis of carcinogenesis and infectious disease [7, 8]. The infection of this disease can initiate or enhance carcinogenesis through three main mechanisms. Firstly, the infection induces chronic inflammation that happened due to the long-term continuation of infectious agents inside the host. The release of nitrogen and reactive oxygen radicals lead to DNA damage of the host cells. Secondly, it induces active oncogene insertion into the host genome. The oncogene causes distinct changes in gene expression in infected patients, leading to cancer development. Thirdly, it induces immune-surveillance reduction as a result of immunosuppression [9], leading to the high tendency of an infected patient to develop cancer. With this regard, infections with *Schistosomiasis* can be related to the aetiology of inflammation, oncogene expression and immunosuppression of various human malignancies, including liver and bladder cancers, as well as recently colorectal cancer.

Schistosomal infections may lead to complications, *e.g.* chronic intestinal and hepatosplenic Schistosomiasis, which has high morbidity and mortality if the disease is not diagnosed and treated early. Many reports describe the association of *S. japonicum* with bowel malignancy [10 - 12] and *S. hematobium* in urinary bladder malignancy [13]. Considerable evidence has also supported an etiological relation between *S. japonicum* and colorectal carcinogenesis. Indeed, existing data demonstrated that Schistosomal colitis caused by *S. mansoni* is more ordinarily related to an earlier stage or beginning of multicentric colorectal carcinoma [8]. However, the precise role of *S. mansoni* in colorectal carcinogenesis remains meagre.

The infectious disease that commonly occurs in the tropics is probably associated with various malignant colorectal diseases [14, 15]. The precursors of colorectal carcinoma have been demonstrated to be chronic inflammatory bowel diseases, *e.g.* Crohn's and ulcerative colitis diseases, though adenomatous polyps also cause colorectal cancer development. Infections of *S. mansoni* and *S. japonicum* in the intestine begin with segregated eggs in the mucosa and submucosa, inciting a severe inflammatory reaction with cellular infiltration and consequent granuloma formation in the intestine [16 - 18]. This reaction, in turn, leads to the development of mucosal ulceration, microabscess formation, polyposis and neoplastic transformation that may result in the development of colorectal cancer. Inflammation due to other factors may also cause colorectal cancer, but inflammation induced by infection agents accelerates the carcinogenesis. Most of the issued data regarding this infection indicate *S. japonicum* and colorectal cancer, whereas the scientific data refer *S. mansoni* to colorectal carcinogenesis remains rare.

2. EVIDENCE ACQUISITION

There are considerable directory and evidence supporting the etiological relation between *S. japonicum* infection and colorectal cancer in the Far East, however, the available data about the role of *S. mansoni* that initiate the carcinogenesis of colorectal more ordinarily remain insignificant. Work of literature have long been suggesting the correlation between *Schistosomiasis* and colorectal malignancy. As such, this review aims to shed light on the evidence that supports the relation between *Schistosomiasis*, including *S. mansoni* infection and colorectal carcinogenesis to prove that studying *S. mansoni* is as important as studying other species of Schistosoma.

3. RESULTS

3.1. Epidemiological Evidence

A few epidemiological studies have reported the possible association between the infection of *S. mansoni* and colorectal cancer. The previous study noted that there was a significant variance in the geographical distribution of infection with *S. mansoni*, where the colorectal cancer was clearly shown to be associated with *S. mansoni* in the African continents [11]. Moreover, this infection is associated with inflammation. Any infection, including with *S. mansoni* that showed a strong effect on inflammation is related to chronic infections of the gastrointestinal tract and is likely to lead to tumour development. For example, a recent study in Uganda and Zimbabwe that compared 950 cases of the infective gastrointestinal disease found that 34 of the patients with the colorectal disease had chronic *Schistosomiasis* or *Amebiasis* [19]. Therefore, it concludes that large bowel cancer is possibly correlated with chronic infections and gastrointestinal diseases that are possibly associated with Schistosomal infections, including *S. mansoni*.

Another study that recruited 93 patients with colorectal cancer with or without *S. mansoni* infection in Sudan reported that 40-43% of the patients diagnosed with malignant colorectal cancer by colonoscopy and histopathology were infected with *S. mansoni* [20]. Furthermore, 40% of the colorectal cancer patients infected with *S. mansoni* were younger than 40 years [21, 22] and as much as 21% of young children were infected with *S. mansoni* in the country [23, 24]. Studies have also shown that 90% of colorectal cancers are affected by environmental factors and only 10% are due to genetics [25]. The factors of genetic include uncommon gene mutations that reduce the penetration defence and inherited gene expression in the family group are unusual. The factors associated with exposure to Schistosoma in young people and children include a contaminated environment, swimming pool water [26, 27] and the westernization of their diet [28]. Processed western foods are often contaminated with chemical substances and microorganisms because of multiple handling processes that are not hygienic.

Studying the correlation of Schistosomal infections with colorectal cancer revealed that men have a higher tendency to develop the infections than women [29 - 32], although McDermott found an equal sex distribution [33] and age groups [34] of the infections. The tendency may also be due to the influence of male hormones [35]. Speculation suggested that the spread of Schistosomal infections in men is caused by more exposure to this infection. Most men work or seek work in agricultural areas that may be exposed to a contaminated environment, in which this infection occurs in the areas rapidly. As a result, men have a higher tendency to develop more Schistosomal infections, including *S. mansoni* infection. This high male tendency to develop an infection is also not fully hormone-dependent [36, 37]. Indeed, women with Schistosomal infections had a 3-4 fold increased risk of getting the Human Immunodeficiency Virus (HIV) compared to women without Schistosomal infections, increasing the ease of transmitting the HIV to their sexual partners [38, 39].

3.2. Pathological Evidence

The pathological changes of *Schistosomiasis* with colorectal carcinoma that have been described may, partially, play an aetiological role in bowel carcinogenesis [11, 40]. Of the cases studied, around 60 cases of Schistosoma granulomatous disease of the large intestine were identified without carcinoma and 36 patients were found to have mild to severe

dysplasia. The changes of dysplastic are considered as the pathological basis for the malignant probability of Schistosomal colitis and these changes are found in long-term ulcerative colitis [11, 41]. Chronic intestinal Schistosomiasis is noted as potentially a pre-cancerous condition [42, 43] and many investigators believe that the mechanism of injury caused by Schistosoma is due to the endogenous production of toxins by eggs rather than a direct carcinogenic action of the eggs [43]. On the other hand, Matsuda believed that Schistosomal ova also displayed some effects on carcinogenesis [17, 44].

In line with the above phenomenon, two cases were reported regarding this phenomenon by Al-Mashat in Saudi Arabia [43]. The first case presented a 46-year-old Saudi male patient with a two-month history of constipation and faecal soiling, whereby *S. mansoni* eggs were found in faecal. The case was also reported to be associated with rectal bleeding, anal pain, loss of weight and appetite. No previous similar symptoms and no family history of colorectal polyps or malignancies were found in the patient. The history before *Schistosomiasis* was not clear, but the results of rectal biopsy could moderately distinguish between adenocarcinoma and Schistosomal colitis. On the other hand, the second case presented a 55-year-old male patient, who lost 8 kg over four months and was under medications for diabetic and hypertensive, without the family history of ulcerative colitis or history of colorectal neoplasms or *Schistosomiasis*. The patient looked well upon examination, whereby the systemic review and abdominal examination were unremarkable; the rectal mass was extending down to the anal verge as observed by rectal examination and invasive moderately differentiated adenocarcinoma with many *S. mansoni* ova was shown in the biopsy.

In addition, other cases have also been reported in Sudan [11]. For example, an elderly man, who aged 35 years presented with a history of stomach cramps in the lower left stomach for four years. He suffered from abdominal pain, bleeding at rectal frequently and almost constant in the last two months of his medical history. This patient, who came from Al-Gezira province, was suffering from anorexia with frequent weight loss. Another reported case was that of a patient from the Al-Gezira state, an area of high endemicity of *Schistosomiasis* in Sudan, at the age of 20 was infected with *S. mansoni*. This patient, who had later received anti-Schistosoma treatment and the abdominal sonography, did not reveal significant periportal fibrosis or splenomegaly. The overall examination of the specimen showed an ulcerated tumour, *S. mansoni* ova in a cancerous tumour and colonic submucosa, where eggs were seen more in tumour tissue than in normal tissue. This case is consistent with the conditions of the infection, whereby intestinal *Schistosomiasis* induces various pathologic conditions, including carcinoma [11, 15, 17, 42, 45, 46], lymphoma [15, 47] polyps [17, 48, 49], carcinoid [43] and pedunculated teratoma [43].

3.3. Molecular Evidence

Parasitism is highly correlated with defective in DNA repair, which is known as microsatellite instability [50]. This errors of DNA replication can affect the target genes in cell replication, *e.g.* transforming growth factor-bRII and insulin-like growth factor-2R. This phenomenon renders cells unable of normal colonocyte homeostasis that can lead to abnormal growth [51]. Farid and his colleagues found a strong association between the Transformation-related Protein 53 (TP53) mutation and *S. mansoni* in colorectal cancer [7]. This close association supports the idea that Schistosoma colorectal cancer and harmful biological behaviour are related to the TP53 mutation [52]. Furthermore, Zhang and his colleagues suggested that the clastogen of TP53 was derived from *S. japonicum*, subsequently, others had found cross-reactivity and antigenic communities in different *Schistosomiasis* species [53, 54]. Consequently, the molecules derived from *S. mansoni* inactivated TP53 resulting in the progression of Schistosoma associated colorectal cancer. Hence, *S. mansoni* is believed to be indirectly implicated in the progression of colorectal cancer.

On the other hand, a report denied the statements that the worms and egg extracts were mutagenic [55], but colorectal cancer was a special clinical entity with a young age predilection, male predominance, distal colorectal prevalence and advanced-stage presentation. A more comprehensive study was developed by Zalata of the expression pattern of B-cell lymphoma 2 (Bcl-2), MYC proto-oncogene (c-myc) and protein 53 (p53) in 75 colorectal cancer cases, in which 24 of the cases were pathologically associated with *S. mansoni* infection [56]. The results showed a significant association between *S. mansoni* and colorectal cancer characterized by overexpression of Bcl-2 with less apoptotic activity than seen commonly in colorectal cancer, whereas the results did not show an association between p53 and c-myc expression with parasitism. This evasion of apoptosis phenomenon through a change in Bcl-2 expression may be due to an alternative molecular pathway, which induces carcinogenesis in intestinal *Schistosomiasis*. It is indicated that many genetic changes occur during the *S. mansoni* colorectal carcinogenesis that plays a significant role in the development and progression of the tumour. The molecular profile of *S. mansoni* colorectal carcinoma is believed to be different than the profile that has been demonstrated in colitis induced carcinomas, indicating that other factors than inflammation are also implicated in the carcinogenic process.

3.4. Immunopathology Evidence

Many explanations to clarify the potential role of *Schistosomiasis* that induces colorectal tumorigenesis have been mentioned in previous studies, where the existence of parasites endogenously generated carcinogens [11, 57, 58]. Therefore, the presence of Schistosomal toxins [59], chronic immune-modulation that results in the impairment of immunological surveillance [60] and symbiotic action of other infective agents [11, 59, 61, 62] in *Schistosomiasis* are believed to induce tumourigenesis. All of these factors might interact to induce chronic inflammation and carcinogenesis. Schistosomal infections affect the host immune response in two ways that extend the carrier state of the parasite. Firstly, by anti-idiotype antibodies produced in patients with chronic *Schistosomiasis* to down-regulate specific immune responses and suppress non-specific immune responses [63 - 65]. Secondly, by modifying the subpopulations of thymus helper cells to lower immune surveillance of infected organism and human [66, 67].

Inflammatory cells produce potential genotoxic mediators, *e.g.* reactive oxygen, nitrogen and pro-inflammatory cytokines that may induce genomic instability and the dysregulation of oncogenes and oncosuppressor genes during Schistosomal infections [68, 69], whereas the mutation of these molecular disorder leads to the development of carcinoma. The existence of concomitant enterobacterial infections in the host might play a significant role in the colorectal carcinogenesis of *Schistosomiasis* patients. Different strains of enteric bacteriaceae have been described in association with Schistosomal infections, granting a survival advantage to bacteria by inducing immune suppression [70]. Part of these organisms is capable of stimulating colorectal carcinogenesis during various pathways, *e.g.* production of reactive oxygen intermediates, dysregulation in the T-cell response and modification the epithelial carbohydrate expression in the host [71]. Patho-

logically, *Schistosomiasis* leading to colorectal cancer is demonstrated by dysplastic morphological changes, aggressiveness in both pathologic variants and the tumour microenvironment, as well as elicitation of a poor host immune response.

Post *S. mansoni* infection, the T-helper 2 cell activity and cytokines involved in eosinophilia and immunoglobulin E secretion are stimulated [72]. On the other hand, the cytokines of T-helper 1 cell activity, *e.g.* Interleukin-2, interferon-gamma and cytotoxic CD8+ T-cells are demonstrated to be down-regulated in BALB/C mice post infected with *S. mansoni*. Other studies have shown that colorectal cancer is usually found in patients with a history of 10 years or more of *Schistosomiasis* and in whom the large bowel is wholly involved [11]. There is a high rate of synchronous tumours in patients with Schistosoma colorectal cancer than in patients with spontaneous colorectal cancer [73]. This phenomenon can be due to the infection that is caused by chronic Schistosomal inflammation throughout the colon and rectum, an event that is similar to that described in the case of colitis-associated cancers. Chronic intestinal inflammation, on the other hand, is a well-known risk factor for colorectal cancer progression [74]. The chronic inflammatory response induced by Schistosome antigens provides the proliferative motivation that is indispensable to enhance the cancer growth from potentially malignant foci. The increase in the epithelial cell proliferation post infection probably participates in cancers, but it is not sufficient to cause carcinogenesis.

CONCLUSION

The compelling epidemiological and molecular data, as well as the immunopathological features of *Schistosomiasis* colorectal cancer, describe a potential role for chronic *Schistosomiasis* in enhancing carcinogenesis of colorectal cancer and the inflammation represents the most important factor in the carcinogenic process. We believe there is more to explain the association between *Schistosomiasis* and colorectal cancer, particularly in the cases infected with *S. mansoni*, but yet to be fully elucidated. Many countries in South East Asia, including Malaysia, the Philippines and other tropical countries that are heavily burdened with the float season and tends to get contaminated river water and other sources of water, have not eliminated these parasites. As the published data linking *S. mansoni* to colorectal cancer occurrence remain rare, we adapted the success stories of Japan and the coastal plain of the People's Republic of China, which have been successfully free from Schistosoma over the last two decades, as the role model to eradicate the diseases. Studying this topic in depth may help to tailor early diagnosis, novel prescription drugs and cost-effective strategies for treatment of infectious disease colorectal cancer, and hence eradicate the disease in the endemic regions in the near future.

LIST OF ABBREVIATIONS

HIV	=	Human Immunodeficiency Virus
TP53	=	Transformation-related Protein 53
Bcl-2	=	B-cell lymphoma 2
c-myc	=	MYC proto-oncogene
p53	=	Protein 53

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

We declare that we have no conflict of interest in the authorship or publication of this contribution.

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