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Mini-review

Helminths in human carcinogenesis

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ABSTRACT

This review examines the salient literature on selected helminths involved in carcinogenicity in humans and updates information in an earlier review on cancer and helminths by Mayer and Fried (2007, Advances in Parasitology 65, 239–296). The earlier review was concerned with various helminths, i.e., trematodes, cestodes, and nematodes, that are definitely implicated as being carcinogenic. This review examines only those helminths, all of which turn out to be trematodes, that are definitely implicated as being carcinogenic. These trematodes are the blood flukes *Schistosoma haematobium*, associated with inducing human carcinoma of the urinary bladder and the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*, associated with inducing cancer of the bile duct (cholangiocarcinoma) and cancer of the liver (hepatocarcinoma) in humans. The review examines mainly the epidemiology and pathology of these helminthic infections in humans and considers what we know about the mechanisms associated with the carcinogenicity of these three trematodes in humans.

1. Introduction

The purpose of this review is to examine the role of selected helminths in human cancer. The three species of selected helminths are all flukes, or parasitic flatworms, known as trematodes. The problem of proving the role of helminths in cancer induction is difficult because of their complicated life-cycles and long asymptomatic latent periods [1]. The International Agency for Research on Cancer (IARC) considered three species of trematodes, *Schistosoma haematobium*, *Opisthorchis viverrini* and *Clonorchis sinensis*, responsible for helminth induced human cancer; they considered *S. haematobium* and *O. viverrini* as group 1 carcinogens and *C. sinensis* as a group 2 carcinogen [2].

Helminth infections are of great importance globally with countless millions of humans being infected or at risk of infection. Mathematical models have been used to calculate the risk of cancer due to infection; the calculated risk factor indicates that about 15% of all cases globally can be attributed to infections including those due to schistosomes and liver flukes. The infectious origin of a cancer implies that it is preventable. Therefore, if infections were prevented by increased educational efforts and improved public health initiatives, there would be considerably fewer cases of cancer in both developed and underdeveloped countries [3].

Our review considers only the above-mentioned three trematodes; an earlier review was concerned with numerous helminths (cestodes, nematodes, and trematodes other than those mentioned above), some of which were suspected as inducing human cancers [3]. This review extends and updates the earlier literature on the group 1 and 2 helminth carcinogens. In the latest update by IARC, *C. sinensis* has been upgraded to group 1 status [4]. The upgraded status of *C. sinensis* as a group 1 carcinogen has also been mentioned [5].

Citations have been listed mainly at the end of a passage and include numbers 1–62. The citations have been arranged mainly chronologically for each helminth covered. Thus, citations begin as early as 1911 and end with several 2009 references at which time the literature searched for this review ceased.

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2. *S.* haematobium

Of four human schistosomes (*S. haematobium*, *S. mansoni*, *S. japonicum*, *S. mekonji*), only the definite carcinogen, *S. haematobium*, is considered herein. *S. haematobium*, typical of schistosomes, is dioecious and the adult female lives in-copulo in the gynecophoral canal of the male; this species of schistosome lives in the venules of the human urinary bladder. Eggs laid in the urinary bladder produce irritation and eventual fibrosis, contributing to the events that lead to human carcinogenicity.

S. hematobium bilharziasis was first linked to urinary bladder cancer in Egypt in 1911 [6]. The incidence of urinary bladder cancer in the Middle East and Africa is greater in areas with high rather than low *S. haematobium* prevalence; the aforementioned study noted that 60% of the Egyptian population was at risk of infection with *S. haematobium*, with rural school children at particular risk because of their proximity to contaminated water. The overall prevalence of *S. haematobium* infection in Egypt is 37–48% and urinary bladder cancer accounts for about 31% of the total incidence of cancers in Egypt; it is the most common type of cancer in males and the second most prevalent, after breast cancer, in females. This compares to bladder cancer's 5th to 7th ranking in males and 7th to 14th ranking in females in schistosome-free nations such as the United States and the United Kingdom. The National Cancer Institute in Cairo reported that 7746 (30.8%) of 25,148 new cancer cases indexed from 1970 through 1981 were urinary bladder cancers, presumably induced by infection with *S. haematobium*. In Egypt, Iraq, Zambia, Zimbabwe, Malawi and Sudan, the incidence of bilharzial bladder cancer peaks at 40–49 years of age; the male to female ratio for bladder cancer is 5:1 in endemic and 3:1 in non-endemic areas. This relates to the fact that it is agricultural workers, mainly men, who have daily exposure to water infected with *S. haematobium* cercariae. In the Nile Delta, almost 100% of bladder cancers found in male agricultural laborers (fellahin) were associated with *S. haematobium* infection, as opposed to about 50% in males with lower-risk occupations [7].

The association between urinary schistosomiasis and bladder cancer is also supported by histopathologic findings. In endemic areas with high worm burdens, squamous cell carcinoma of the bladder is most frequent, while transitional cell carcinoma occurs mainly in areas of low endemicity such as in North America and Europe. A 54–81% incidence of squamous cell cancer was found in all cases of bladder cancers in endemic areas, opposed to 3–10% in Western countries. The higher incidence of squamous cell cancer is probably due to exposure to carcinogens such as *N-nitroso* compounds that are abundantly present in the urine of patients with *S. haematobium* bilharziasis [8].

IARC analyzed seven case–control studies on the association between cancer of the urinary bladder and *S. haematobium* infection. The intensity of infection was determined by urinary egg counts, pelvic X-rays, urinary bladder and rectal biopsies and examination of the bladder tissue following digestion and centrifugation. The results were probably confounded by smoking, a recognized cause of bladder cancer in non-endemic countries, and was considered in only one study but thought not to affect the validity of the findings. Six of the seven studies showed a positive association between bladder cancer and *S. haematobium* infection with odds ratios ranging from 2 to 14 (using all other cancer cases as controls, relative to no such history and adjusted for age, smoking history, education, occupation and geographic area of origin). *S. haematobium* infection did predispose the subjects to bladder cancer, especially the squamous cell type. The more heavily infected individuals were with this schistosome, the more likely they were to develop bladder cancer, and at a younger age [2].

Most of the pathological findings of schistosomiasis are due to an inflammatory and immunological response to egg deposition. Granulomatous areas form around the eggs and induce an exudative cellular response consisting of lymphocytes, polymorphonuclear leukocytes and eosinophils; the early stage of *S. haematobium* infection is characterized by egg deposition in the lower ureters and urinary bladder [9]. Resultant perioval granulomas, fibrosis and muscular hypertrophy are seen histologically. In the ureter, lesions can cause stenosis, leading to hydronephrosis (dilatation of the renal calyces). In the urinary bladder, masses of large granulomatous inflammatory polyps containing eggs are found at the bladder apex, dome, trigone and posterior wall. Polyps may ulcerate and slough, producing haematuria. Hyperplasia of the urothelium occurred in 38% of the autopsied *S. haematobium* cases as opposed to 21% in non-infected cases; also, metaplasia in 31.6% versus 11.5% and dysplasia in 27.2% versus 8.5% cases were found. Late-stage infections were characterized by schistosomal bladder ulcers and sandy patches, and irregularly thickened or atrophic mucosa in the posterior bladder or trigone area. Histologically, fibrosis with some round cell infiltration was seen; old granulomas containing calcified or disintegrating eggs were also seen [10].

The inflammatory and fibrotic response to egg deposition could lead to calcification of the urinary bladder, infection and stone disease and these changes are frequently associated with urinary bladder cancer [11]. *S. haematobium* eggs were found in 902 (82.4%) of 1095 bladder cancer cases in Egypt. Patients with egg deposition in the bladder wall mainly developed squamous cell subtypes, and at an earlier age. Of 798 cases of squamous cell cancer, 691 (86.6%) occurred in patients with *S. haematobium* positive urinary bladders. The cascade syndrome of hyperplasia, metaplasia, dysplasia and squamous cell cancer was associated with late-stage schistosome infection; the egg burden associated with urinary bladder tumors was almost twice that of non-tumor areas of the bladder [12]. Bilharzial granulomas and transformation of the urothelium in response to *S. haematobium* infection has been studied and CD3þ T cells and CD68þ histiocytes were the main cell populations in these lesions. Alterations in the deposition of fibronectin and laminin basement membrane proteins were characteristic of schistosomal bladder changes. Fibronectin deposition increased as lesions progressed from cellular loose fibrillary networks to fibrocellular dense fibrillary networks, and ultimately to fibrotic tight conglomerates. Normal and metaplastic urothelium had continuous basement membranes, whereas breaks in the